Synthesis and Late-Stage Functionalization of Complex Molecules through C-H Fluorination and Nucleophilic Aromatic Substitution

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Supporting Information

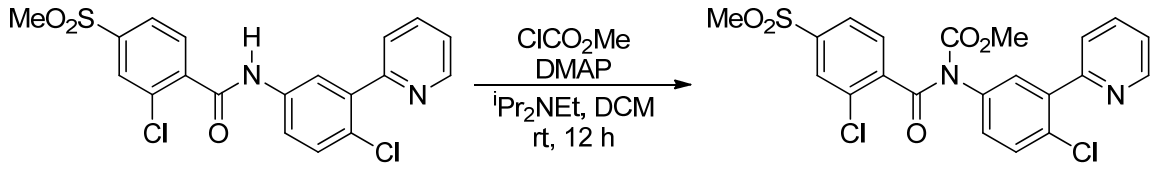
General Experimental Details

Unless otherwise noted, all reactions were assembled under an inert atmosphere with a nitrogen-filled glovebox except for reactions involving aqueous solutions. All reactions were conducted in oven-dried 4-mL or 20-mL vials fitted with a Teflon-lined screw cap under an atmosphere of nitrogen unless otherwise noted.

Silver difluoride (AgF_2) was purchased from Alfa Aesar and used as received (black microcrystalline solid). Acetonitrile was distilled from CaH_2 and stored over molecular sieves. THF was collected from a solvent purification system containing a column of activated alumina under nitrogen. Anhydrous DMF and DMSO (extra dry over molecular sieves, AcroSeal) were purchased from Acros and used as received. Substrates **1**, **5**, and **10** were purchased from commercial suppliers and used as received. Substrates **2**,[1] **3**,[2] **4**,[3] **9**,[4] **11**,[5] **12**,[6] and **14**[7] were prepared according to literature procedures. **(CO_2Me)-Vismodegib**, and substrates **6**, **7**, **8**, **13**, and **15** were prepared according to the procedures described below. All other reagents were purchased from commercial suppliers and used as received.

NMR chemical shifts are reported in ppm and referenced to residual solvent peaks ($CHCl_3$ in $CDCl_3$: 7.26 ppm for ^1H and 77.0 ppm for ^{13}C) or to an external standard (1% $CFCl_3$ in $CDCl_3$: 0 ppm for ^{19}F). Coupling constants are reported in hertz.

Preparation of (CO_2Me)-Vismodegib:



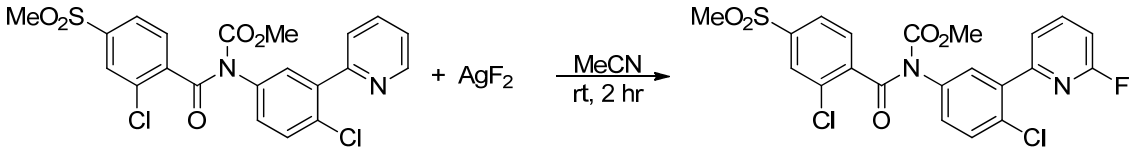
To a 25 mL round bottom flask was added vismodegib[8] (632 mg, 1.50 mmol, 1.00 equiv), DMAP (18 mg, 0.15 mmol, 0.10 equiv), $^{i}Pr_2NEt$ (520 µL, 3.0 mmol, 2.0 equiv) and CH_2Cl_2 (15 mL). The reaction vessel was sparged with N_2 for 5 minutes, and $ClCO_2Me$ (230 µL, 3.0 mmol, 2.0 equiv) was added at once. The reaction mixture was stirred at room temperature for 12 h; a change in the color of the solution from light yellow to orange occurred over the first hour. The mixture was diluted with CH_2Cl_2 (15 mL), and washed once with H_2O (30 mL). The organic phase was concentrated, and the product was purified by silica gel chromatography eluting with 1:3 hexanes : ethyl acetate to afford (CO_2Me)-vismodegib as a light yellow solid (683 mg, 1.42 mmol, 95% yield).

Note: A trace amount of EtOAc remained bound to the solid even after prolonged drying under vacuum at 50 ^{o}C.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.78 – 8.73 (m, 1H), 7.99 (d, *J* = 1.6 Hz, 1H), 7.93 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.82 (td, *J* = 7.7, 1.7 Hz, 1H), 7.77 (m, 1H), 7.64 – 7.59 (m, 3H), 7.37 – 7.32 (m, 1H), 7.30 (dd, *J* = 8.5, 2.6 Hz, 1H), 3.68 (s, 3H), 3.10 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 167.61, 155.23, 153.18, 149.48, 142.28, 141.76, 140.04, 136.04, 135.30, 132.69, 131.25, 131.14, 130.80, 129.18, 128.57, 128.21, 125.91, 124.93, 122.81, 54.45, 44.29.

Preparation of Fluoro-(CO_2Me)-vismodegib:



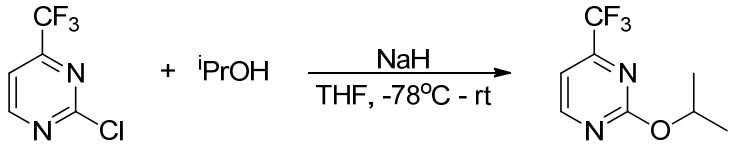
To an oven-dried vial was added (CO_2Me)-vismodegib (96 mg, 0.20 mmol, 1.0 equiv) and MeCN (2.0 mL). While the solution was stirring rapidly, AgF_2 (88 mg, 0.60 mmol, 3.0 equiv) was added at once. The vial was sealed with a Teflon-lined cap and stirred at room temperature for 2 h. The reaction was poured into a separatory funnel containing 10 mL of saturated aqueous $NaHCO_3$ and extracted with 10 mL of Et_2O. The organic layer was washed once with 10 mL of brine, dried over $MgSO_4$, and concentrated. The product was purified by silica gel chromatography eluting with 1:1 hexanes : ethyl acetate (R_f = 0.32) to afford the title compound as a pale yellow solid (90 mg, 0.18 mmol, 90% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 1.6 Hz, 1H), 7.95 – 7.88 (m, 2H), 7.69 (dd, *J* = 7.4, 2.1 Hz, 1H), 7.64 – 7.59 (m, 3H), 7.31 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.99 (dd, *J* = 8.1, 2.6 Hz, 1H), 3.68 (s, 3H), 3.10 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 167.71, 163.10 (d, *J* = 240.0 Hz), 153.67 (d, *J* = 13.3 Hz), 153.22, 142.41, 141.80, 141.15 (d, *J* = 7.7 Hz), 138.48, 135.44, 132.84, 131.43, 131.42, 130.95, 129.64, 128.68, 128.37, 126.03, 122.39 (d, *J* = 4.1 Hz), 108.84 (d, *J* = 36.8 Hz), 54.59, 44.46.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -69.09.

Preparation of Substrate 6:



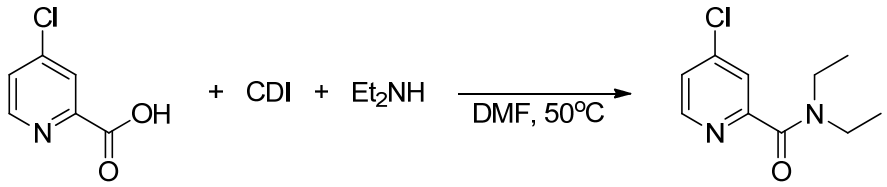
6

To a 25 mL round bottom flask was added NaH (180 mg, 7.5 mmol, 1.5 equiv) and THF (10 mL). The suspension was cooled to 0 °C, and ^{i}PrOH (570 µL, 7.5 mmol, 1.5 equiv) was added dropwise over 10 minutes. The resulting solution was cooled to -78 °C, and 2-chloro-4-trifluoromethylpyrimidine (600 µL, 5.0 mmol, 1.0 equiv) was added dropwise over 5 minutes. The reaction mixture was allowed to slowly warm to room temperature over ~30 minutes and quenched with aqueous NH_4Cl (5 mL) and H_2O (15 mL). The mixture was extracted 2 x 20 mL EtOAc. The organic phase was concentrated, and the product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate to afford **6** as a clear oil (800 mg, 3.90 mmol, 78% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.73 (d, *J* = 4.8 Hz, 1H), 7.21 (d, *J* = 4.9 Hz, 1H), 5.34 (hept, *J* = 6.2 Hz, 1H), 1.42 (d, *J* = 6.2 Hz, 6H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 165.09, 161.85, 157.63 (q, *J* = 36.3 Hz), 120.12 (q, *J* = 275.3 Hz), 109.82, 71.68, 21.60.

Preparation of Substrate 7:



7

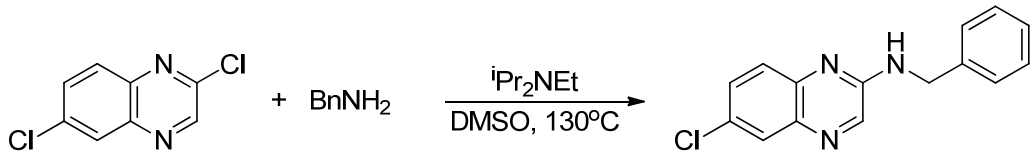
To a 25 mL round bottom flask was added 4-chloropicolinic acid (473 mg, 3.00 mmol, 1.00 equiv) and DMF (4 mL). The suspension was heated at 50 °C, and a solution of 1,1'-carbonyldiimidazole (486 mg, 3.00 mmol, 1.00 equiv) in 5 mL of DMF was added over 3 minutes. The resulting solution was stirred at 50 °C for 30 minutes. Et_2NH (680 µL, 6.6 mmol, 2.2 equiv) was added over 5 minutes, and the resulting mixture was stirred at 50 °C for 12 hours. The solution was cooled, diluted with EtOAc (40 mL), and washed 3 x 20 mL with a 50% saturated aqueous NaCl solution. The organic phase was concentrated, and the product was purified by silica gel chromatography eluting with 2:1 hexanes : ethyl acetate to afford **7** as a clear oil (510 mg, 2.40 mmol, 80% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.48 (s, 1H), 7.61 (s, 1H), 7.33 (dd, *J* = 5.2, 1.7 Hz, 1H), 3.55 (q, *J* = 7.1 Hz, 2H), 3.37 (q, *J* = 7.1 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 167.06, 156.22, 149.09, 145.03, 124.46, 123.66, 43.17, 40.22, 14.22, 12.71..

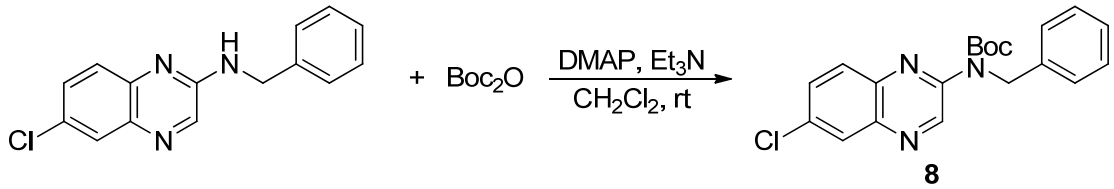
Preparation of Substrate 8:

Step 1:



To an oven dried vial was added 2,6-dichloroquinoxaline (398 mg, 2.00 mmol, 1.00 equiv), ^{i}Pr$_2$NEt (380 µL, 2.2 mmol, 1.1 equiv), DMSO (2 mL) and benzylamine (240 µL, 2.2 mmol, 1.1 equiv). The vial was sealed with a Teflon-lined cap and stirred at 130°C for 12 h. The reaction was diluted with EtOAc (20 mL) and washed 3 x 20 mL H_2O. The organic phase was concentrated, and the product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate to afford N-benzyl-6-chloroquinoxalin-2-amine as a dark oil (540 mg, 2.00 mmol, quantitative yield) that was used directly in step 2.

Step 2:



8

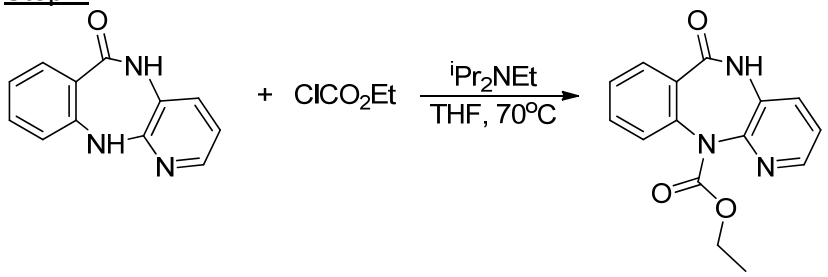
To a round bottom flask was added N-benzyl-6-chloroquinoxalin-2-amine (540 mg, 2.0 mmol, 1.0 equiv), Et_3N (420 µL, 3.0 mmol, 1.5 equiv), DMAP (12 mg, 0.1 mmol, 5 mol %) and CH_2Cl_2 (5 mL). To this solution was added Boc_2O (510 µL, 2.2 mmol, 1.1 equiv) and the resulting mixture was stirred at room temperature for 14 hours. The solvent was removed in vacuo, and the product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate to afford **8** as a white solid (621 mg, 1.68 mmol, 84% yield).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.31 (s, 1H), 8.03 (d, *J* = 2.3 Hz, 1H), 7.81 (d, *J* = 8.9 Hz, 1H), 7.62 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.36 (d, *J* = 7.4 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 5.30 (s, 2H), 1.47 (s, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 153.64, 149.68, 143.74, 139.16, 138.92, 138.47, 133.57, 130.79, 129.18, 128.28, 127.70, 127.51, 127.07, 82.94, 49.58, 28.05..

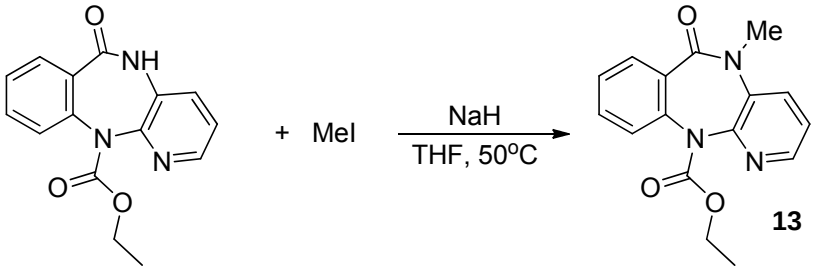
Preparation of Substrate 13:

Step 1:



To an 25 mL round bottom flask was added 5,6-Dihydro-6-oxo-11H-pyrido-[2,3-b][1,4]benzodiazepine (1.06 g, 5.00 mmol, 1.00 equiv; from Matrix Scientific, CAS # 885-70-1), ^{i}Pr$_2$NEt (1.1 mL, 6.0 mmol, 1.2 equiv) and THF (10 mL). The suspension was heated to 70 ^{o}C, and $ClCO_2Et$ was added over 3 minutes. The reaction was held at 70 ^{o}C for 1 h, and then at room temperature for 12 h. H_2O was added (70 mL) to precipitate the product as a tan solid. The solid was collected, washed with H_2O (2 x 15 mL), and dried to afford the product as a tan solid (1.16 g, 4.09 mmol, 82% yield) that was used directly in step 2.

Step 2:



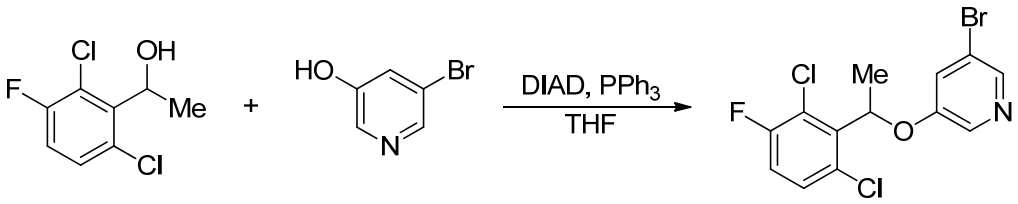
13

To a round bottom flask was added NaH (40 mg, 1.7 mmol, 1.1 equiv) and THF (3 mL). The solid from step 1 (425 mg, 1.50 mmol, 1.00 equiv) was added in portions over 5 minutes. The suspension was stirred at room temperature for 15 minutes, during which the solution became clear and homogeneous. MeI (100 µL, 1.7 mmol, 1.1 equiv) was added, and the mixture was heated to 50 °C for 90 minutes at which time ^{1}H NMR analysis of an aliquot showed complete conversion of the starting material to **13** (Note: the starting material and product have identical R_f values by TLC; therefore reaction conversion must be measured by an alternative method). The reaction was quenched with aqueous NH_4Cl (200 µL). The solvent was removed in vacuo and the product was purified by silica gel chromatography eluting with ethyl acetate (R_f = 0.56) to afford **13** as a light yellow solid (370 mg, 1.25 mmol, 83% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.37 (d, *J* = 4.1 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.52 (m, 2H), 7.41 – 7.29 (m, 2H), 4.36 – 4.15 (m, 2H), 3.59 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 166.67, 153.12, 148.28, 145.55, 141.37, 135.58, 132.47, 131.38, 131.30, 129.42, 127.62, 127.12, 123.63, 62.58, 37.00, 14.25.

Preparation of Substrate 15:



To a 25 mL round bottom flask was added PPh_3 (1.47 g, 5.60 mmol, 1.4 equiv) and THF (20 mL). The solution was cooled to 0 ^oC and DIAD (1.1 mL, 5.6 mmol, 1.4 equiv) was added. The resulting slurry was stirred at 0 ^oC for 5 minutes after which time a solution was added containing 1-(2,6-dichloro-3-fluorophenyl)ethanol[9] (836 mg, 4.00 mmol, 1.00 equiv) and 5-bromo-3-hydroxypyridine (766 mg, 4.4 mmol, 1.1 equiv) in 10 mL of THF. The clear orange solution was stirred at room temperature for 4 h and the solvent was removed in vacuo. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate to afford **15** as a white solid (1.3 g, 3.6 mmol, 89% yield).

^1H NMR (500 MHz, Chloroform-*d*) δ 8.26 (s, 1H), 8.17 (s, 1H), 7.36 (t, *J* = 2.1 Hz, 1H), 7.30 (dd, *J* = 8.9, 4.8 Hz, 1H), 7.11 – 7.05 (m, 1H), 6.05 (q, *J* = 6.7 Hz, 1H), 1.83 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 157.42 (d, *J* = 250.1 Hz), 153.54, 143.23, 136.17, 136.09, 129.94, 128.71 (d, *J* = 3.7 Hz), 125.38, 121.76 (d, *J* = 19.3 Hz), 120.26, 116.79 (d, *J* = 23.2 Hz), 73.33, 18.90..

General Procedure for Tandem C-H fluorination/S_NAr

To an oven-dried vial was added the heteroarene (0.20 mmol, 1.0 equiv) and MeCN (2.0 - 8.0 mL). While the solution was stirring rapidly, AgF_2 (88 mg, 0.60 mmol, 3.0 equiv) was added at once. The vial was sealed with a Teflon-lined cap, and stirred at room temperature for 1 h, unless otherwise noted below. The reaction was filtered into a 20 mL vial through a pipette containing ~500 mg of silica wet with Et_2O. The silica was rinsed with 4-5 mL of Et_2O, and the filtrate was concentrated in vacuo. The resulting crude material was subjected to the following S_NAr reaction conditions:

Reactions with 1^o, 2^o, or 3^o alcohols:

The crude material from the fluorination reaction was dissolved in 1 mL of THF and the 1^o or 2^o alcohol (0.24 mmol, 1.2 equiv) was added followed by KO^tBu (0.24 mmol, 1.2 equiv). For 3^o alcohol nucleophiles, the potassium 3^o alkoxide salt (0.24 mmol, 1.2 equiv) was used directly. The vial was sealed with a Teflon-lined cap, and stirred at 50 ^oC for 3 h. The reaction mixture was concentrated in vacuo, and the crude material was purified by silica gel chromatography.

Reactions with phenols:

The crude material from the fluorination reaction was dissolved in 1 mL of DMF and the phenol (0.24 mmol, 1.2 equiv) was added followed by KO^tBu (0.24 mmol, 1.2 equiv). The vial was sealed with a Teflon-lined cap, and stirred at 80 ^oC for 6 h. The reaction mixture was diluted with EtOAc (20 mL) and washed 4 x 20 mL H_2O (or 4 x 20 mL brine). The organic layer was concentrated and purified by silica gel chromatography.

Reactions with 1^o or 2^o amines:

The crude material from the fluorination reaction was dissolved in 500 µL of DMSO and $^iPr_2NEt$ (0.30 mmol, 1.5 equiv) and amine (0.30 mmol, 1.5 equiv) were added. The vial was sealed with a Teflon-lined cap, and stirred at 120 ^oC for 18 h. The reaction mixture was diluted with EtOAc (20 mL) and washed 4 x 20 mL H_2O (or 4 x 20 mL brine). The organic layer was concentrated and purified by silica gel chromatography.

Reactions with amides:

The crude material from the fluorination reaction was dissolved in 1 mL of DMF, and amide (0.24 mmol, 1.2 equiv) was added. NaH (0.24 mmol, 1.2 equiv) was added slowly, and the resulting mixture was stirred at room temperature for 5 minutes, or until H_2 evolution stopped. The vial was sealed with a Teflon-lined cap, and stirred at 100 ^{o}C for 3 h. The reaction mixture was diluted with EtOAc (20 mL) and washed with 4 x 20 mL of H_2O (or 4 x 20 mL brine). The organic layer was concentrated and purified by silica gel chromatography.

Reactions with nitrogen heterocycles:

The crude material from the fluorination reaction was dissolved in 1 mL of DMF and the nitrogen heterocycle (0.24 mmol, 1.2 equiv) was added. NaH (0.24 mmol, 1.2 equiv) was added slowly, and the resulting mixture was stirred at room temperature for 5 minutes, or until H_2 evolution stopped. The vial was sealed with a Teflon-lined cap, and stirred at 100 ^{o}C for 1-3 h. The reaction mixture was diluted with EtOAc (20 mL) and washed with 4 x 20 mL of H_2O (or 4 x 20 mL brine). The organic layer was concentrated and purified by silica gel chromatography.

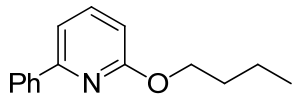
Reactions with KCN:

The crude material from the fluorination reaction was dissolved in 500 µL of DMSO and KCN (0.60 mmol, 3.0 equiv) was added. The vial was sealed with a Teflon-lined cap, and stirred at 120 ^{o}C for 18 h. The reaction mixture was diluted with EtOAc (20 mL) and washed with 4 x 20 mL of H_2O (or 4 x 20 mL brine). The organic layer was concentrated and purified by silica gel chromatography.

Reactions with sodium thiolate salts:

The crude material from the fluorination reaction was dissolved in 1 mL of THF and the sodium thiolate salt (0.24 mmol, 1.2 equiv) was added. The vial was sealed with a Teflon-lined cap, and stirred at 50 ^{o}C for 3 h. The reaction mixture was concentrated in vacuo, and the crude material was purified by silica gel chromatography.

Synthesis of 2-butoxy-6-phenylpyridine (1a)



The general procedure for tandem C-H fluorination/S_NAr was performed with 2-phenylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate (R_f = 0.44) to afford **1a** as a colorless oil (38 mg, 0.17 mmol, 84% yield).

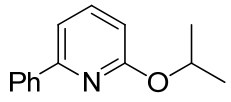
^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.06 (d, *J* = 7.4 Hz, 2H), 7.63 (t, *J* = 7.8 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.34 (d, *J* = 7.4 Hz, 1H), 6.69 (d, *J* = 8.1 Hz, 1H), 4.46 (t, *J* = 6.6 Hz, 2H), 1.84 (p, *J* = 6.8 Hz, 2H), 1.55 (h, *J* = 7.4 Hz, 2H), 1.02 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 163.65, 154.58, 139.14, 139.04, 128.71, 128.53, 126.64, 112.53, 109.33, 65.49, 31.19, 19.37, 13.93.

Calculated exact mass: 227.13

EI Mass Spectrum: 227.1 (M^+, 13% relative intensity), 171.1 ($[M-56]^+$, base peak)

Synthesis of 2-isopropoxy-6-phenylpyridine (1b)



The general procedure for tandem C-H fluorination/S_NAr was performed with 2-phenylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 20:1 hexanes : ethyl acetate (R_f = 0.59) to afford **1b** as a colorless oil (36 mg, 0.17 mmol, 84% yield).

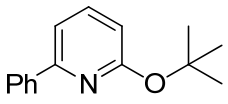
^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.06 (d, *J* = 7.6 Hz, 2H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.33 (d, *J* = 7.4 Hz, 1H), 6.66 (d, *J* = 8.2 Hz, 1H), 5.54 (hept, *J* = 6.2 Hz, 1H), 1.45 (d, *J* = 6.2 Hz, 6H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 163.04, 154.50, 139.20, 139.09, 128.67, 128.52, 126.60, 112.28, 109.86, 67.72, 22.07.

Calculated exact mass: 213.12

EI Mass Spectrum: 213.1 (M^+, 22% relative intensity), 171.1 ($[M-42]^+$, base peak)

Synthesis of 2-(tert-butoxy)-6-phenylpyridine (1c)



The general procedure for tandem C-H fluorination/S_NAr was performed with 2-phenylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 20:1 hexanes : ethyl acetate (R_f = 0.57) to afford **1c** as a colorless oil (37 mg, 0.16 mmol, 81% yield).

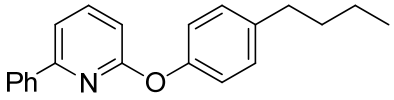
^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.02 (d, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.31 (d, *J* = 7.4 Hz, 1H), 6.60 (d, *J* = 8.2 Hz, 1H), 1.69 (s, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 163.55, 154.22, 139.42, 138.84 (two overlapping peaks), 128.56, 126.62, 112.15, 111.64, 79.38, 28.81.

Calculated exact mass: 227.13

EI Mass Spectrum: 227.1 (M^+, 3% relative intensity), 171.1 ($[M-56]^+$, base peak)

Synthesis of 2-(4-butylphenoxy)-6-phenylpyridine (1d)



The general procedure for tandem C-H fluorination/S_NAr was performed with 2-phenylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 20:1 hexanes : ethyl acetate (R_f = 0.51) to afford **1d** as a colorless oil (44 mg, 0.15 mmol, 73% yield).

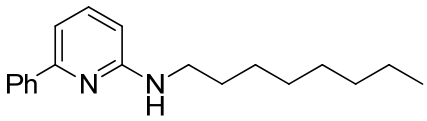
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 7.2 Hz, 2H), 7.71 (t, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.1 Hz, 1H), 2.68 – 2.63 (m, 2H), 1.65 (p, *J* = 7.6 Hz, 2H), 1.40 (h, *J* = 7.3 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 163.64, 155.56, 152.08, 139.92, 139.00, 138.40, 129.34, 129.00, 128.54, 126.75, 120.91, 114.39, 109.04, 35.01, 33.67, 22.29, 13.96.

Calculated exact mass: 303.16

EI Mass Spectrum: 303.2 (M^+, 67% relative intensity), 302.2 ($[M-1]^+$, base peak)

Synthesis of N-octyl-6-phenylpyridin-2-amine (1e)



The general procedure for tandem C-H fluorination/S_NAr was performed with 2-phenylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 20:1 hexanes : ethyl acetate (R_f = 0.29) to afford **1e** as a colorless oil (34 mg, 0.12 mmol, 60% yield).

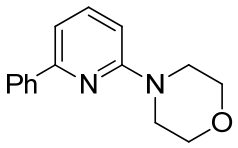
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 7.7 Hz, 2H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 6.34 (d, *J* = 8.2 Hz, 1H), 4.71 (br, 1H), 3.32 (q, *J* = 6.6 Hz, 2H), 1.66 (p, *J* = 7.2 Hz, 2H), 1.43 (p, *J* = 6.8 Hz, 2H), 1.38 – 1.25 (m, 8H), 0.89 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 158.70, 155.70, 139.80, 138.12 (two overlapping peaks), 128.44, 126.75, 109.40, 104.70, 42.38, 31.82, 29.64, 29.38, 29.25, 27.12, 22.64, 14.08.

Calculated exact mass: 282.21

EI Mass Spectrum: 282.2 (M^+, 25% relative intensity), 183.1 ($[M-99]^+$, base peak)

Synthesis of 4-(6-phenylpyridin-2-yl)morpholine (1f)



The general procedure for tandem C-H fluorination/S_NAr was performed with 2-phenylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate (R_f = 0.28) to afford **1f** as a colorless oil (36 mg, 0.15 mmol, 75% yield).

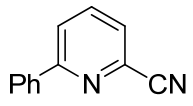
^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 7.3 Hz, 2H), 7.61 – 7.55 (m, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 3.88 – 3.86 (m, 4H), 3.64 – 3.60 (m, 4H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 159.06, 155.11, 139.64, 138.17, 128.56, 128.40, 126.66, 110.12, 105.22, 66.76, 45.52.

Calculated exact mass: 240.13

EI Mass Spectrum: 240.1 (M^+, 57% relative intensity), 209.1 ($[M-31]^+$, base peak)

Synthesis of 6-phenylpicolinonitrile (1g)



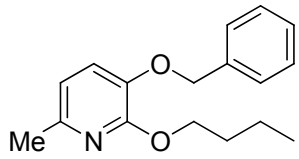
The general procedure for tandem C-H fluorination/S_NAr was performed with 2-phenylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate (R_f = 0.33) to afford **1g** as a white solid (22 mg, 0.12 mmol, 61% yield).

NMR spectra were in accord with previously reported spectral data.[10]

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.02 (d, *J* = 7.1 Hz, 2H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.88 (t, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.49 (m, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 158.86, 137.68, 137.09, 133.69, 130.10, 128.91, 126.97, 126.52, 123.43, 117.37.

Synthesis of 3-(benzyloxy)-2-butoxy-6-methylpyridine (2a)



The general procedure for tandem C-H fluorination/S_NAr was performed with 5-(benzyloxy)-2-methylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate (R_f = 0.67) to afford **2a** as a colorless oil (42 mg, 0.15 mmol, 77% yield).

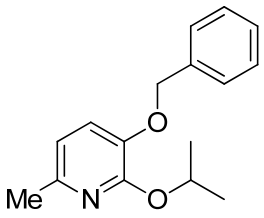
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.43 (d, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.56 (d, *J* = 7.8 Hz, 1H), 5.11 (s, 2H), 4.41 (t, *J* = 6.7 Hz, 2H), 2.37 (s, 3H), 1.84 (p, *J* = 6.9 Hz, 2H), 1.53 (h, *J* = 7.4 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 154.39, 147.10, 140.45, 137.04, 128.42, 127.77, 127.23, 122.34, 114.91, 71.36, 65.63, 31.17, 23.21, 19.34, 13.92.

Calculated exact mass: 271.16

EI Mass Spectrum: 271.1 (M^+, 12% relative intensity), 91.1 ($[C_7H_7]^+$, base peak)

Synthesis of 3-(benzyloxy)-2-isopropoxy-6-methylpyridine (2b)



The general procedure for tandem C-H fluorination/S_NAr was performed with 5-(benzyloxy)-2-methylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate (R_f = 0.69) to afford **2b** as a colorless oil (40 mg, 0.16 mmol, 78% yield).

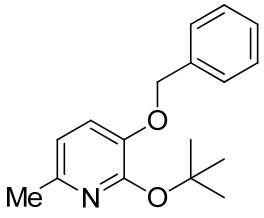
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.43 (d, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.53 (d, *J* = 7.8 Hz, 1H), 5.46 (hept, *J* = 6.1 Hz, 1H), 5.12 (s, 2H), 2.36 (s, 3H), 1.42 (d, *J* = 6.2 Hz, 6H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 153.93, 147.26, 140.56, 137.19, 128.39, 127.72, 127.23, 122.96, 114.67, 71.52, 67.90, 23.28, 22.11.

Calculated exact mass: 257.14

EI Mass Spectrum: 257.1 (M^+, 11% relative intensity), 91.0 ($[C_7H_7]^+$, base peak)

Synthesis of 3-(benzyloxy)-2-(tert-butoxy)-6-methylpyridine (2c)



The general procedure for tandem C-H fluorination/S_NAr was performed with 5-(benzyloxy)-2-methylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate (R_f = 0.69) to afford **2c** as a colorless oil (42 mg, 0.15 mmol, 77% yield).

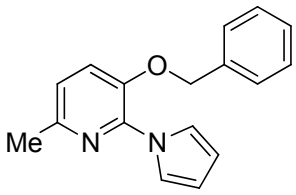
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.43 (d, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.56 (d, *J* = 7.8 Hz, 1H), 5.06 (s, 2H), 2.36 (s, 3H), 1.64 (s, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 154.23, 147.30, 141.74, 137.33, 128.37, 127.72, 127.36, 123.65, 115.10, 80.12, 71.74, 28.82, 23.32.

Calculated exact mass: 271.16

EI Mass Spectrum: 271.1 (M^+, 1% relative intensity), 215.1 ($[M-56]^+$, 33% relative intensity), 91.1 ($[C_7H_7]^+$, base peak)

Synthesis of 3-(benzyloxy)-6-methyl-2-(1H-pyrrol-1-yl)pyridine (2d)

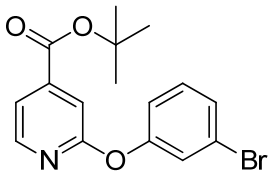


The general procedure for tandem C-H fluorination/S_NAr was performed with 5-(benzyloxy)-2-methylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate (R_f = 0.41) to afford **2d** as a light yellow oil (31 mg, 0.12 mmol, 59% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.69 (t, *J* = 2.2 Hz, 2H), 7.40 (d, *J* = 6.8 Hz, 4H), 7.35 (m, 1H), 7.27 (d, *J* = 8.1, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.32 – 6.30 (m, 2H), 5.10 (s, 2H), 2.49 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 149.15, 143.24, 141.13, 136.00, 128.66, 128.17, 127.32, 123.29, 120.88, 120.17, 109.52, 71.37, 23.28.

Synthesis of tert-butyl 2-(3-bromophenoxy)isonicotinate (3a)



The general procedure for tandem C-H fluorination/S_NAr was performed with tert-butyl isonicotinate. The fluorination step was performed with 4 mL of MeCN at 50 ^{o}C for 2 h. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate to afford **3a** as a colorless oil (28 mg, 0.080 mmol, 40% yield).

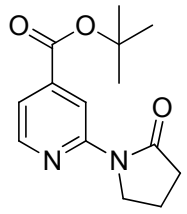
^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.28 (d, *J* = 5.1 Hz, 1H), 7.52 (d, *J* = 5.1 Hz, 1H), 7.45 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 1.9 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.09 (dd, *J* = 8.1, 2.1 Hz, 1H), 1.61 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.72, 163.45, 154.50, 148.11, 143.32, 130.71, 128.05, 124.58, 122.67, 119.93, 118.20, 111.73, 82.71, 28.02.

Calculated exact mass: 349.03 (100.0%), 351.03 (97.3%)

EI Mass Spectrum: 349.0 ([M with ^{79}Br]$^+$, 18% relative intensity), 351.1 ([M with ^{81}Br]$^+$, 18% relative intensity), 293.9 ([M-55]$^+$, base peak)

Synthesis of tert-butyl 2-(2-oxopyrrolidin-1-yl)isonicotinate (3b)



The general procedure for tandem C-H fluorination/S_NAr was performed with tert-butyl isonicotinate. The fluorination step was performed with 4 mL of MeCN at 50 ^oC for 2 h. The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate (R_f = 0.27) to afford **3b** as a light yellow oil (24 mg, 0.091 mmol, 46% yield).

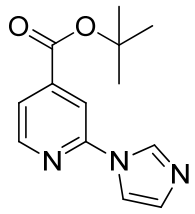
^1H NMR (600 MHz, Chloroform-*d*) δ 8.86 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 7.55 – 7.49 (m, 1H), 4.10 (t, *J* = 7.1 Hz, 2H), 2.67 (t, *J* = 8.1 Hz, 2H), 2.14 (p, *J* = 7.8 Hz, 2H), 1.59 (s, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 174.94, 164.11, 152.53, 147.84, 141.03, 118.49, 114.24, 82.31, 47.49, 33.52, 28.00, 17.65.

Calculated exact mass: 262.13

EI Mass Spectrum: 262.1 (M^+, 12% relative intensity), 151.0 ($[M-111]^+$, base peak)

Synthesis of tert-butyl 2-(1H-imidazol-1-yl)isonicotinate (3c)

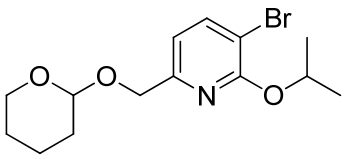


The general procedure for tandem C-H fluorination/S_NAr was performed with tert-butyl isonicotinate. The fluorination step was performed with 4 mL of MeCN at 50 ^oC for 2 h. The product was purified by silica gel chromatography eluting with 99:1 ethyl acetate : triethylamine (R_f = 0.16) to afford **3c** as a light yellow oil (22 mg, 0.090 mmol, 45% yield).

^1H NMR (600 MHz, Chloroform-*d*) δ 8.58 (d, *J* = 5.0 Hz, 1H), 8.46 (s, 1H), 7.85 (s, 1H), 7.72 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.69 (s, 1H), 7.23 (s, 1H), 1.62 (s, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 163.04, 149.82, 149.64, 142.53, 134.94, 130.46, 121.26, 116.21, 111.70, 83.29, 28.00.

Synthesis of 3-bromo-2-isopropoxy-6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridine (4a)



The general procedure for tandem C-H fluorination/S_NAr was performed with 5-bromo-2-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate (R_f = 0.67) to afford **4a** as a colorless oil (49 mg, 0.15 mmol, 74% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 5.32 (hept, *J* = 6.1 Hz, 1H), 4.76 (t, *J* = 3.3 Hz, 1H), 4.70 (d, *J* = 13.8 Hz, 1H), 4.48 (d, *J* = 13.8 Hz, 1H), 3.93 – 3.88 (m, 1H), 3.55 (dd, *J* = 10.3, 5.0 Hz, 1H), 1.92 – 1.84 (m, 1H), 1.80 – 1.73 (m, 1H), 1.70 (m, 1H), 1.65 – 1.51 (m, 3H), 1.36 (dd, *J* = 6.2, 2.0 Hz, 6H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 158.67, 155.11, 141.79, 114.39, 105.42, 98.19, 69.44, 68.92, 62.08, 30.50, 25.40, 21.89, 19.25.

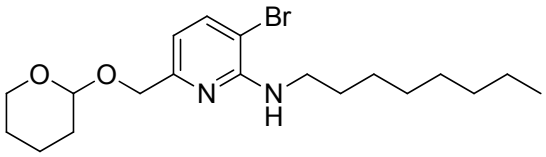
Chemical formula: $C_{14}H_{20}BrNO_3$

Calculated exact mass: 329.0627

Observed formula by ESIMS: $C_{14}H_{21}BrNO_3$

Observed exact mass: 330.0702 (calculated exact mass + ^{1}H)

Synthesis of 3-bromo-N-octyl-6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridin-2-amine (4b)



The general procedure for tandem C-H fluorination/S_NAr was performed with 5-bromo-2-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 20:1 hexanes : ethyl acetate to afford **4b** as a colorless oil (56 mg, 0.14 mmol, 70% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.55 (d, *J* = 7.8 Hz, 1H), 6.57 (d, *J* = 7.8 Hz, 1H), 4.95 (br, 1H), 4.77 (t, *J* = 3.3 Hz, 1H), 4.68 (d, *J* = 13.7 Hz, 1H), 4.46 (d, *J* = 13.7 Hz, 1H), 3.96 – 3.88 (m, 1H), 3.53 (dt, *J* = 10.2, 4.4 Hz, 1H), 3.42 (q, *J* = 6.7 Hz, 2H), 1.89 (m, 1H), 1.76 (m,, 1H), 1.69 (m, 1H), 1.65 – 1.51 (m, 5H), 1.40 – 1.22 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 1H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 156.02, 153.95, 139.55, 110.12, 103.56, 98.14, 69.30, 62.02, 41.65, 31.79, 30.52, 29.58, 29.33, 29.21, 27.00, 25.44, 22.61, 19.28, 14.05.

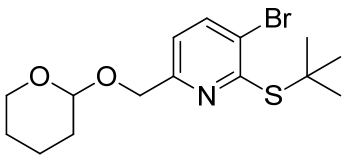
Chemical formula: $C_{19}H_{31}BrN_2O_2$

Calculated exact mass: 398.1569

Observed formula by ESIMS: $C_{19}H_{32}BrN_2O_2$

Observed exact mass: 399.1642 (calculated exact mass + ^{1}H)

Synthesis of 3-bromo-2-(tert-butylthio)-6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridine (4c)



The general procedure for tandem C-H fluorination/S_NAr was performed with 5-bromo-2-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 20:1 hexanes : ethyl acetate (R_f = 0.37) to afford **4c** as a colorless oil (37 mg, 0.10 mmol, 51% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.67 (d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 4.81 (d, *J* = 13.7 Hz, 1H), 4.77 (t, *J* = 3.3 Hz, 1H), 4.56 (d, *J* = 13.7 Hz, 1H), 3.93 – 3.87 (m, 1H), 3.59 – 3.52 (m, 1H), 1.88 (m, 1H), 1.78 (m, 1H), 1.74 – 1.67 (m, 1H), 1.64 – 1.53 (m, 12H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 159.03, 156.60, 139.71, 117.27, 117.18, 98.43, 69.19, 62.12, 48.66, 30.51, 30.07, 25.39, 19.23.

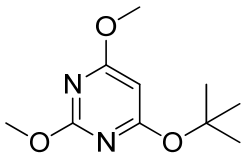
Chemical formula: $C_{15}H_{22}BrNO_2S$

Calculated exact mass: 359.0555 for **4c** with ^{79}Br isotope

Observed formula by ESIMS: $C_{15}H_{22}BrNO_2SNa$

Observed exact mass: 382.0447 (calculated exact mass + ^{23}Na)

Synthesis of 4-(tert-butoxy)-2,6-dimethoxypyrimidine (5a)



The general procedure for tandem C-H fluorination/S_NAr was performed with 2,4-dimethoxypyrimidine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 20:1 hexanes : ethyl acetate (R_f = 0.41) to afford **5a** as a colorless oil (30 mg, 0.14 mmol, 71% yield).

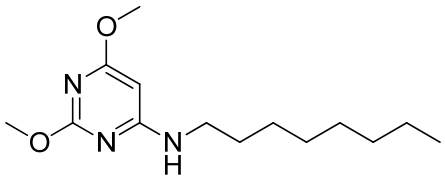
^{1}H NMR (600 MHz, Chloroform-*d*) δ 5.62 (s, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 1.58 (s, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 172.58, 172.09, 164.35, 85.49, 81.33, 54.60, 53.76, 28.69.

Calculated exact mass: 212.12

EI Mass Spectrum: 212.1 (M^+, 3% relative intensity), 156.0 ($[M-56]^+$, base peak)

Synthesis of 2,6-dimethoxy-N-octylpyrimidin-4-amine (5b)



The general procedure for tandem C-H fluorination/S_NAr was performed with 2,4-dimethoxypyrimidine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate (R_f = 0.44) to afford **5b** as a colorless oil which solidified to a white solid on standing (38 mg, 0.14 mmol, 71% yield).

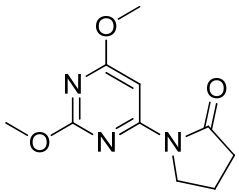
^{1}H NMR (600 MHz, Chloroform-*d*) δ 5.31 (s, 1H), 4.92 (s, 1H), 3.86 (two overlapping methyl peaks, 6H), 3.16 (s, 2H), 1.55 (q, *J* = 6.8 Hz, 2H), 1.38 – 1.17 (m, 10H), 0.85 (t, *J* = 6.5 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 172.00, 165.51, 164.90, 78.34, 54.05, 53.42, 41.74, 31.70, 29.20 (2 overlapping peaks), 29.12, 26.86, 22.54, 13.98.

Calculated exact mass: 267.19

EI Mass Spectrum: 267.2 (M^+, 16% relative intensity), 168.0 ($[M-99]^+$, base peak)

Synthesis of 1-(2,6-dimethoxypyrimidin-4-yl)pyrrolidin-2-one (5c)



The general procedure for tandem C-H fluorination/S_NAr was performed with 2,4-dimethoxypyrimidine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 2:1 hexanes : ethyl acetate (R_f = 0.36) to afford **5c** as a white solid (28 mg, 0.13 mmol, 63% yield).

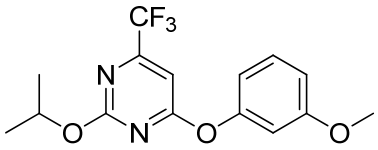
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.41 (s, 1H), 4.05 (t, *J* = 7.2 Hz, 2H), 3.93 (two overlapping peaks, 6H), 2.61 (t, *J* = 8.1 Hz, 2H), 2.09 (p, *J* = 7.8 Hz, 2H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 175.53, 172.88, 164.27, 159.27, 88.48, 54.47, 54.01, 46.87, 33.59, 17.56.

Calculated exact mass: 223.10

EI Mass Spectrum: 223.1 (M^+, 46% relative intensity), 168.1 ($[M-55]^+$, base peak)

Synthesis of 2-isopropoxy-4-(3-methoxyphenoxy)-6-(trifluoromethyl)pyrimidine (6a)



The general procedure for tandem C-H fluorination/S_NAr was performed with 2-isopropoxy-4-(trifluoromethyl)pyrimidine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 20:1 hexanes : ethyl acetate (R_f = 0.26) to afford **6a** as a colorless oil (33 mg, 0.10 mmol, 50% yield).

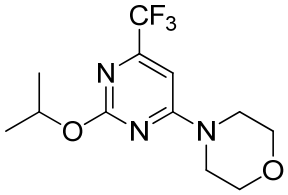
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.33 (t, *J* = 8.2 Hz, 1H), 6.83 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.76 (s, 1H), 6.75 – 6.72 (m, 1H), 6.69 (s, 1H), 5.11 (hept, *J* = 6.2 Hz, 1H), 3.81 (s, 3H), 1.32 (d, *J* = 6.2 Hz, 6H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 172.24, 165.22, 160.84, 158.88 (q, *J* = 35.9 Hz), 152.82, 130.19, 120.15 (q, *J* = 274.9 Hz), 113.54, 111.90, 107.46, 97.72 (q, *J* = 2.9 Hz), 71.92, 55.47, 21.55.

Calculated exact mass: 328.10

EI Mass Spectrum: 328.1 (M^+, 27% relative intensity), 149.0 ($[M-179]^+$, base peak)

Synthesis of 4-(2-isopropoxy-6-(trifluoromethyl)pyrimidin-4-yl)morpholine (6b)

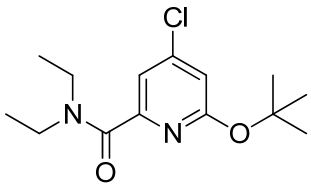


The general procedure for tandem C-H fluorination/S_NAr was performed with 2-isopropoxy-4-(trifluoromethyl)pyrimidine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate (R_f = 0.24) to afford **6b** as a colorless oil (29 mg, 0.10 mmol, 50% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.44 (s, 1H), 5.23 (hept, *J* = 6.1 Hz, 1H), 3.79 – 3.74 (m, 4H), 3.70 (br, 4H), 1.36 (d, *J* = 6.2 Hz, 6H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 164.98, 164.33, 156.61 (q, *J* = 34.5 Hz), 120.75 (q, *J* = 274.7 Hz), 92.79 (q, *J* = 3.2 Hz), 70.44, 66.34, 44.43, 21.77.

Synthesis of 6-(tert-butoxy)-4-chloro-N,N-diethylpicolinamide (7a)



The general procedure for tandem C-H fluorination/S_NAr was performed with 4-chloro-N,N-diethylpicolinamide. The fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate (R_f = 0.29) to afford **7a** as a colorless oil (40 mg, 0.14 mmol, 70% yield).

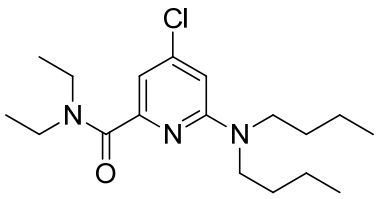
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.00 (d, *J* = 1.7 Hz, 1H), 6.66 (d, *J* = 1.7 Hz, 1H), 3.52 (q, *J* = 7.1 Hz, 2H), 3.34 (q, *J* = 7.1 Hz, 2H), 1.53 (s, 9H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 167.50, 163.45, 153.23, 145.56, 115.68, 113.61, 80.96, 42.43, 39.41, 28.54, 14.29, 12.68.

Calculated exact mass: 284.13

EI Mass Spectrum: 284.1 (M^+, 1% relative intensity), 227.0 ($[M-57]^+$, 13% relative intensity), 72.1 ($[C_4H_{10}N]^+$, base peak)

Synthesis of 4-chloro-6-(dibutylamino)-N,N-diethylpicolinamide (7b)



The general procedure for tandem C-H fluorination/S_NAr was performed with 4-chloro-N,N-diethylpicolinamide. The fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate (R_f = 0.28) to afford **7b** as a colorless oil (48 mg, 0.14 mmol, 71% yield).

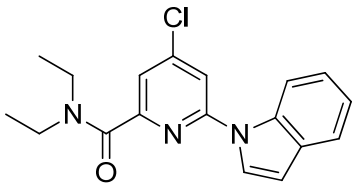
^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.67 (s, 1H), 6.35 (s, 1H), 3.49 (q, *J* = 6.6 Hz, 2H), 3.36 (m, 6H), 1.51 (m, 4H), 1.29 (m, 4H), 1.19 (t, *J* = 6.8 Hz, 3H), 1.13 (t, *J* = 6.7 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 168.20, 157.45, 154.55, 144.85, 110.02, 105.09, 48.40, 42.58, 39.50, 29.51, 20.13, 14.28, 13.83, 12.65.

Calculated exact mass: 339.21

EI Mass Spectrum: 339.2 (M^+, 52% relative intensity), 240.1 ($[M-99]^+$, base peak)

Synthesis of 4-chloro-N,N-diethyl-6-(1H-indol-1-yl)picolinamide (7c)



The general procedure for tandem C-H fluorination/S_NAr was performed with 4-chloro-N,N-diethylpicolinamide. The fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate to afford **7c** as a light yellow oil (40 mg, 0.12 mmol, 61% yield).

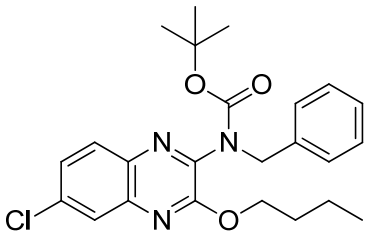
^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.17 (d, *J* = 8.3 Hz, 1H), 7.72 (s, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.55 (s, 1H), 7.44 (s, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.3 Hz, 1H), 6.73 (s, 1H), 3.60 (q, *J* = 6.7 Hz, 2H), 3.43 (q, *J* = 6.6 Hz, 2H), 1.30 (t, *J* = 6.9 Hz, 3H), 1.21 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 166.68, 155.37, 151.83, 146.61, 134.85, 130.62, 125.65, 123.54, 121.86, 121.25, 119.46, 114.31, 113.09, 106.64, 43.14, 40.16, 14.37, 12.73.

Calculated exact mass: 327.11

EI Mass Spectrum: 327.1 (M^+, 13% relative intensity), 72.1 ($[C_4H_{10}N]^+$, base peak)

Synthesis of tert-butyl benzyl(3-butoxy-6-chloroquinoxalin-2-yl)carbamate (8a)



The general procedure for tandem C-H fluorination/S_NAr was performed with tert-butyl benzyl(6-chloroquinoxalin-2-yl)carbamate. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 20:1 hexanes : ethyl acetate to afford **8a** as a light yellow oil (81 mg, 0.18 mmol, 92% yield).

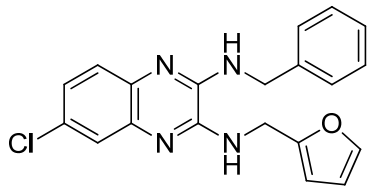
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.8 Hz, 1H), 7.76 (s, 1H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.35 (d, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 1H), 5.08 (s, 2H), 4.40 (s, 2H), 1.75 (p, *J* = 6.8 Hz, 2H), 1.44 (m, 2H), 1.40 (s, 9H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 154.48, 153.60, 143.08, 140.13, 137.93, 135.83, 134.80, 129.03, 128.13, 127.73, 127.16, 127.06, 125.64, 81.40, 66.79, 51.80, 30.72, 28.05, 19.12, 13.75.

Calculated exact mass: 441.18

EI Mass Spectrum: 341.1 ($[M\text{-Boc}]^+$, 57% relative intensity), 91.0 ($[C_7H_7]^+$, base peak)

Synthesis of N2-benzyl-6-chloro-N3-(furan-2-ylmethyl)quinoxaline-2,3-diamine (8b)



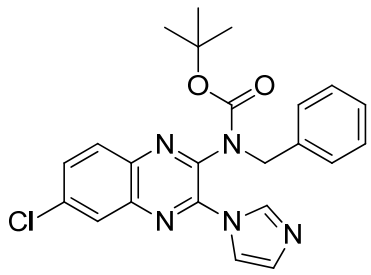
The general procedure for tandem C-H fluorination/S_NAr was performed with tert-butyl benzyl(6-chloroquinoxalin-2-yl)carbamate. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate to afford **8b** as a white solid (60 mg, 0.16 mmol, 82% yield).

Note: The Boc group was cleaved during the S_NAr reaction.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.95 (s, 1H), 7.86 (d, *J* = 8.7 Hz, 1H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.36 – 7.31 (m, 3H), 7.31 – 7.26 (m, 1H), 6.49 (s, 1H), 6.32 (s, 1H), 5.18 (two overlapping peaks, 4H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 153.54, 148.35, 142.69, 139.75, 139.57, 139.46, 137.57, 135.51, 132.28, 128.81, 128.71, 128.11, 127.55, 126.93, 110.53, 109.56, 43.58, 36.22.

Synthesis of tert-butyl benzyl(6-chloro-3-(1H-imidazol-1-yl)quinoxalin-2-yl)carbamate (8c)



The general procedure for tandem C-H fluorination/S_NAr was performed with tert-butyl benzyl(6-chloroquinoxalin-2-yl)carbamate. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 1:1 hexanes : ethyl acetate (R_f = 0.32) to afford **8c** as a light yellow oil (72 mg, 0.17 mmol, 83% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.05 (s, 1H), 7.98 (m, 2H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.37 (d, *J* = 7.3 Hz, 2H), 7.34 – 7.23 (m, 4H), 7.09 (s, 1H), 5.28 (s, 2H), 1.16 (br, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 152.54, 142.90, 141.74, 139.44, 138.20, 136.65, 136.35, 136.02, 131.26, 129.20, 129.04 (two overlapping peaks), 128.79, 128.10, 127.17, 117.58, 83.08, 51.74, 27.53.

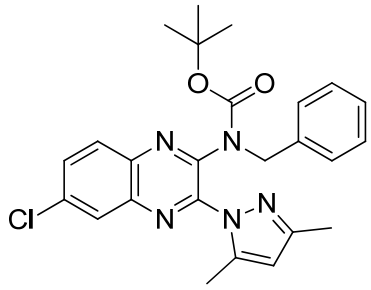
Chemical formula: $C_{24}H_{23}ClN_4O_2$

Calculated exact mass: 434.1510

Observed formula by ESIMS: $C_{24}H_{25}ClN_4O_2$

Observed exact mass: 436.1535 (calculated exact mass + $^1H_2$)

Synthesis of tert-butyl benzyl(6-chloro-3-(3,5-dimethyl-1H-pyrazol-1-yl)quinoxalin-2-yl)carbamate (8d)



The general procedure for tandem C-H fluorination/S_NAr was performed with tert-butyl benzyl(6-chloroquinoxalin-2-yl)carbamate. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate (R_f = 0.61) to afford **8d** as a white solid (63 mg, 0.14 mmol, 68% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.98 – 7.96 (m, 1H), 7.90 (d, *J* = 8.9 Hz, 1H), 7.64 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.25 (d, *J* = 8.9 Hz, 1H), 6.01 (s, 1H), 5.08 (br, 2H), 2.56 (s, 3H), 2.28 (s, 3H), 1.11 (s, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 152.86, 150.17, 143.75, 142.17, 138.96, 138.83, 138.15, 135.15, 130.52, 129.29, 128.20 (two overlapping peaks), 127.99, 127.04, 126.86, 108.01, 81.16, 53.23, 27.59, 13.67, 12.93.

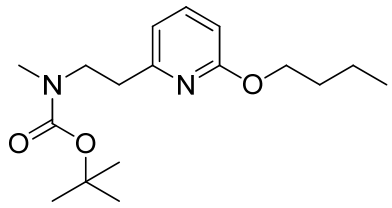
Chemical formula: $C_{26}H_{27}ClN_4O_2$

Calculated exact mass: 462.1823

Observed formula by ESIMS: $C_{26}H_{29}ClN_4O_2$

Observed exact mass: 464.1846 (calculated exact mass + $^1H_2$)

Synthesis of tert-butyl (2-(6-butoxypyridin-2-yl)ethyl)(methyl)carbamate (9a)



The general procedure for tandem C-H fluorination/S_NAr was performed with Boc-betahistine. The fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate (R_f = 0.43) to afford **9a** as a colorless oil (37 mg, 0.12 mmol, 60% yield).

Note: Slow rotation about the R_2N-$CO_2{}^tBu$ bond results in the appearance of broad and/or diastereomeric peaks in the ^1H and ^{13}C NMR spectra corresponding to the atoms to the left of the pyridine ring.

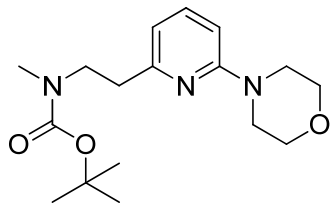
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.43 (t, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 34.9 Hz, 1H), 6.52 (d, *J* = 6.6 Hz, 1H), 4.25 (t, *J* = 6.5 Hz, 2H), 3.54 (s, 2H), 2.80 (m, 5H), 1.73 (p, *J* = 6.8 Hz, 2H), 1.50 – 1.34 (m, 11H), 0.95 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 163.64, 157.10, 155.59, 138.69, 115.55, 107.93, 79.04, 65.47, 49.08, 36.46, 34.28, 31.18, 28.34, 19.27, 13.85.

Calculated exact mass: 308.21

EI Mass Spectrum: 308.2 (M^+, 10% relative intensity), 109.0 ($[M-199]^+$, base peak)

Synthesis of tert-butyl methyl(2-(6-morpholinopyridin-2-yl)ethyl)carbamate (9b)



The general procedure for tandem C-H fluorination/S_NAr was performed with Boc-betahistine. The fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate to afford **9b** as a colorless oil (30 mg, 0.093 mmol, 47% yield).

Note: Slow rotation about the R_2N-$CO_2{}^tBu$ bond results in the appearance of broad and/or diastereomeric peaks in the ^1H and ^{13}C NMR spectra corresponding to the atoms to the left of the pyridine ring.

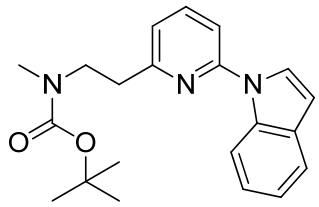
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.39 (t, *J* = 7.5 Hz, 1H), 6.59 – 6.41 (m, 2H), 3.84 – 3.77 (m, 4H), 3.51 (m, 6H), 2.81 (s, 5H), 1.40 (9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 159.16, 157.63, 155.62, 137.81, 113.10, 104.19, 79.02, 66.77, 49.13, 45.59, 36.77, 34.35, 28.38.

Calculated exact mass: 321.21

EI Mass Spectrum: 321.2 (M^+, 9% relative intensity), 178.1 ($[M-143]^+$, base peak)

Synthesis of tert-butyl (2-(6-(1H-indol-1-yl)pyridin-2-yl)ethyl)(methyl)carbamate (9c)



The general procedure for tandem C-H fluorination/S_NAr was performed with Boc-betahistine. The fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate (R_f = 0.24) to afford **9c** as a colorless oil (36 mg, 0.10 mmol, 51% yield).

Note: Slow rotation about the R_2N-$CO_2{}^tBu$ bond results in the appearance of broad and/or diastereomeric peaks in the ^1H and ^{13}C NMR spectra corresponding to the atoms to the left of the pyridine ring.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.25 (s, 1H), 7.76 – 7.69 (m, 2H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 6.2 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 48.4 Hz, 1H), 6.71 (s, 1H), 3.68 (br, 2H), 3.07 (br, 2H), 2.87 (d, *J* = br, 3H), 1.41 (br, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 159.13, 155.62, 152.14, 138.68, 135.05, 130.43, 125.99, 122.95, 121.14, 121.00, 119.50, 113.20, 111.89, 105.33, 79.29, 49.15, 36.73, 34.44, 28.39.

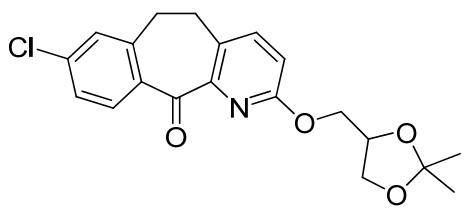
Chemical formula: $C_{21}H_{25}N_3O_2$

Calculated exact mass: 351.1947

Observed formula by ESIMS: $C_{21}H_{28}N_3O_2$

Observed exact mass: 354.1812 (calculated exact mass + $^1H_3$)

Synthesis of 8-chloro-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11(6H)-one (10a)



The general procedure for tandem C-H fluorination/S_NAr was performed with 8-chloro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11(6H)-one. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate (R_f = 0.27) to afford **10a** as a colorless oil (35 mg, 0.94 mmol, 47% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.97 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.22 (s, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 4.50 (td, *J* = 12.1, 9.9, 4.7 Hz, 2H), 4.40 (dd, *J* = 10.4, 6.0 Hz, 1H), 4.13 (t, *J* = 7.3 Hz, 1H), 3.84 (t, *J* = 7.3 Hz, 1H), 3.17 – 3.13 (m, 2H), 3.09 – 3.05 (m, 2H), 1.45 (s, 3H), 1.39 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 192.65, 161.93, 150.35, 143.10, 140.77, 138.58, 135.98, 132.61, 130.69, 129.39, 127.08, 114.87, 109.72, 74.21, 66.77, 66.44, 34.53, 31.54, 26.69, 25.48.

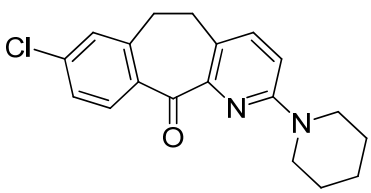
Chemical formula: $C_{20}H_{20}ClNO_4$

Calculated exact mass: 373.1081

Observed formula by ESIMS: $C_{20}H_{20}ClNO_4Na$

Observed exact mass: 396.0972 (calculated exact mass + ^{23}Na)

Synthesis of 8-chloro-2-(piperidin-1-yl)-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11(6H)-one (10b)



The general procedure for tandem C-H fluorination/S_NAr was performed with 8-chloro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11(6H)-one. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate (R_f = 0.38) to afford **10b** as a yellow oil (20 mg, 0.061 mmol, 31% yield).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.95 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.28 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.20 (d, *J* = 1.9 Hz, 1H), 6.82 (br, 1H), 3.57 (m, 4H), 3.15 – 3.09 (m, 2H), 3.02 – 2.98 (m, 2H), 1.64 (br, 6H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 193.81, 157.94, 143.26, 139.43 (two overlapping peaks), 138.16, 136.48, 132.56, 129.27, 126.87, 125.76, 110.69, 46.23, 34.80, 31.42, 25.51, 24.52.

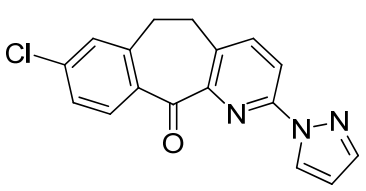
Chemical formula: $C_{19}H_{19}ClN_2O$

Calculated exact mass: 326.1186

Observed formula by ESIMS: $C_{19}H_{20}ClN_2O$

Observed exact mass: 327.1258 (calculated exact mass + ^{1}H)

Synthesis of 8-chloro-2-(1H-pyrazol-1-yl)-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11(6H)-one (10c)



The general procedure for tandem C-H fluorination/S_NAr was performed with 8-chloro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11(6H)-one. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 1:1 hexanes : ethyl acetate (R_f = 0.28) to afford **10c** as a yellow oil (25 mg, 0.081 mmol, 40% yield).

Note: The product was contaminated with ~8% of an inseparable impurity

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.68 (d, *J* = 2.4 Hz, 1H), 8.07 (dd, *J* = 15.8, 8.4 Hz, 2H), 7.79 – 7.73 (m, 2H), 7.36 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.28 (d, *J* = 2.8 Hz, 1H), 6.49 – 6.47 (m, 1H), 3.27 – 3.23 (m, 2H), 3.23 – 3.19 (m, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 192.41, 152.19, 150.44, 143.15, 142.20, 140.39, 139.01, 135.49, 134.23, 132.76, 129.70, 127.52, 127.26, 115.30, 107.91, 34.49, 31.70.

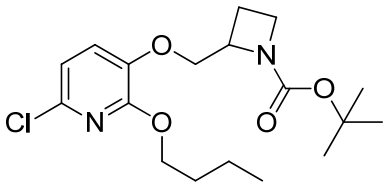
Chemical formula: $C_{17}H_{12}ClN_3O$

Calculated exact mass: 309.0669

Observed formula by ESIMS: $C_{17}H_{12}ClN_3ONa$

Observed exact mass: 332.0560 (calculated exact mass + ^{23}Na)

Synthesis of N-Boc-2-butoxytebanicline (11a)



The general procedure for tandem C-H fluorination/S_NAr was performed with Boc-tebanicline. The fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate (R_f = 0.34) to afford **11a** as a colorless oil (39 mg, 0.11 mmol, 53% yield).

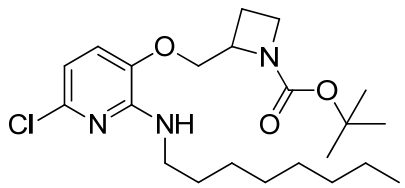
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.08 (d, *J* = 7.7 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 4.46 (s, 1H), 4.32 (two overlapping peaks, 3H), 4.07 (d, *J* = 10.2 Hz, 1H), 3.91 – 3.80 (m, 2H), 2.32 (m, 2H), 1.77 (p, *J* = 6.8 Hz, 2H), 1.47 (h, *J* = 7.4 Hz, 2H), 1.38 (s, 9H), 0.96 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 155.99, 154.43, 142.42, 138.27, 123.14, 115.49, 79.51, 69.91, 66.58, 60.31, 47.34, 30.88, 28.35, 19.22, 19.03, 13.81.

Calculated exact mass: 370.17

EI Mass Spectrum: 370.2 (M^+, 3% relative intensity), 70.1 (base peak)

Synthesis of N-Boc-2-octylaminotebanicline (11b)



The general procedure for tandem C-H fluorination/S_NAr was performed with Boc-tebanicline. The fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate (R_f = 0.49) to afford **11b** as a light yellow oil (48 mg, 0.11 mmol, 56% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.75 (d, *J* = 7.9 Hz, 1H), 6.41 – 6.37 (d, *J* = 7.9 Hz, 1H), 4.53 (s, 1H), 4.24 – 4.17 (m, 1H), 4.06 – 3.99 (s, 1H), 3.93 – 3.82 (m, 2H), 3.39 (s, 2H), 2.35 (dt, *J* = 17.2, 9.2 Hz, 1H), 2.14 (s, 1H), 1.62 (p, *J* = 7.3 Hz, 2H), 1.46 – 1.22 (m, 19H), 0.86 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 156.31, 150.27, 140.22, 140.01, 117.33, 109.04, 79.75, 70.02, 59.97, 47.35, 41.02, 31.80, 29.58, 29.34, 29.20, 28.34, 27.03, 22.61, 18.97, 14.05.

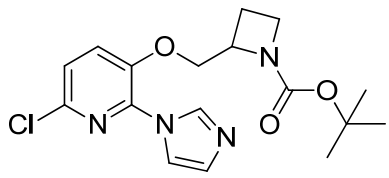
Chemical formula: $C_{22}H_{36}ClN_3O_3$

Calculated exact mass: 425.2445

Observed formula by ESIMS: $C_{22}H_{37}ClN_3O_3$

Observed exact mass: 426.2516 (calculated exact mass + ^{1}H)

Synthesis of N-Boc-2-imidazolyltebanicline (11c)



The general procedure for tandem C-H fluorination/S_NAr was performed with Boc-tebanicline. The fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 99:1 ethyl acetate : triethylamine (R_f = 0.38) to afford **11c** as a light yellow oil (28 mg, 0.077 mmol, 38% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.61 (s, 1H), 7.85 (s, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.19 (s, 1H), 4.55 (s, 1H), 4.47 (s, 1H), 4.22 (dd, *J* = 10.2, 2.4 Hz, 1H), 3.92 – 3.84 (m, 1H), 3.80 (m, 1H), 2.37 – 2.28 (m, 1H), 2.21 (m, 1H), 1.39 (s, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 156.25, 144.89, 140.49, 137.80, 136.65, 127.56, 125.02, 123.05, 118.59, 80.09, 70.30, 59.49, 47.39, 28.30, 18.93.

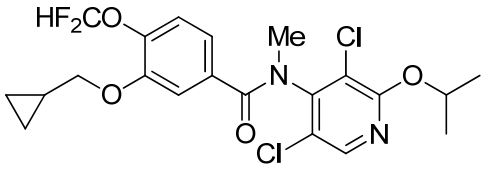
Chemical formula: $C_{17}H_{21}ClN_4O_3$

Calculated exact mass: 364.1302

Observed formula by ESIMS: $C_{17}H_{22}ClN_4O_3$

Observed exact mass: 365.1374 (calculated exact mass + ^{1}H)

Synthesis of N-methyl-2-isopropoxyroflumilast (12a)



The general procedure for tandem C-H fluorination/S_NAr was performed with N-methylroflumilast. The fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate to afford **12a** as a colorless oil (42 mg, 0.088 mmol, 44% yield).

Note: The product exists as two amide diastereomers (~10:1) that do not interconvert on the NMR time scale

Major diastereomer:

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.98 (s, 1H), 7.06 (s, 1H), 6.96 (m, 2H), 6.57 (t, *J* = 75.0 Hz, 1H), 5.23 (hept, *J* = 5.3, 1H), 3.78 – 3.67 (m, 2H), 3.27 (s, 3H), 1.36 – 1.30 (m, 6H), 1.22 – 1.15 (m, 1H), 0.61 (d, *J* = 7.5 Hz, 2H), 0.30 (d, *J* = 4.5 Hz, 2H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.67, 158.96, 149.54, 148.38, 144.01, 142.15 (t, *J* = 3.1 Hz), 133.08, 122.46, 121.39, 120.41, 118.12, 115.82 (t, *J* = 260.2 Hz), 113.80, 73.86, 71.07, 34.76, 21.74, 9.93, 3.17.

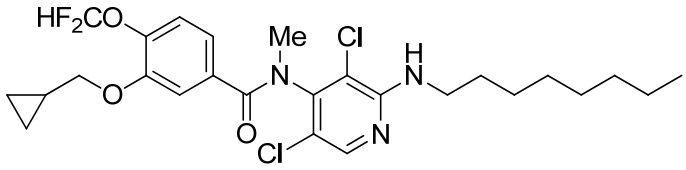
Chemical formula: $C_{21}H_{22}Cl_2F_2N_2O_4$

Calculated exact mass: 474.0925

Observed formula by ESIMS: $C_{21}H_{22}Cl_2F_2N_2O_4Na$

Observed exact mass: 497.0825 (calculated exact mass + ^{23}Na)

Synthesis of N-methyl-2-octylaminoroflumilast (12b)



The general procedure for tandem C-H fluorination/S_NAr was performed with N-methylroflumilast. The fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate to afford **12b** as a colorless oil (51 mg, 0.094 mmol, 47% yield).

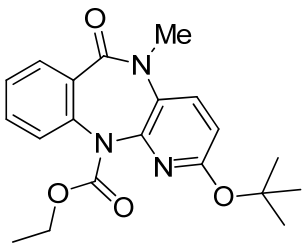
Note: The product exists as two amide diastereomers (~10:1) that do not interconvert on the NMR time scale

Major diastereomer:

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.97 (s, 1H), 7.06 (s, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 6.58 (t, *J* = 75.0 Hz, 1H), 4.97 (t, *J* = 4.4 Hz, 1H), 3.72 (d, *J* = 6.9 Hz, 2H), 3.40 (m, 1H), 3.32 (m, 1H), 3.26 (s, 3H), 1.58 (m, 2H), 1.30 (m, 10H), 0.87 (t, *J* = 6.6 Hz, 3H), 0.60 (d, *J* = 7.6 Hz, 2H), 0.29 (d, *J* = 4.4 Hz, 2H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.65, 154.08, 149.46, 146.33, 145.84, 142.14 (t, *J* = 3.1 Hz), 133.13, 121.35, 120.51, 117.26, 115.86 (t, *J* = 260.0 Hz), 113.86, 113.79, 73.87, 41.90, 34.85, 31.76, 29.36, 29.25, 29.15, 26.93, 22.59, 14.03, 9.94, 3.20.

Synthesis of ethyl 2-(tert-butoxy)-5-methyl-6-oxo-5H-benzo[e]pyrido[3,2-b][1,4]diazepine-11(6H)-carboxylate (13a)

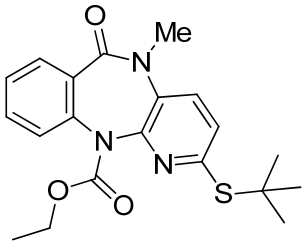


The general procedure for tandem C-H fluorination/S_NAr was performed with ethyl 5-methyl-6-oxo-5H-benzo[e]pyrido[3,2-b][1,4]diazepine-11(6H)-carboxylate. The fluorination step was performed with 4 mL of MeCN at room temperature for 2 h. The product was purified by silica gel chromatography eluting with 1:1 hexanes : ethyl acetate (R_f = 0.48) to afford **13a** as a colorless oil (32 mg, 0.087 mmol, 43% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.83 (d, *J* = 7.7 Hz, 1H), 7.50 – 7.42 (m, 3H), 7.33 – 7.29 (m, 1H), 6.61 (d, *J* = 8.7 Hz, 1H), 4.24 (q, *J* = 6.7 Hz, 2H), 3.51 (s, 3H), 1.57 (s, 9H), 1.23 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 166.91, 160.03, 153.20, 144.88, 142.20, 133.75, 132.01, 131.22, 129.94, 127.48, 127.25, 126.72, 113.14, 80.65, 62.31, 36.78, 28.34, 14.34.

Synthesis of ethyl 2-(tert-butylthio)-5-methyl-6-oxo-5H-benzo[e]pyrido[3,2-b][1,4]diazepine-11(6H)-carboxylate (13b)



The general procedure for tandem C-H fluorination/S_NAr was performed with ethyl 5-methyl-6-oxo-5H-benzo[e]pyrido[3,2-b][1,4]diazepine-11(6H)-carboxylate. The fluorination step was performed with 4 mL of MeCN at room temperature for 2 h. The product was purified by silica gel chromatography eluting with 2:1 hexanes : ethyl acetate (R_f = 0.36) to afford **13b** as a colorless oil (41 mg, 0.11 mmol, 53% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.82 (d, *J* = 7.5 Hz, 1H), 7.49 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.34 – 7.30 (m, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 4.29 – 4.17 (m, 2H), 3.54 (s, 3H), 1.53 (s, 9H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 166.72, 155.13, 153.09, 147.36, 141.60, 132.35, 131.98, 131.25, 131.12, 129.58, 127.48, 126.97, 125.68, 62.47, 48.24, 36.84, 30.59, 14.31.

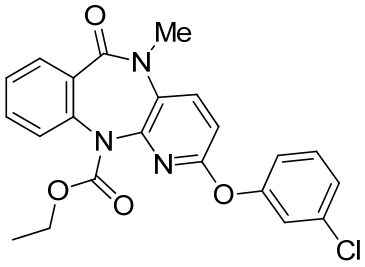
Chemical formula: $C_{20}H_{23}N_3O_3S$

Calculated exact mass: 385.1460

Observed formula by ESIMS: $C_{20}H_{24}N_3O_3S$

Observed exact mass: 386.1536 (calculated exact mass + ^{1}H)

Synthesis of ethyl 2-(3-chlorophenoxy)-5-methyl-6-oxo-5H-benzo[e]pyrido[3,2-b][1,4]diazepine-11(6H)-carboxylate (13c)



The general procedure for tandem C-H fluorination/S_NAr was performed with ethyl 5-methyl-6-oxo-5H-benzo[e]pyrido[3,2-b][1,4]diazepine-11(6H)-carboxylate. The fluorination step was performed with 4 mL of MeCN at room temperature for 2 h. The product was purified by silica gel chromatography eluting with 1:1 hexanes : ethyl acetate (R_f = 0.46) to afford **13c** as a colorless oil (41 mg, 0.10 mmol, 48% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.83 (d, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.47 (s, 2H), 7.35 – 7.28 (m, 2H), 7.17 (m, 2H), 7.04 (d, *J* = 8.1 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 4.27 – 4.18 (m, 2H), 3.56 (s, 3H), 1.23 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 166.75, 158.46, 154.57, 152.94, 146.10, 141.61, 134.97, 134.73, 132.31, 131.30, 130.92, 130.26, 129.51, 127.56, 127.12, 124.80, 120.91, 118.69, 111.81, 62.60, 37.05, 14.33.

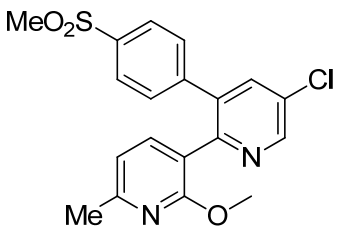
Chemical formula: $C_{22}H_{18}ClN_3O_4$

Calculated exact mass: 423.0986

Observed formula by ESIMS: $C_{22}H_{18}ClN_3O_4Na$

Observed exact mass: 446.0878 (calculated exact mass + ^{23}Na)

Synthesis of 2-methoxyetoricoxib (14a)



The general procedure for tandem C-H fluorination/S_NAr was performed with etoricoxib. The fluorination step was performed with 2 mL of MeCN at 50 ^oC for 2 h. The product was purified by silica gel chromatography eluting with 1:1 hexanes : ethyl acetate (R_f = 0.52) to afford **14a** as a white solid (43 mg, 0.11 mmol, 55% yield).

^1H NMR (600 MHz, Chloroform-*d*) δ 8.67 (d, *J* = 2.3 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 2.3 Hz, 1H), 7.65 (d, *J* = 7.4 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 7.4 Hz, 1H), 3.38 (s, 3H), 3.03 (s, 3H), 2.42 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 158.82, 157.68, 151.99, 147.76, 144.54, 140.15, 139.60, 136.94, 136.63, 130.87, 129.16, 127.19, 118.61, 116.18, 52.46, 44.43, 24.01.

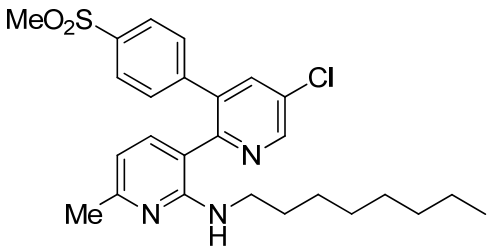
Chemical formula: $C_{19}H_{17}ClN_2O_3S$

Calculated exact mass: 388.0648

Observed formula by ESIMS: $C_{19}H_{18}ClN_2O_3S$

Observed exact mass: 389.0725 (calculated exact mass + ^1H)

Synthesis of 2-octylaminoetoricoxib (14b)



The general procedure for tandem C-H fluorination/S_NAr was performed with etoricoxib. The fluorination step was performed with 2 mL of MeCN at 50 ^oC for 2 h. The product was purified by silica gel chromatography eluting with 2:1 hexanes : ethyl acetate (R_f = 0.46) to afford **14b** as a light yellow oil (50 mg, 0.10 mmol, 51% yield).

^1H NMR (600 MHz, Chloroform-*d*) δ 8.63 (d, *J* = 2.4 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.76 (d, *J* = 2.4 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 6.64 (d, *J* = 7.5 Hz, 1H), 6.18 (br, 1H), 6.10 (d, *J* = 7.6 Hz, 1H), 3.47 – 3.40 (m, 2H), 3.05 (s, 3H), 2.35 (s, 3H), 1.57 (p, *J* = 7.3 Hz, 2H), 1.31 m, 10H), 0.87 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 157.67, 155.85, 154.02, 147.25, 144.10, 139.81, 139.65, 138.52, 136.30, 130.27, 130.03, 127.69, 112.98, 110.65, 44.38, 41.46, 31.78, 29.63, 29.32, 29.22, 27.11, 24.42, 22.61, 14.06.

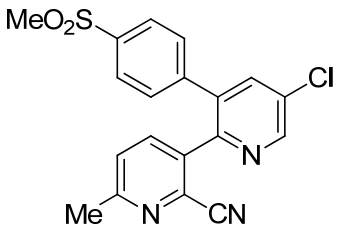
Chemical formula: $C_{26}H_{32}ClN_3O_2S$

Calculated exact mass: 485.1904

Observed formula by ESIMS: $C_{26}H_{33}ClN_3O_2S$

Observed exact mass: 486.1972 (calculated exact mass + ^1H)

Synthesis of 2-cyanoetoricoxib (14c)



The general procedure for tandem C-H fluorination/S_NAr was performed with etoricoxib. The fluorination step was performed with 2 mL of MeCN at 50 ^oC for 2 h. The product was purified by silica gel chromatography eluting with 1:1 hexanes : ethyl acetate to afford **14c** as a light yellow oil (31 mg, 0.081 mmol, 40% yield).

^1H NMR (500 MHz, Chloroform-*d*) δ 8.77 (d, *J* = 2.3 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.84 (d, *J* = 2.3 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 1H), 3.07 (s, 3H), 2.61 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 160.39, 149.90, 148.61, 142.24, 140.54, 138.52, 137.86, 136.61, 136.59, 132.80, 132.49, 130.57, 127.83, 126.25, 116.27, 44.39, 24.20.

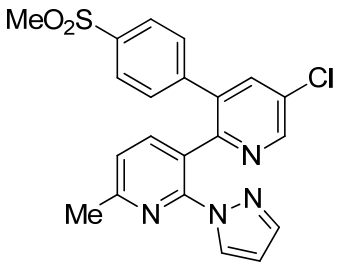
Chemical formula: $C_{19}H_{14}ClN_3O_2S$

Calculated exact mass: 383.0495

Observed formula by ESIMS: $C_{19}H_{14}ClN_3O_2SNa$

Observed exact mass: 406.0391 (calculated exact mass + ^{23}Na)

Synthesis of 2-pyrazolyletoricoxib (14d)



The general procedure for tandem C-H fluorination/S_NAr was performed with etoricoxib. The fluorination step was performed with 2 mL of MeCN at 50 ^oC for 2 h. The product was purified by silica gel chromatography eluting with 1:2 hexanes : ethyl acetate to afford **14d** as a white solid (41 mg, 0.10 mmol, 48% yield).

^1H NMR (500 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 2.3 Hz, 1H), 7.73 – 7.66 (m, 4H), 7.58 (d, *J* = 2.3 Hz, 1H), 7.35 (s, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.20 – 6.17 (m, 1H), 3.01 (s, 3H), 2.56 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 158.22, 153.66, 148.01, 147.67, 142.70, 141.71, 141.30, 139.58, 136.60, 135.78, 130.85, 129.52, 128.14, 127.14, 122.97, 121.51, 106.96, 44.40, 24.07.

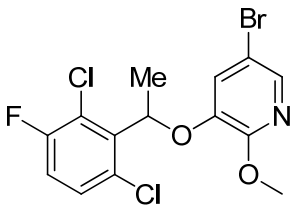
Chemical formula: $C_{21}H_{17}ClN_4O_2S$

Calculated exact mass: 424.0761

Observed formula by ESIMS: $C_{21}H_{18}ClN_4O_2S$

Observed exact mass: 425.0836 (calculated exact mass + ^1H)

Synthesis of 5-bromo-3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)-2-methoxypyridine (15a)



The general procedure for tandem C-H fluorination/S_NAr was performed with 3-bromo-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridine. The fluorination step was performed with 8 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 20:1 hexanes : ethyl acetate to afford **15a** as a white solid (55 mg, 0.14 mmol, 70% yield).

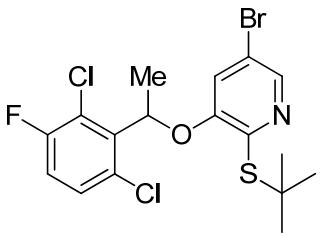
The product was obtained as a 7:1 mixture of regioisomeric products

Major isomer:

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.74 (s, 1H), 7.28 (m, 1H), 7.05 (t, *J* = 8.4 Hz, 1H), 6.97 (s, 1H), 5.99 (q, *J* = 6.6 Hz, 1H), 3.97 (s, 3H), 1.83 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.46 (d, *J* = 249.0 Hz), 154.38, 141.90, 138.43, 136.55, 131.23 (d, *J* = 2.2 Hz), 128.97 (d, *J* = 3.7 Hz), 124.20, 122.07 (d, *J* = 19.3 Hz), 116.65 (d, *J* = 23.2 Hz), 110.55, 73.94, 53.95, 18.96.

Synthesis of 5-bromo-2-(tert-butylthio)-3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridine (15b)



The general procedure for tandem C-H fluorination/S_NAr was performed with 3-bromo-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridine. The fluorination step was performed with 8 mL of MeCN at room temperature for 1 h. The S_NAr step was performed with 3 equivalents of sodium thiolate salt. The product was purified by silica gel chromatography eluting with 20:1 hexanes : ethyl acetate to afford **15b** as a colorless oil (76 mg, 0.17 mmol, 84% yield).

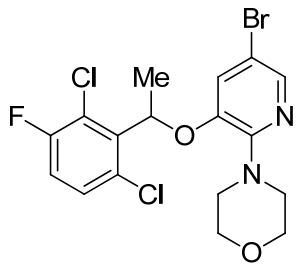
The product was obtained as a 7:1 mixture of regioisomeric products

Major isomer:

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.07 (d, *J* = 1.8 Hz, 1H), 7.29 (dd, *J* = 8.9, 4.8 Hz, 1H), 7.08 – 7.03 (m, 1H), 6.82 (d, *J* = 1.8 Hz, 1H), 5.91 (q, *J* = 6.7 Hz, 1H), 1.83 (d, *J* = 6.7 Hz, 3H), 1.59 (s, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 157.45 (d, *J* = 247.6 Hz), 150.55, 150.17, 141.31, 136.36, 129.72, 128.95 (d, *J* = 3.0 Hz), 122.16 (d, *J* = 18.1 Hz), 120.48, 116.67 (d, *J* = 23.3 Hz), 115.06, 73.79, 47.06, 30.50, 18.93.

Synthesis of 4-(5-bromo-3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-2-yl)morpholine (15c)



The general procedure for tandem C-H fluorination/S_NAr was performed with 3-bromo-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridine. The fluorination step was performed with 8 mL of MeCN at room temperature for 1 h. The S_NAr step was performed with 3 equivalents of sodium thiolate salt. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate (R_f = 0.38) to afford **15c** as a light yellow oil (56 mg, 0.12 mmol, 62% yield).

The product was obtained as a 7:1 mixture of regioisomeric products

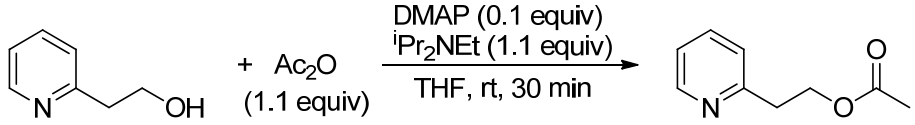
Major isomer:

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.86 (d, *J* = 1.9 Hz, 1H), 7.31 (dd, *J* = 8.9, 4.8 Hz, 1H), 7.08 (t, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 1.9 Hz, 1H), 5.98 (q, *J* = 6.7 Hz, 1H), 3.81 (m, 4H), 3.47 (m, 4H), 1.80 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 157.47 (d, *J* = 249.1 Hz), 150.88, 144.81, 139.82, 136.58, 129.96, 128.86 (d, *J* = 3.7 Hz), 124.37, 121.96 (d, *J* = 19.3 Hz), 116.80 (d, *J* = 23.2 Hz), 110.37, 74.20, 66.90, 48.77, 18.89.

Synthesis of 2-methylamino-6-(2-hydroxyethyl)pyridine (16)

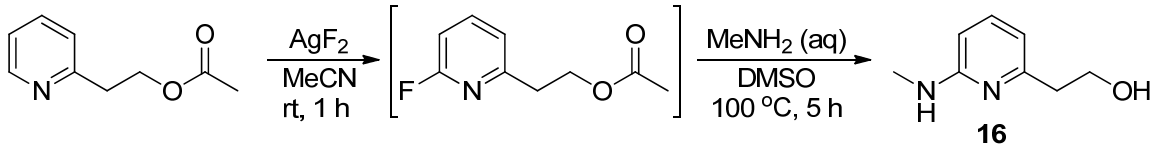
Step 1:



To a 100 mL round bottom flask was added 2-pyridineethanol (560 µL, 5.0 mmol, 1.0 equiv), DMAP (61 mg, 0.50 mmol, 0.10 equiv), $^{i}Pr_2NEt$ (960 µL, 5.5 mmol, 1.1 equiv) and THF (15 mL). Acetic anhydride (520 µL, 5.5 mmol, 1.1 equiv) was added over 1 minute. The resulting pale yellow solution was stirred at room temperature for 30 minutes and the solvent was removed in vacuo. The resulting oil was filtered through ~10 grams of silica with 40 mL of ethyl acetate and the filtrate was concentrated to afford 2-(2-pyridinyl)ethyl acetate as a light yellow oil (822 mg, 4.98 mmol, quantitative yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.55 (d, *J* = 4.6 Hz, 1H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.21 – 7.12 (m, 2H), 4.46 (t, *J* = 6.7 Hz, 2H), 3.12 (t, *J* = 5.9 Hz, 2H), 2.01 (s, 3H).

Step 2:



16

To an oven-dried vial was added 2-(2-pyridinyl)ethyl acetate (83 mg, 0.50 mmol, 1.0 equiv) and MeCN (5.0 mL). While the solution was stirring rapidly, AgF_2 (220 mg, 1.5 mmol, 3.0 equiv) was added at once. The vial was sealed with a Teflon-lined cap and stirred at room temperature for 1 h. The reaction was filtered into a 20 mL vial through a pipette containing ~500 mg of silica wet with Et_2O. The silica was rinsed with 4-5 mL of Et_2O and the filtrate was concentrated in vacuo. The resulting crude material was dissolved in 2 mL of DMSO and 40% aqueous $MeNH_2$ (1 mL, 12 mmol, 24 equiv) was added. The vial was sealed with a Teflon-lined cap and stirred at 100 ^oC for 5 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (10 mL) and brine (10 mL) and extracted with ethyl acetate (3 x 15 mL). The organic layer was washed 1 x 10 mL brine and concentrated. The product was purified by silica gel chromatography eluting with 3% methanol in dichloromethane to afford **16** as a light yellow oil (49 mg, 0.32 mmol, 64% yield).

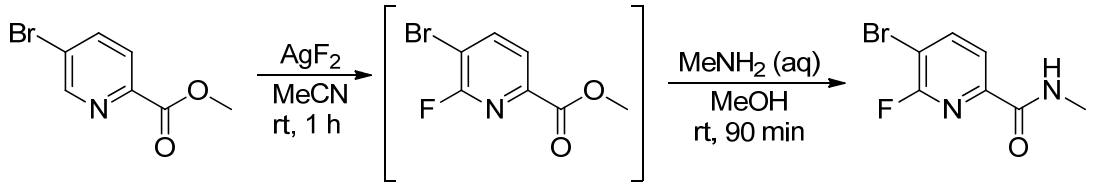
NMR spectra were in accord with previously reported spectral data.[11]

^1H NMR (600 MHz, Chloroform-*d*) δ 7.35 (t, *J* = 7.7 Hz, 1H), 6.40 (d, *J* = 7.2 Hz, 1H), 6.26 (d, *J* = 8.3 Hz, 1H), 4.98 (br, 1H), 4.78 (br, 1H), 3.95 (t, *J* = 5.2 Hz, 2H), 2.88 (s, 3H), 2.83 (t, *J* = 5.2 Hz, 2H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 158.87, 158.52, 138.22, 111.58, 104.26, 62.00, 38.07, 28.90.

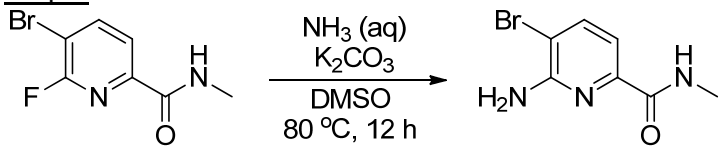
Synthesis of PF-1247324

Step 1:



To an oven-dried vial was added methyl 5-bromopicolinate (108 mg, 0.50 mmol, 1.0 equiv) and MeCN (5.0 mL). While the solution was stirring rapidly, AgF_2 (220 mg, 1.5 mmol, 3.0 equiv) was added at once. The vial was sealed with a Teflon-lined cap and stirred at room temperature for 1 h. The reaction was filtered into a 20 mL vial through a pipette containing ~500 mg of silica wet with Et_2O. The silica was rinsed with 4-5 mL of Et_2O and the filtrate was concentrated in vacuo. The resulting crude material was dissolved in 5 mL of MeOH and 40% aqueous $MeNH_2$ (220 µL, 2.5 mmol, 5.0 equiv) was added. The vial was sealed with a Teflon-lined cap and stirred at room temperature for 90 min. The reaction mixture was diluted with brine (15 mL) and extracted with ethyl acetate (2 x 15 mL). The organic layer was dried with $MgSO_4$ and concentrated to afford crude 5-bromo-6-fluoro-N-methylpicolinamide as a white solid (114 mg crude mass, about 0.49 mmol). The crude material was used directly in step 2.

Step 2:

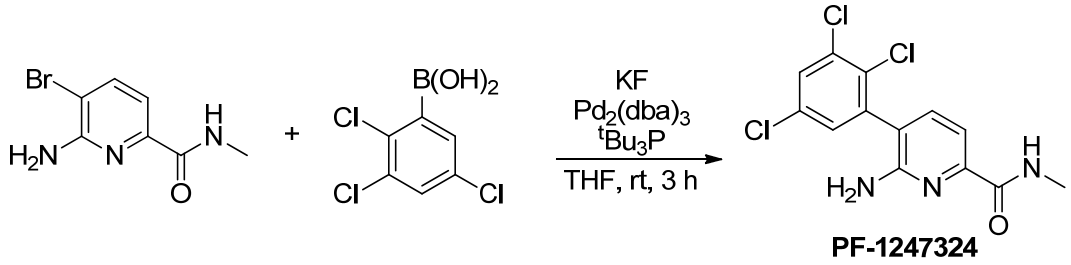


The crude material from step 1 was dissolved in 2 mL of DMSO in a 20 mL vial. K_2CO_3 (140 mg, 1.0 mmol, 2.0 equiv) was added, followed by aqueous ammonium hydroxide (1 mL, 15 mmol, 30 equiv). The vial was sealed with a Teflon-lined cap and stirred at 80 °C for 12 h. The reaction mixture was diluted with brine (15 mL) and extracted with ethyl acetate (2 x 15 mL). The product was purified by silica gel chromatography eluting with 1:5 hexanes : ethyl acetate to afford 6-amino-5-bromo-N-methylpicolinamide as a white solid (71 mg, 0.31 mmol, 62% yield from methyl 5-bromopicolinate).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.73 (br, 2H), 7.39 (d, *J* = 7.8 Hz, 1H), 5.03 (br, 2H), 2.93 (d, *J* = 4.6 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 164.49, 153.93, 147.18, 141.27, 113.58, 107.55, 25.95.

Step 3:



PF-1247324

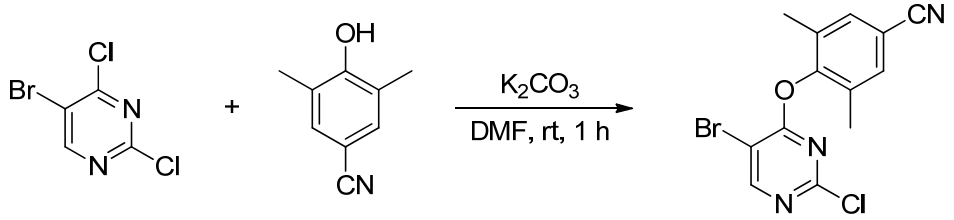
To an oven-dried round bottom flask was added 6-amino-5-bromo-N-methylpicolinamide (46 mg, 0.20 mmol), KF (38 mg, 0.66 mmol, 3.3 equiv), THF (600 µL) and H_2O (4 µL). A solution of $Pd_2(dba)_3$ (5.5 mg, 6.0 mol % Pd) and $^tBu_3P$ (2.4 mg, 6.0 mol %) in 200 µL THF was added, and the resulting mixture was stirred at room temperature for 2 minutes. A solution of 2,3,5-trichlorobenzeneboronic acid (50 mg, 0.22 mmol, 1.1 equiv) in 200 µL of THF was added and the reaction was stirred at room temperature for 3 h. The solvent was removed in vacuo and the residue was purified by silica gel chromatography eluting with ethyl acetate to afford PF-1247324 as a white solid (55 mg, 0.17 mmol, 83% yield).

NMR spectra were in accord with previously reported spectral data.[12]

^{1}H NMR (600 MHz, Methanol-d_4) δ 7.68 (d, J = 2.0 Hz, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.34 (d, J = 2.0 Hz, 1H), 2.95 (s, 3H).^{13}C NMR (151 MHz, Methanol-d_4) δ 167.14, 156.69, 148.96, 140.61, 140.53, 135.63, 134.39, 132.14, 131.29, 131.02, 122.51, 111.85, 26.37..

Synthesis of Intelence (etravirine)

Step 1:

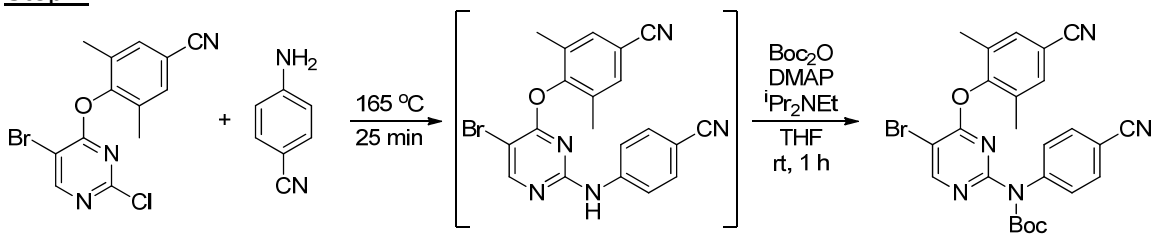


To a 100 mL round bottom flask was added 2,4-dichloro-5-bromopyrimidine (1.14 g, 5.00 mmol, 1.00 equiv), K_2CO_3 (760 mg, 5.5 mmol, 1.1 equiv) and DMF (15 mL). While the suspension was stirring rapidly, a solution of 2,6-dimethyl-4-cyanophenol in DMF (5 mL) was added over 5 minutes. The resulting mixture was stirred at room temperature for 1 h, during which the product began to precipitate. After 1 h, 50 mL of H_2O was added and stirring was continued for 5 minutes. The white solid was collected by suction filtration, washed with H_2O (2 x 20 mL) and Et_2O (1 x 20 mL) and dried under vacuum to afford 4-((5-bromo-2-chloropyrimidin-4-yl)oxy)-3,5-dimethylbenzonitrile as a white solid (1.54 g, 4.54 mmol, 91% yield).

^{1}H NMR (600 MHz, DMSO-d_6) δ 8.98 (s, 1H), 7.76 (s, 2H), 2.10 (s, 6H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 164.61, 161.35, 158.90, 152.51, 132.74, 132.15, 118.31, 110.50, 104.51, 16.29..

Step 2:

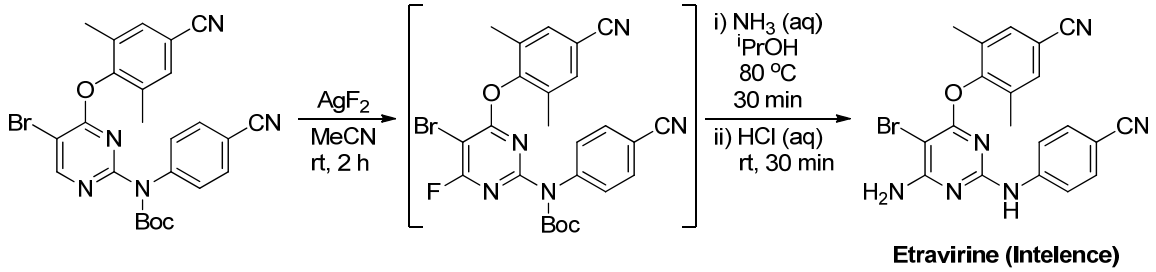


To a 20 mL vial was added 4-((5-bromo-2-chloropyrimidin-4-yl)oxy)-3,5-dimethylbenzonitrile (339 mg, 1.00 mmol, 1.00 equiv) and 4-aminobenzonitrile (154 mg, 1.30 mmol, 1.3 equiv) and the solids were mixed evenly. The vial was sealed with a Teflon-lined cap and heated at 165 °C for 15 minutes. The solids were mixed again and heated for an additional 10 minutes at 165 °C. The resulting solid residue was triturated with 1 M HCl (3 mL) and H_2O (3 x 3 mL). THF (5 mL), $^{i}Pr_2NEt$ (350 µL, 2.0 mmol, 2.0 equiv) and DMAP (12 mg, 0.10 mmol, 10 mol %) were added, followed by Boc_2O (510 µL, 2.2 mmol, 2.2 equiv). The solution was stirred at room temperature for 1 h and the solvent was removed in vacuo. The residue was purified by silica gel chromatography eluting with 5:1 hexanes : ethyl acetate to afford tert-butyl (5-bromo-4-(4-cyano-2,6-dimethylphenoxy)pyrimidin-2-yl)(4-cyanophenyl)carbamate as a white solid (460 mg, 0.88 mmol, 88% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.32 (s, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 2.03 (s, 6H), 1.32 (s, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 164.02, 160.87, 158.49, 152.84, 151.47, 144.57, 132.64, 132.37, 132.24, 127.88, 118.16, 118.08, 110.54, 110.02, 100.80, 83.52, 27.76, 16.20..

Step 3:



Etravirine (Intelence)

To an oven-dried vial was added tert-butyl (5-bromo-4-(4-cyano-2,6-dimethylphenoxy)pyrimidin-2-yl)(4-cyanophenyl)carbamate (260 mg, 0.50 mmol, 1.0 equiv) and MeCN (10.0 mL). While the solution was stirring rapidly, AgF_2 (220 mg, 1.5 mmol, 3.0 equiv) was added at once. The vial was sealed with a Teflon-lined cap and stirred at room temperature for 2 h. The reaction was filtered into a 20 mL vial through a pipette containing ~500 mg of silica wet with Et_2O. The silica was rinsed with 4-5 mL of Et_2O and the filtrate was concentrated in vacuo. The resulting crude material was dissolved in 2.5 mL of ^{i}PrOH and ammonium hydroxide (100 µL, 1.5 mmol, 3.0 equiv) was added and the mixture was stirred at 80 ^{o}C for 30 minutes. The reaction was cooled to room temperature and concentrated HCl (1.3 mL, 16 mmol, 32 equiv) was added over 2 minutes. The mixture was stirred at room temperature for 30 minutes, diluted with 20 mL of H_2O and basified to pH = 8 with 10% aqueous K_2CO_3. The aqueous mixture was extracted with 2 x 30 mL dichloromethane, dried with $MgSO_4$ and concentrated onto ~2 grams of silica gel. The product was purified by silica gel chromatography eluting with 2:1 hexanes : ethyl acetate (R_f = 0.35) to afford etravirine as a white solid (122 mg, 0.280 mmol, 56% yield).

NMR spectra were in accord with previously reported spectral data.[13]

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.59 (s, 1H), 7.72 (d, J = 3.6 Hz, 2H), 7.54 (s, 2H), 7.47 – 7.33 (m, 2H), 7.11 (br, 2H), 2.12 (s, 6H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 163.77, 162.90, 157.04, 154.47, 145.29, 133.10, 132.89, 132.78, 119.89, 119.03, 118.52, 108.72, 102.49, 74.75, 16.13.

Competition experiments between pyridines and diazines with AgF_2

To an oven-dried vial was added MeCN (1 mL) and 0.10 mmol each (1.0 equiv. each) of two heteroarenes. While the solution was stirring rapidly, AgF_2 (29mg, 0.20 mmol, 2.0 equiv) was added at once. The vial was sealed with a Teflon-lined cap, and stirred at room temperature for 15 minutes (25% ± 2% conversion). The reaction was quenched by the addition of 100 μL of saturated aqueous $NaHCO_3$. $PhCF_3$ (0.033 mmol, 0.10 mmol of ^{19}F, 1.0 equiv of ^{19}F) was added as an internal standard, and the reaction mixture was analyzed by ^{19}F NMR spectroscopy to determine the amounts and relative ratios of products resulting from fluorination of each heteroarene.

References

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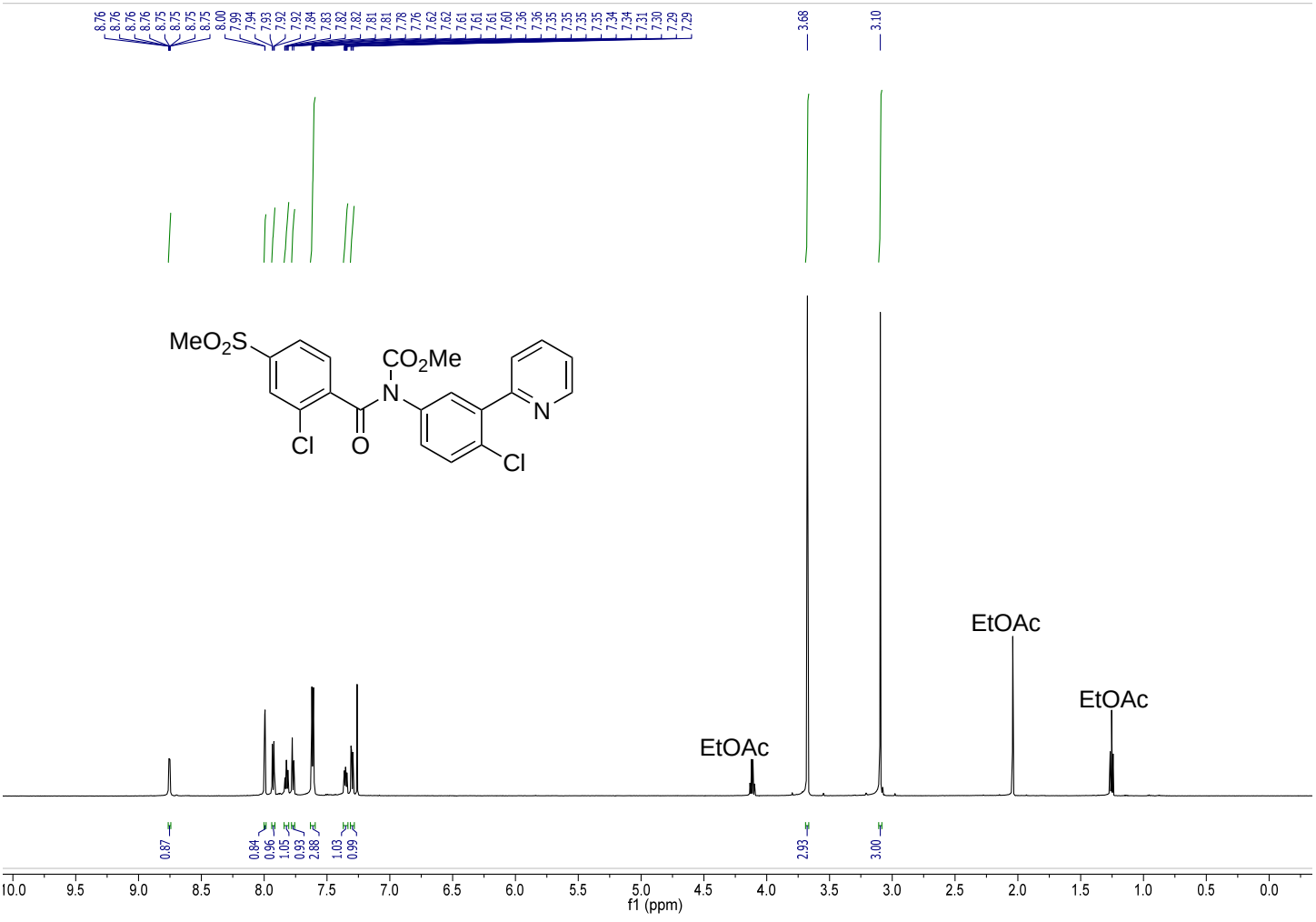
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8.76
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8.75
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7.92
7.84
7.83
7.82
7.82
7.81
7.81
7.78
7.76
7.62
7.62
7.61
7.61
7.61
7.60
7.36
7.36
7.35
7.35
7.35
7.35
7.34
7.34
7.31
7.30
7.29
7.29
3.68
3.10
MeO2S
CO2Me
N
N
Cl
O
Cl
EtOAc
EtOAc
EtOAc
0.87
0.84
0.96
1.05
0.93
2.88
1.03
0.99
2.93
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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3.0
2.5
2.0
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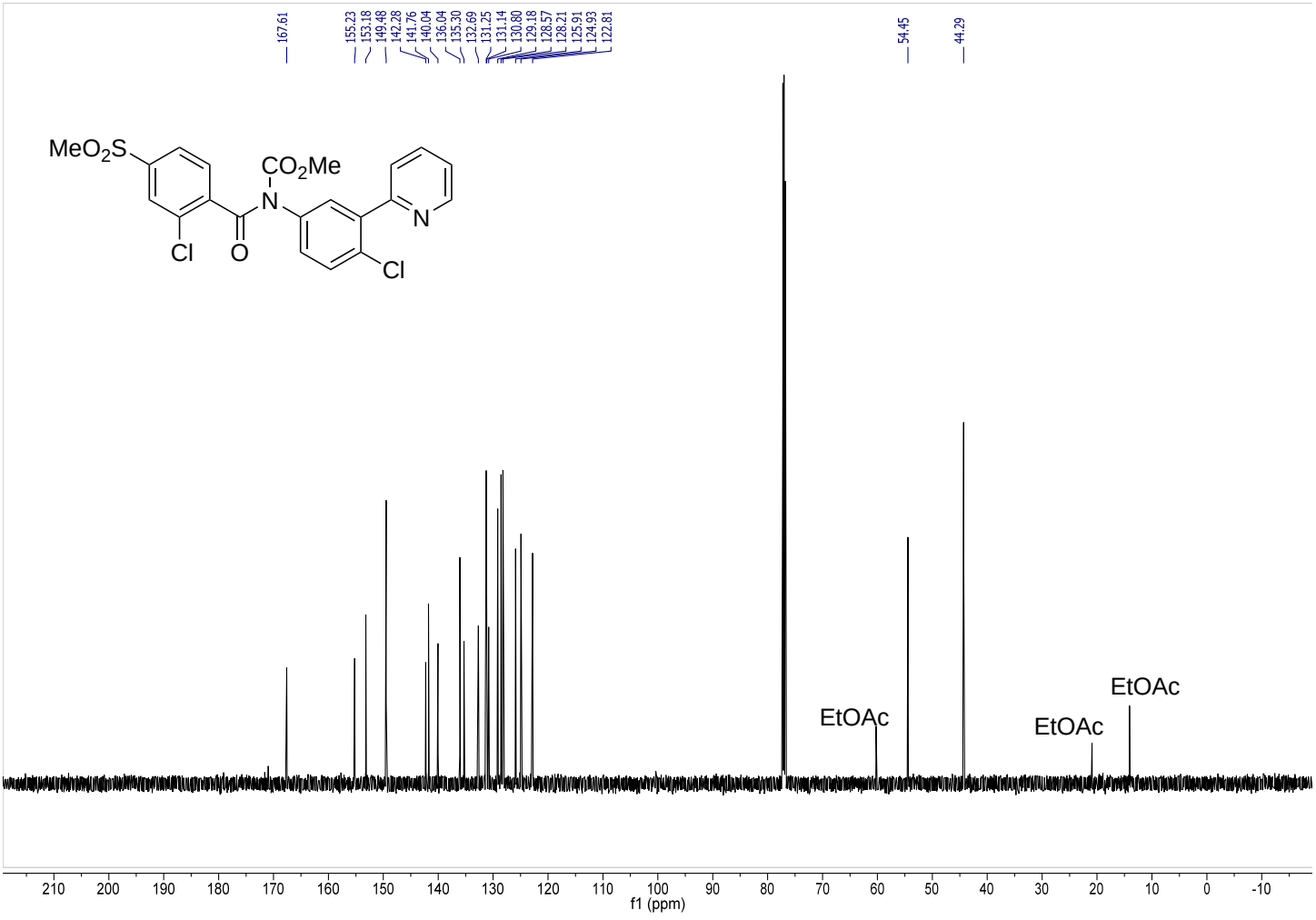
f1 (ppm)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136.04
135.30
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131.14
130.80
129.18
128.57
128.21
125.91
124.93
122.81
54.45
44.29
MeO2S
CO2Me
N
Cl
O
N
Cl
EtOAc
EtOAc
EtOAc
210
200
190
180
170
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100
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80
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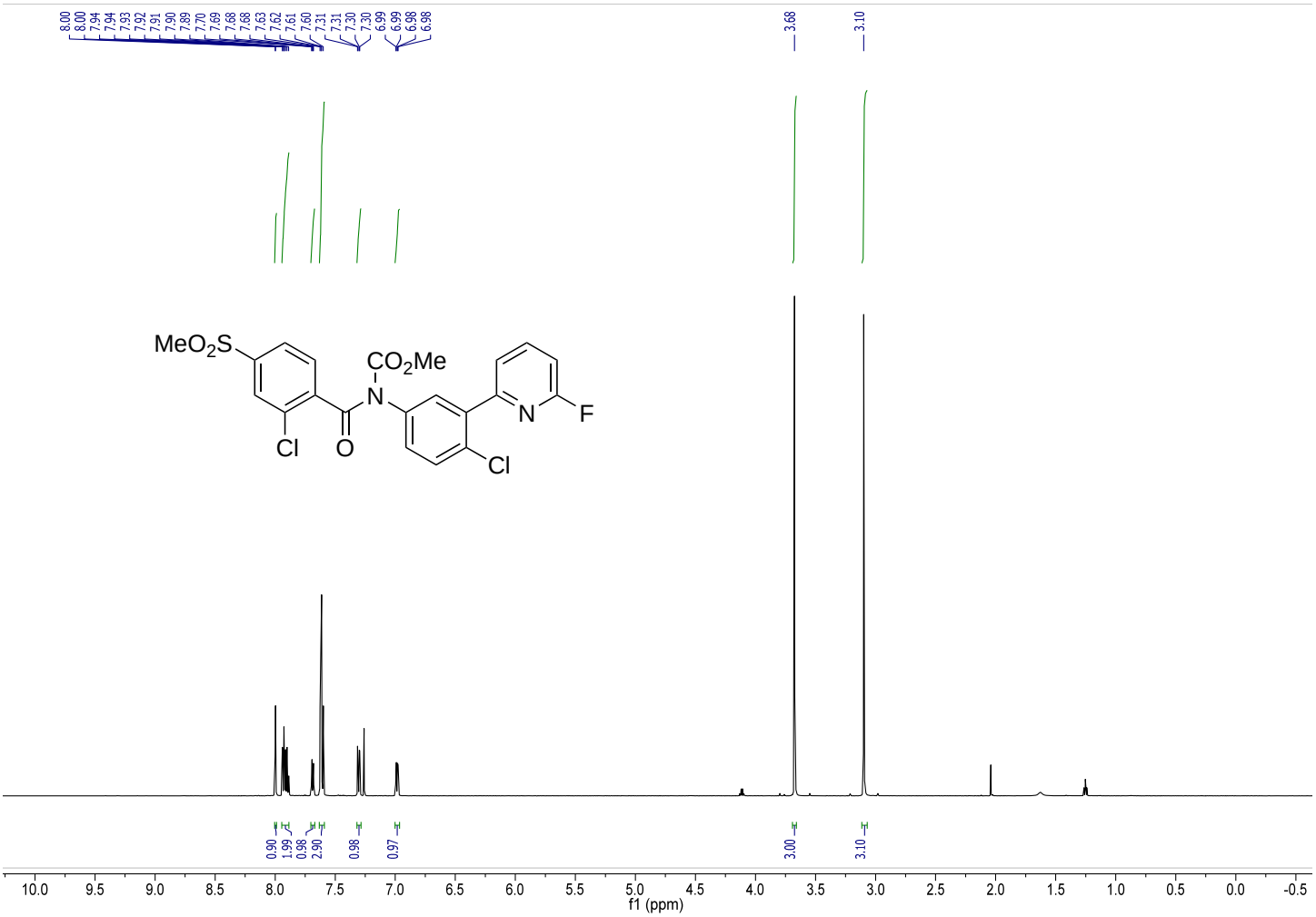
f1 (ppm)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7.68
7.68
7.63
7.62
7.61
7.60
7.31
7.31
7.30
7.30
6.99
6.99
6.98
6.98
3.68
3.10
MeO2S
CO2Me
N
O
Cl
N
F
Cl
0.90
1.99
0.98
2.90
0.98
0.97
3.00
3.10
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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2.5
2.0
1.5
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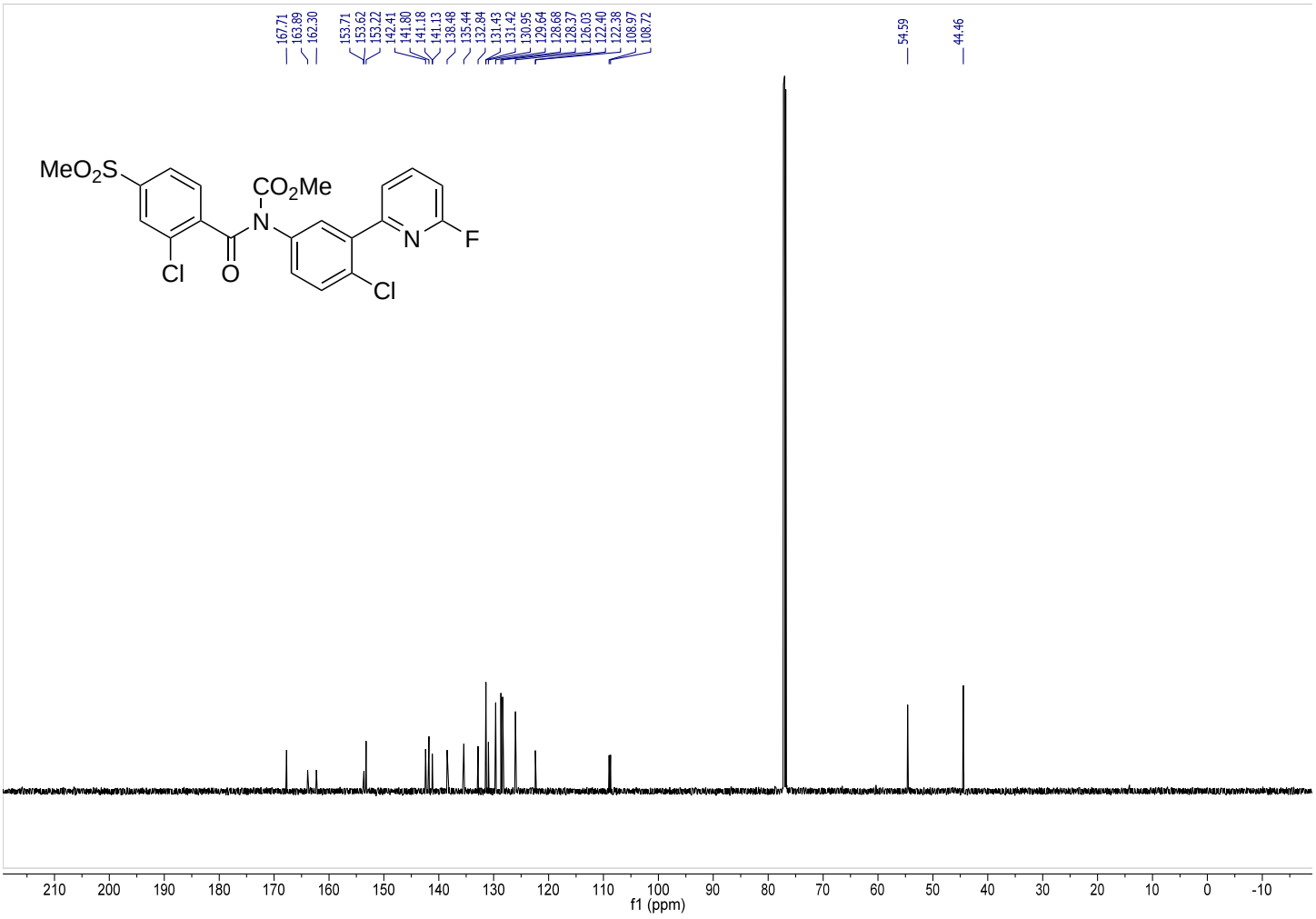
f1 (ppm)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131.42
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129.64
128.68
128.37
126.03
122.40
122.38
108.97
108.72
54.59
44.46
MeO2S
CO2Me
N
O
Cl
Cl
N
F
210
200
190
180
170
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100
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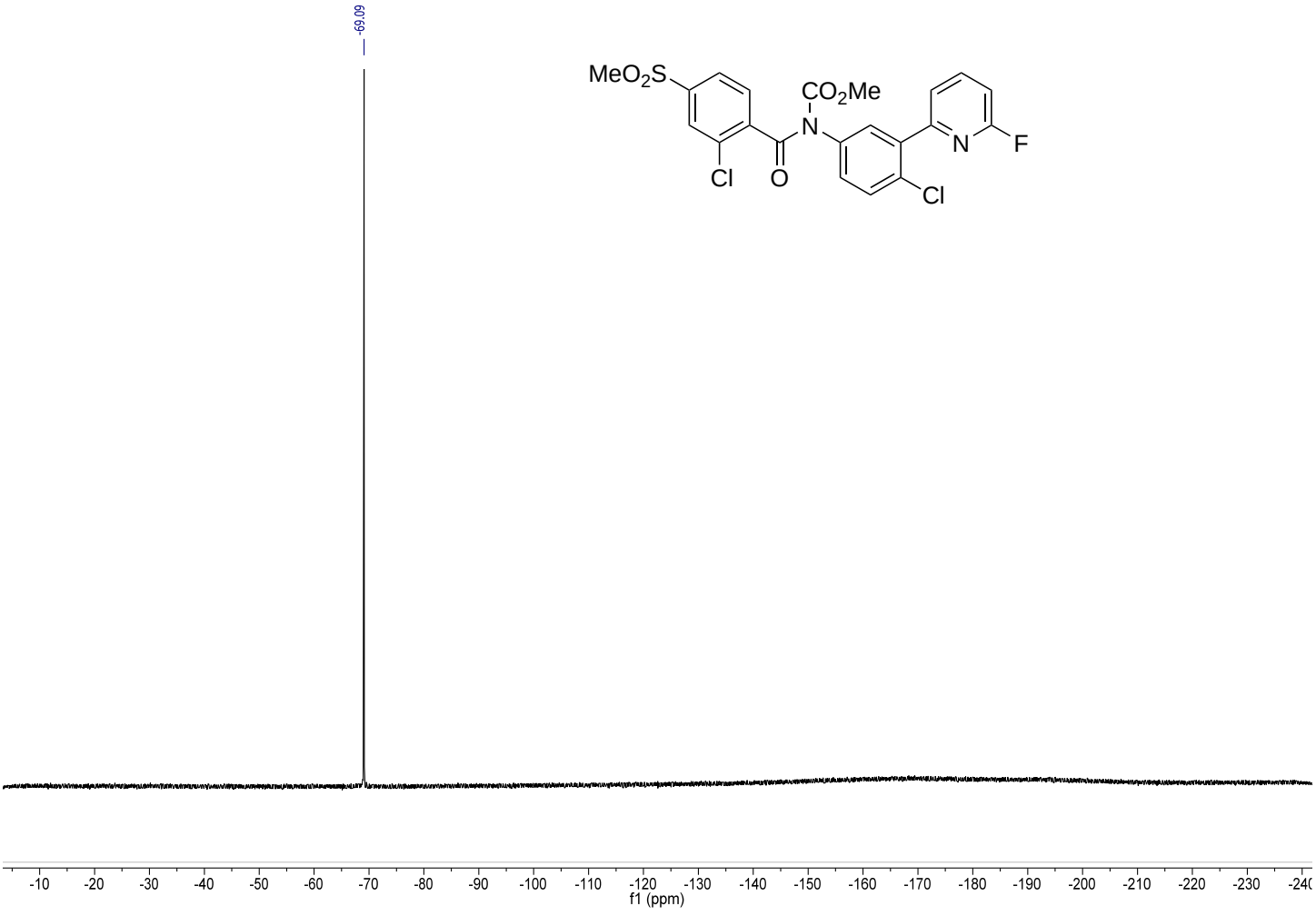
-10
f1 (ppm)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CO2Me
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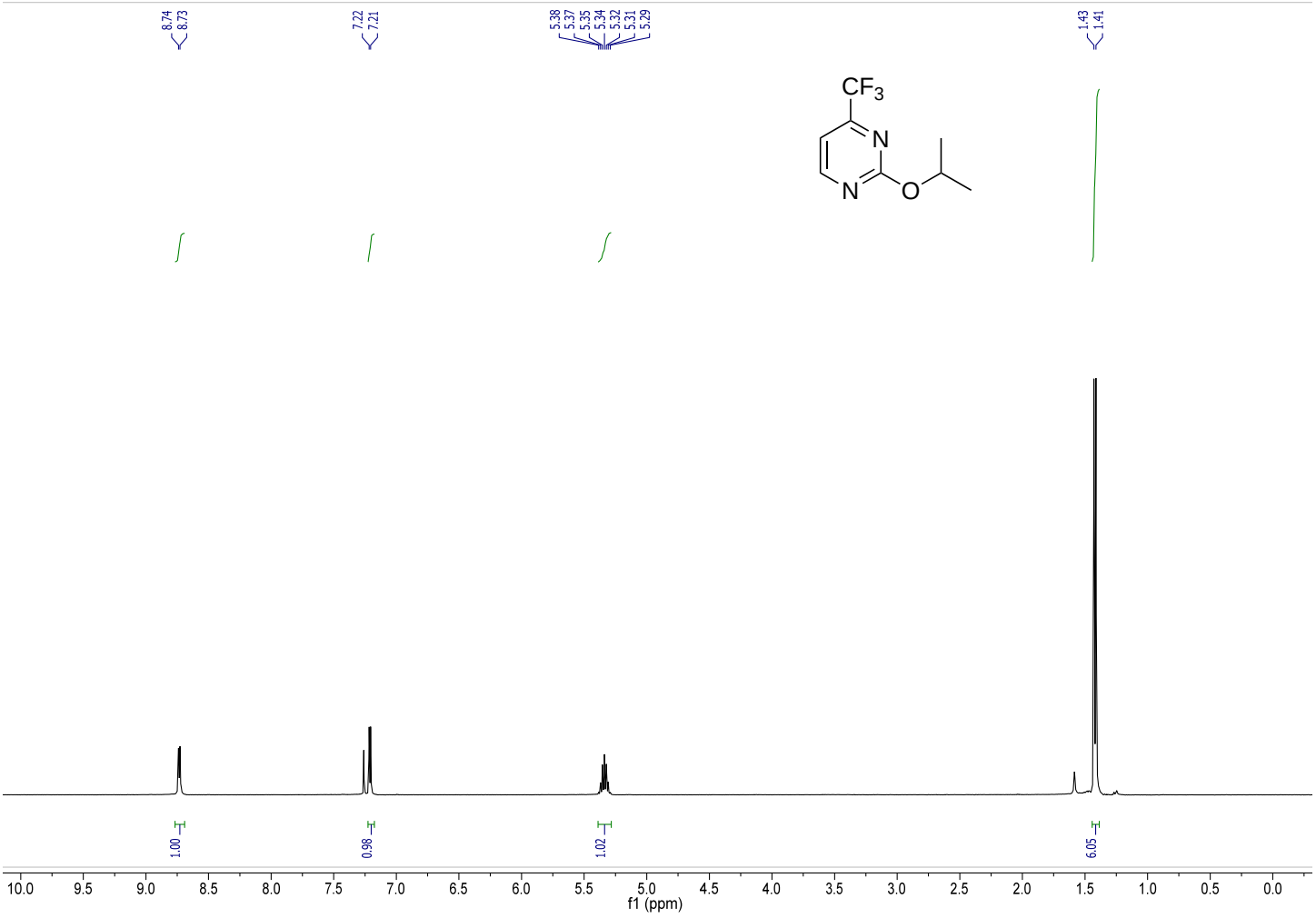
F
Cl
O
Cl
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)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5.34
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5.31
5.29
1.43
1.41
CF3
N
N
O
1.00
0.98
1.02
6.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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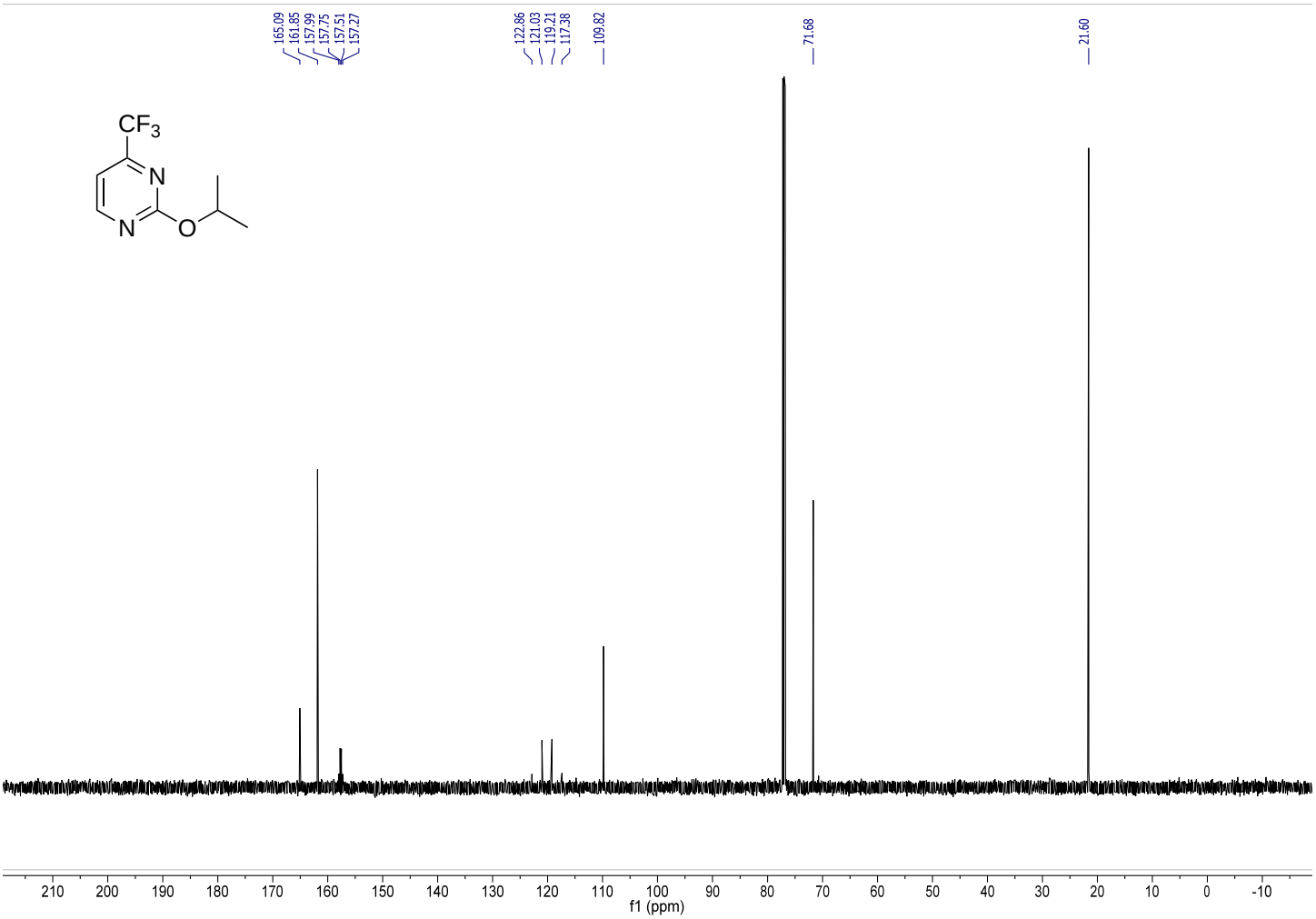
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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121.03
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117.38
109.82
71.68
21.60
CF3
N
N
O
210
200
190
180
170
160
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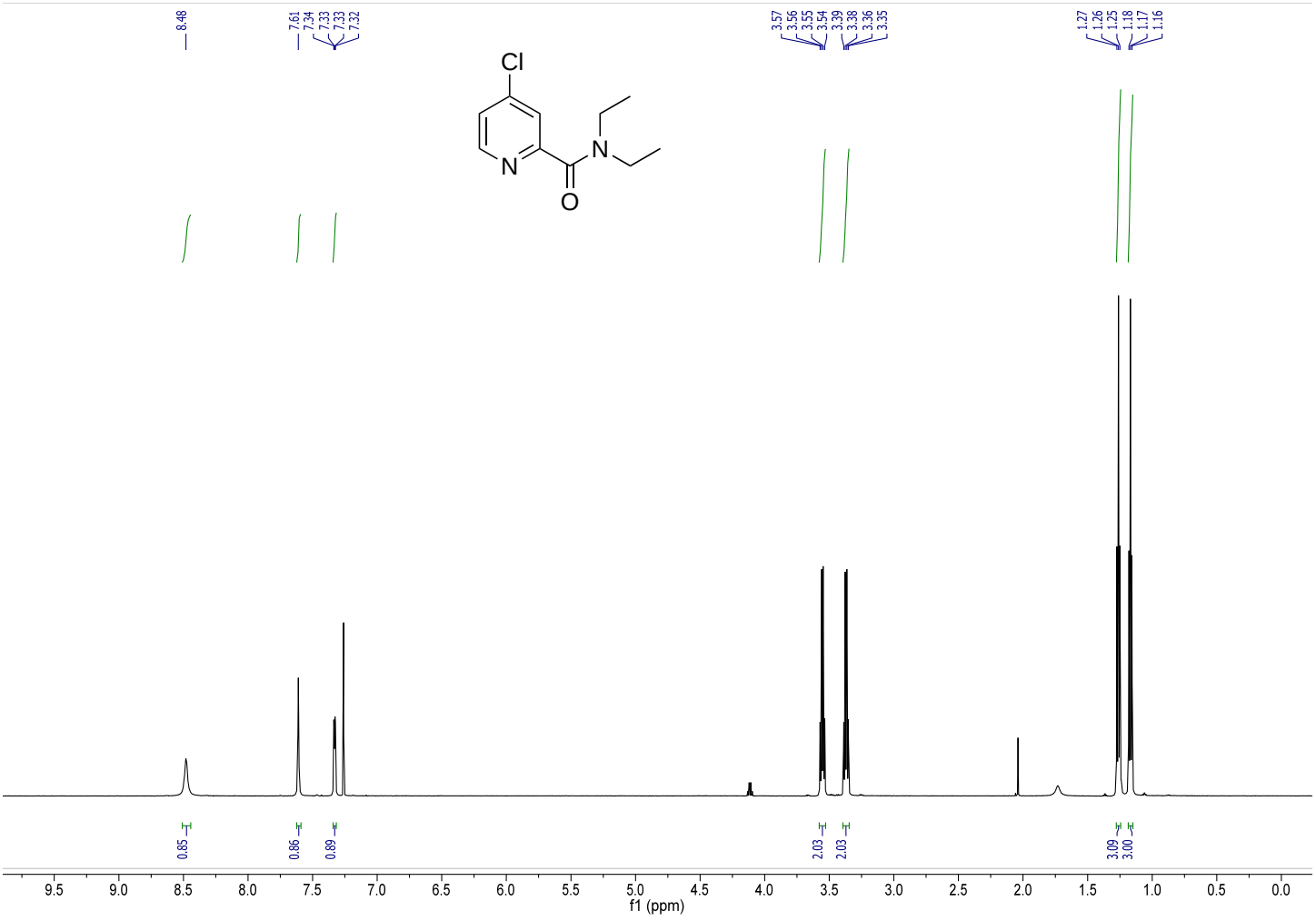
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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3.56
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3.54
3.39
3.38
3.36
3.35
1.27
1.26
1.25
1.18
1.17
1.16
Cl
N
N
O
0.85
0.86
0.89
2.03
2.03
3.09
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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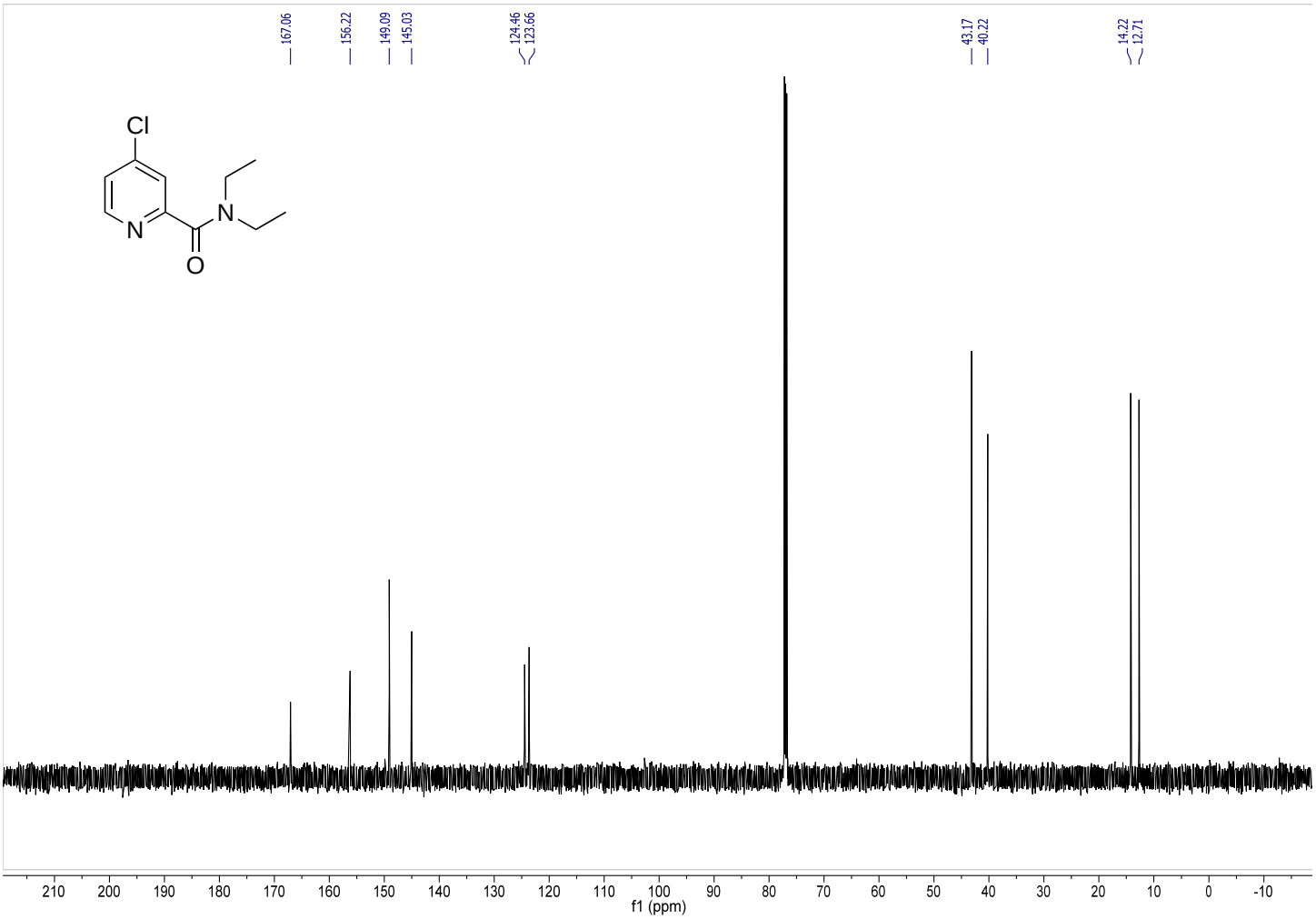
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123.66
43.17
40.22
14.22
12.71
Cl
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200
190
180
170
160
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140
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120
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100
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80
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60
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30
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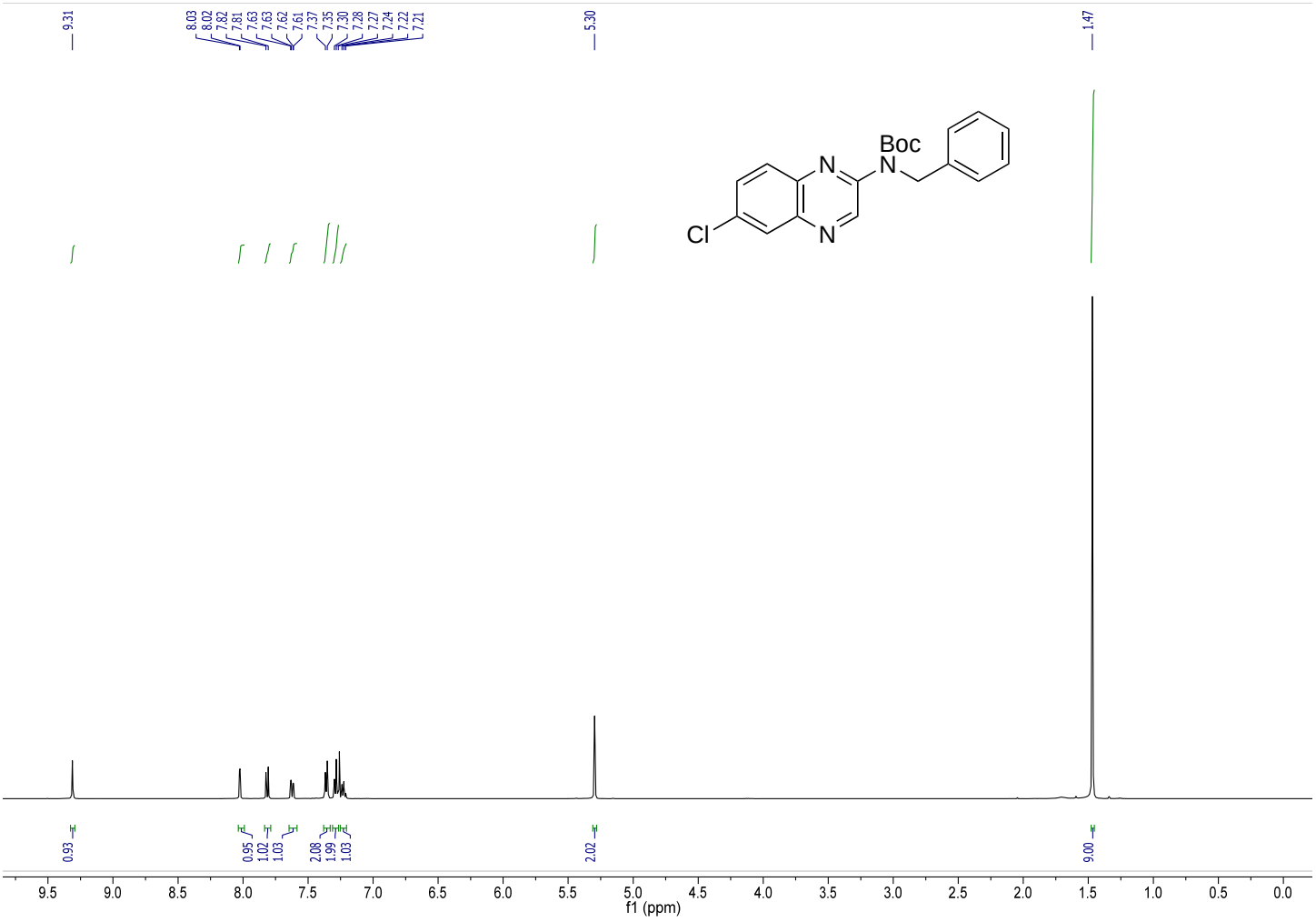
0
-10
f1 (ppm)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7.37
7.35
7.30
7.28
7.27
7.24
7.22
7.21
5.30
1.47
Boc
N
N
Cl
N
0.93
0.95
1.02
1.03
2.08
1.99
1.03
2.02
9.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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2.0
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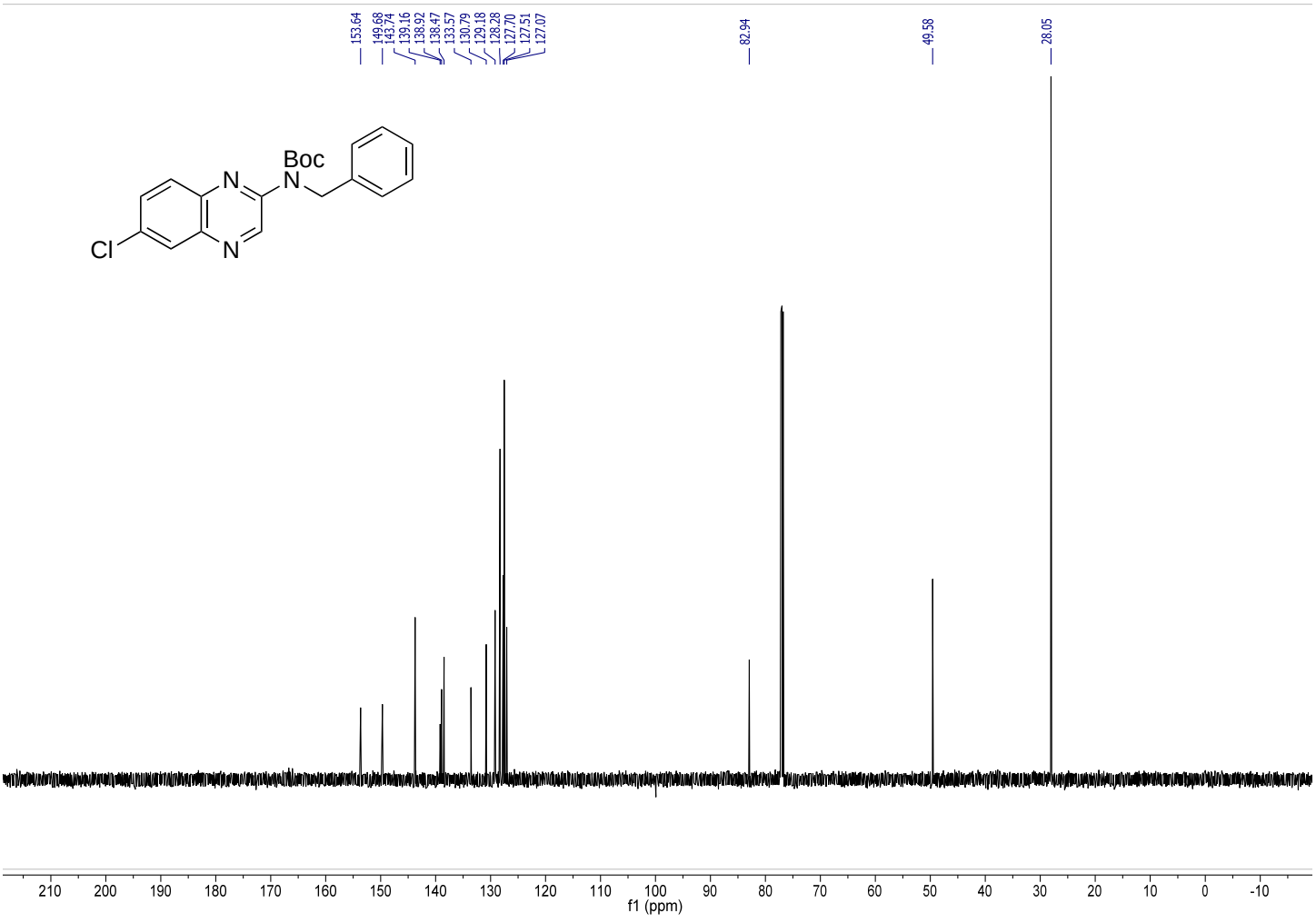
f1 (ppm)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127.70
127.51
127.07
82.94
49.58
28.05
Boc
N
N
N
Cl
210
200
190
180
170
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100
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80
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40
30
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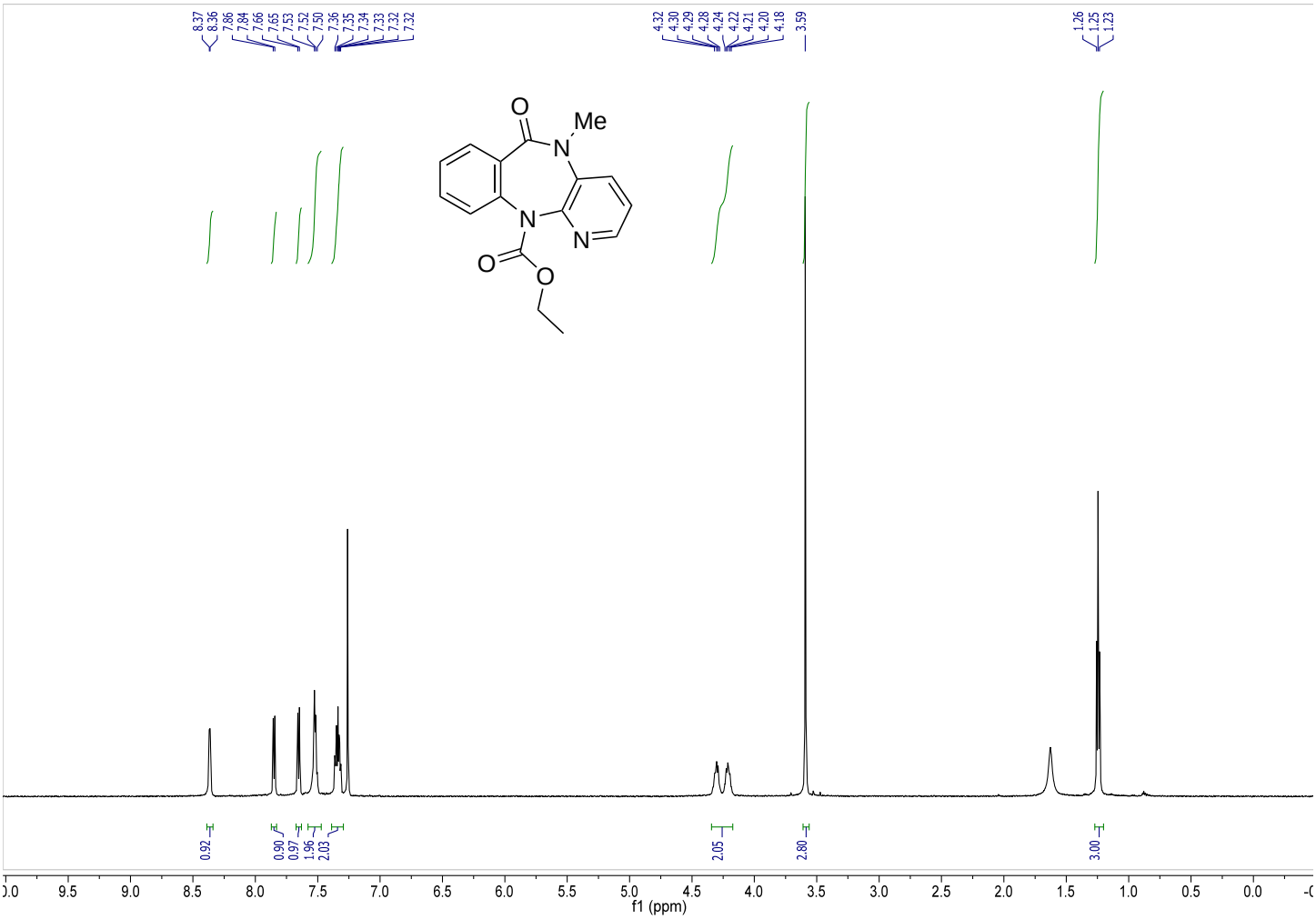
f1 (ppm)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7.33
7.32
7.32
4.32
4.30
4.29
4.28
4.24
4.22
4.21
4.20
4.18
3.59
1.26
1.25
1.23
O
Me
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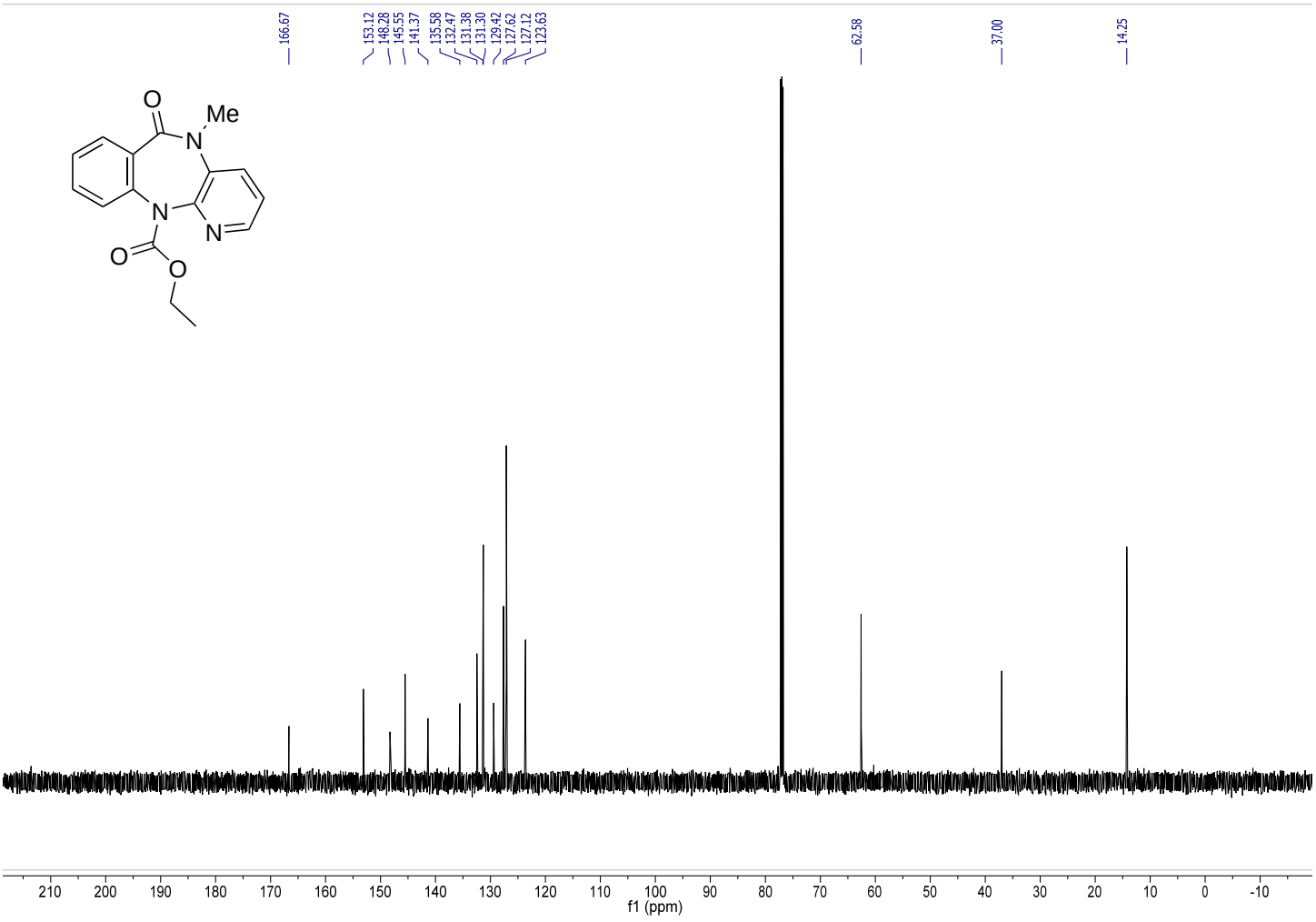
2.05
2.80
3.00
f1 (ppm)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129.42
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127.12
123.63
62.58
37.00
14.25
O
Me
N
N
N
O
O
210
200
190
180
170
160
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140
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120
110
100
90
80
70
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50
40
30
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10
0
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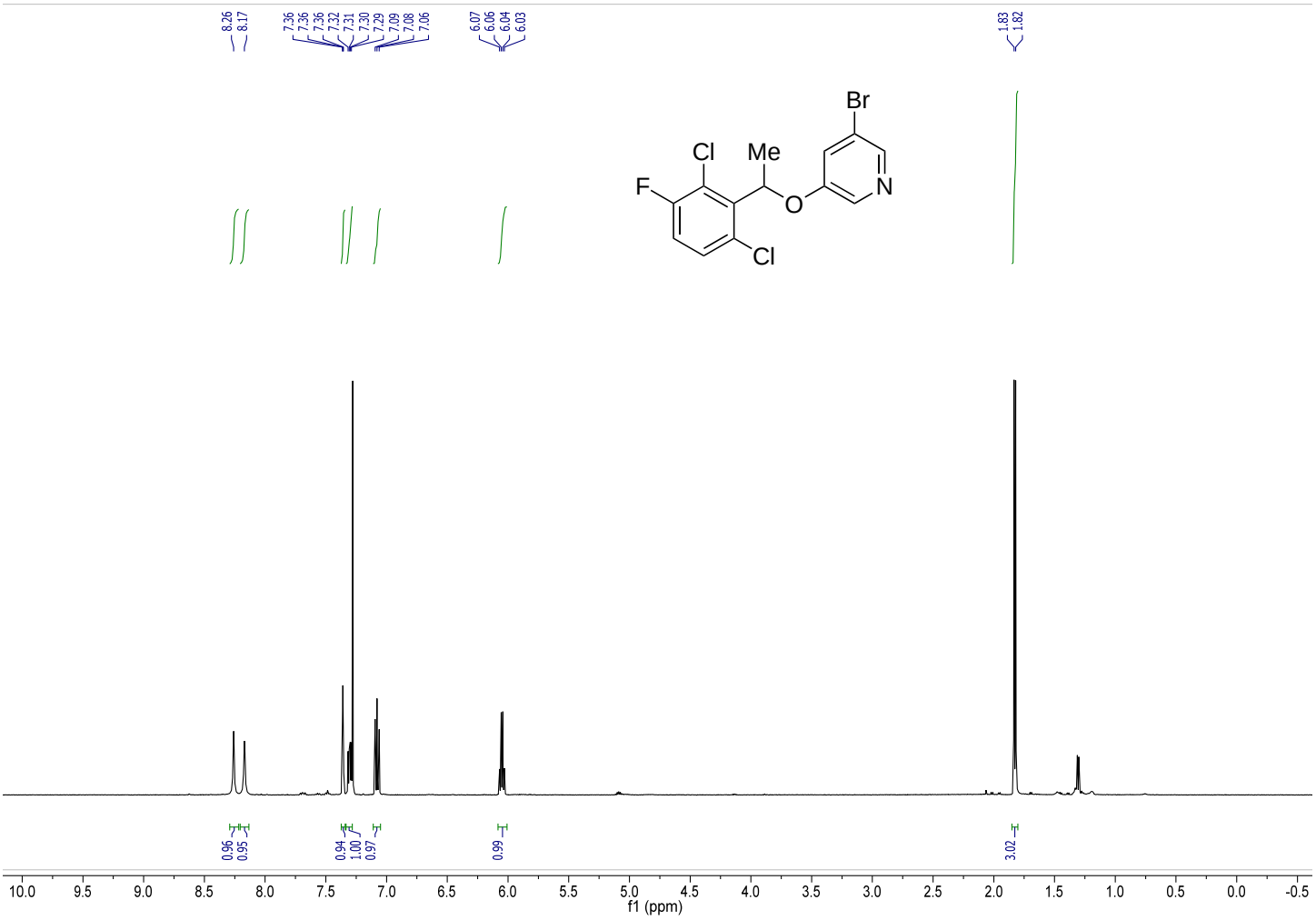
f1 (ppm)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7.30
7.29
7.09
7.08
7.06
6.07
6.06
6.04
6.03
1.83
1.82
Br
Cl
Me
F
O
N
Cl
0.96
0.95
0.94
1.00
0.97
0.99
3.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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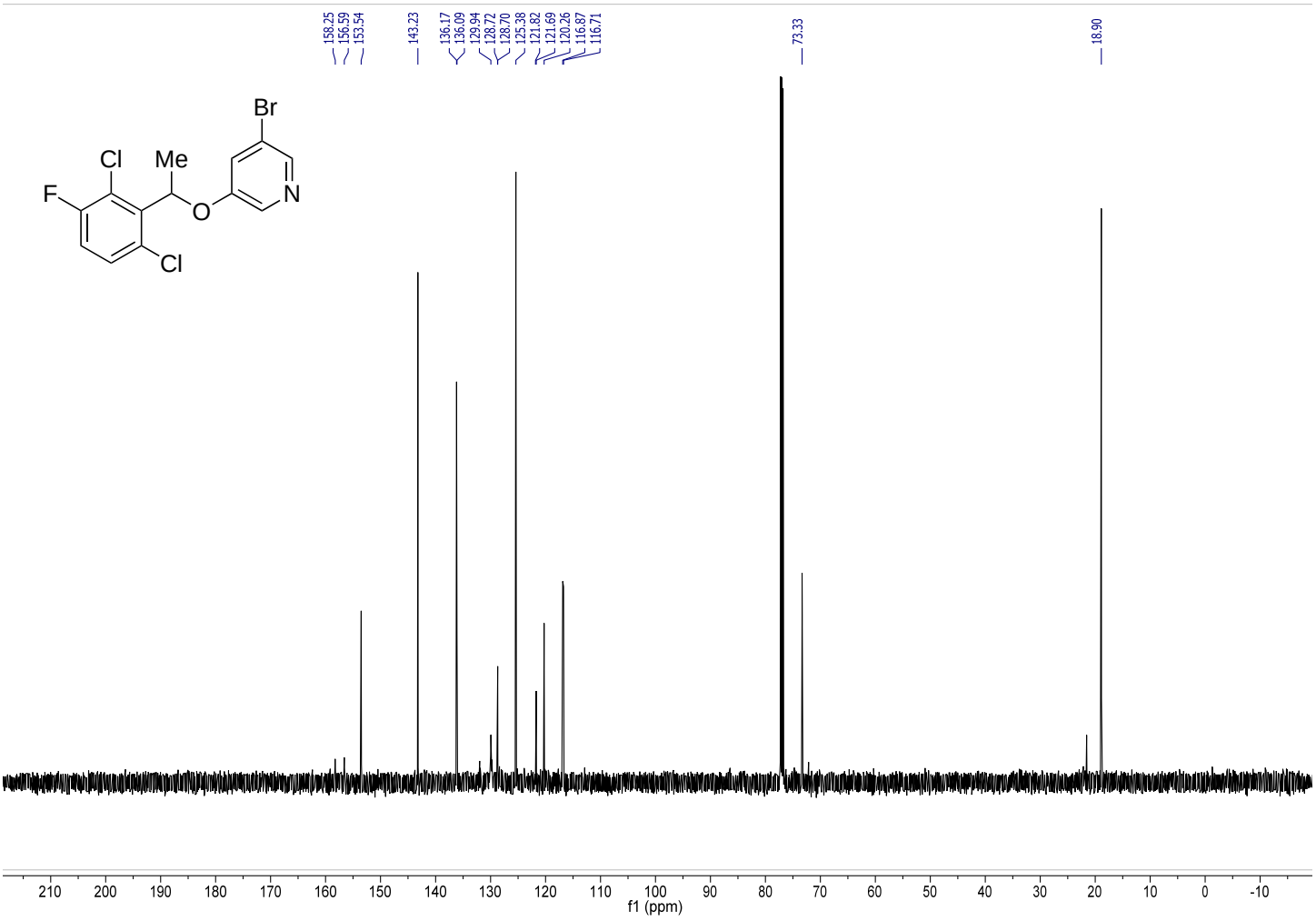
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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136.09
129.94
128.72
128.70
125.38
121.82
121.69
120.26
116.87
116.71
73.33
18.90
Br
Cl
Me
F
O
N
Cl
210
200
190
180
170
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140
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120
110
100
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80
70
60
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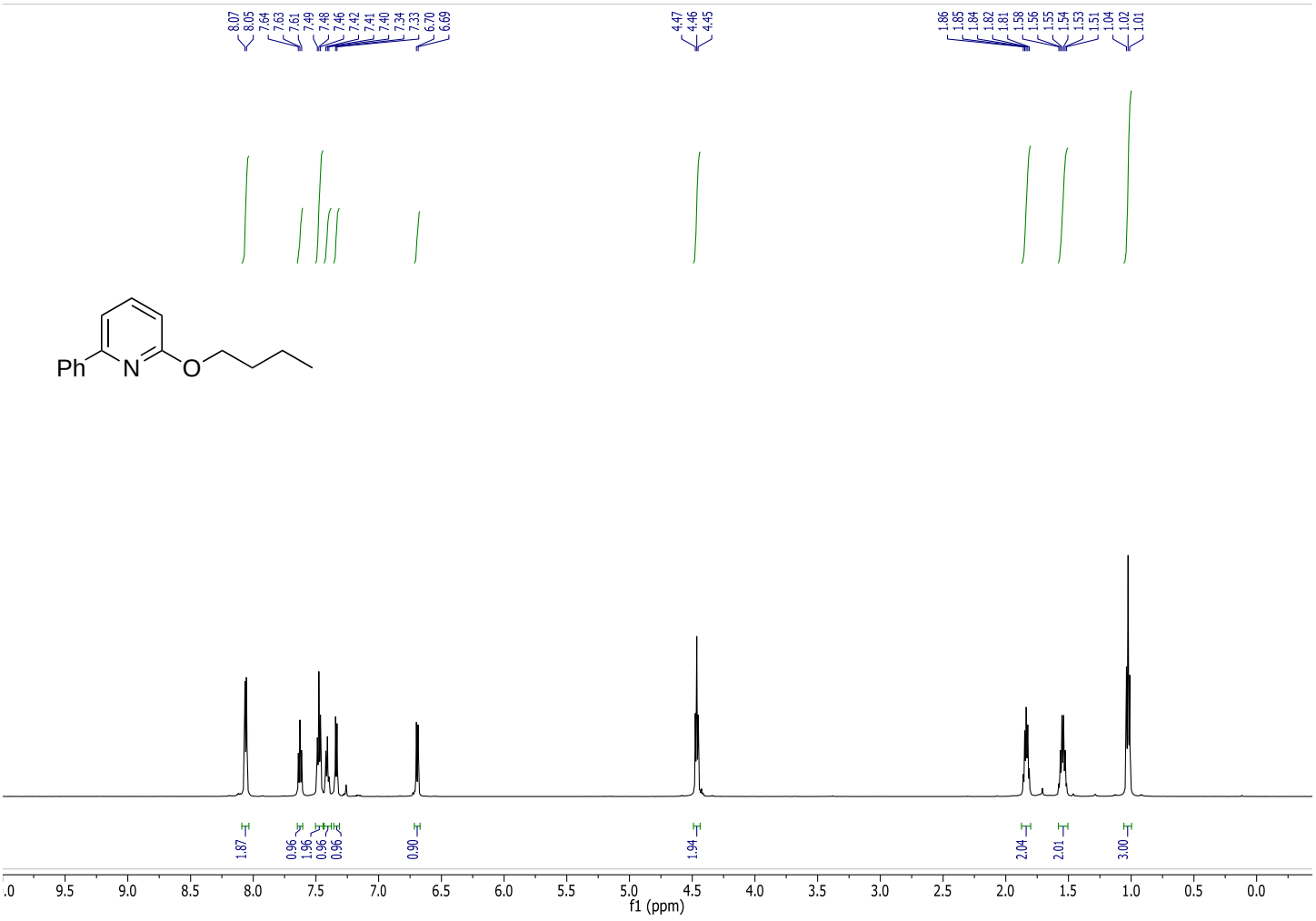
40
30
20
10
0
-10
f1 (ppm)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7.46
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7.41
7.40
7.34
7.33
6.70
6.69
4.47
4.46
4.45
1.86
1.85
1.84
1.82
1.81
1.58
1.56
1.55
1.54
1.53
1.51
1.04
1.02
1.01
Ph
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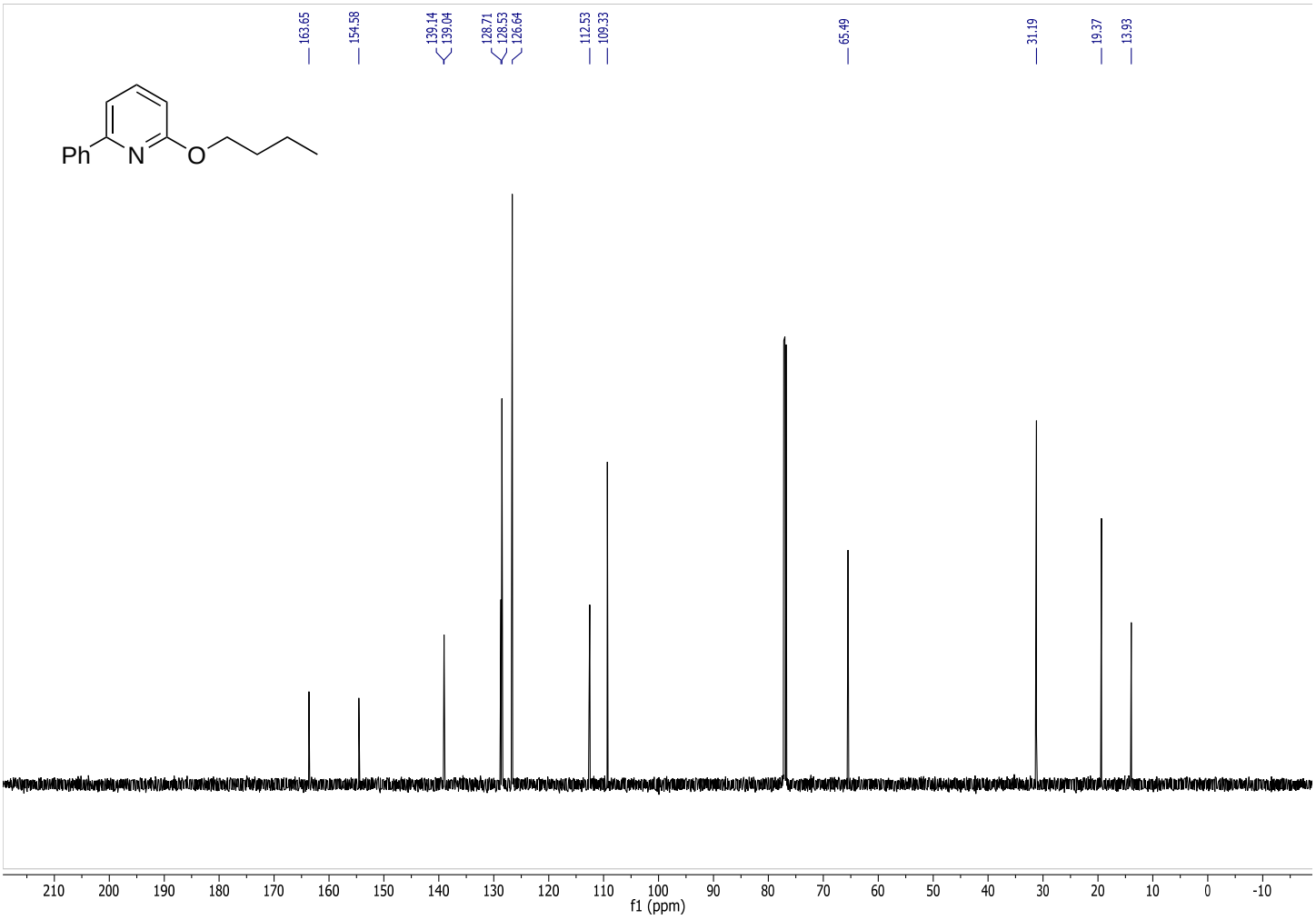
0.96
0.96
0.90
1.94
2.04
2.01
3.00
f1 (ppm)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139.04
128.71
128.53
126.64
112.53
109.33
65.49
31.19
19.37
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Ph
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200
190
180
170
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120
110
100
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80
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60
50
40
30
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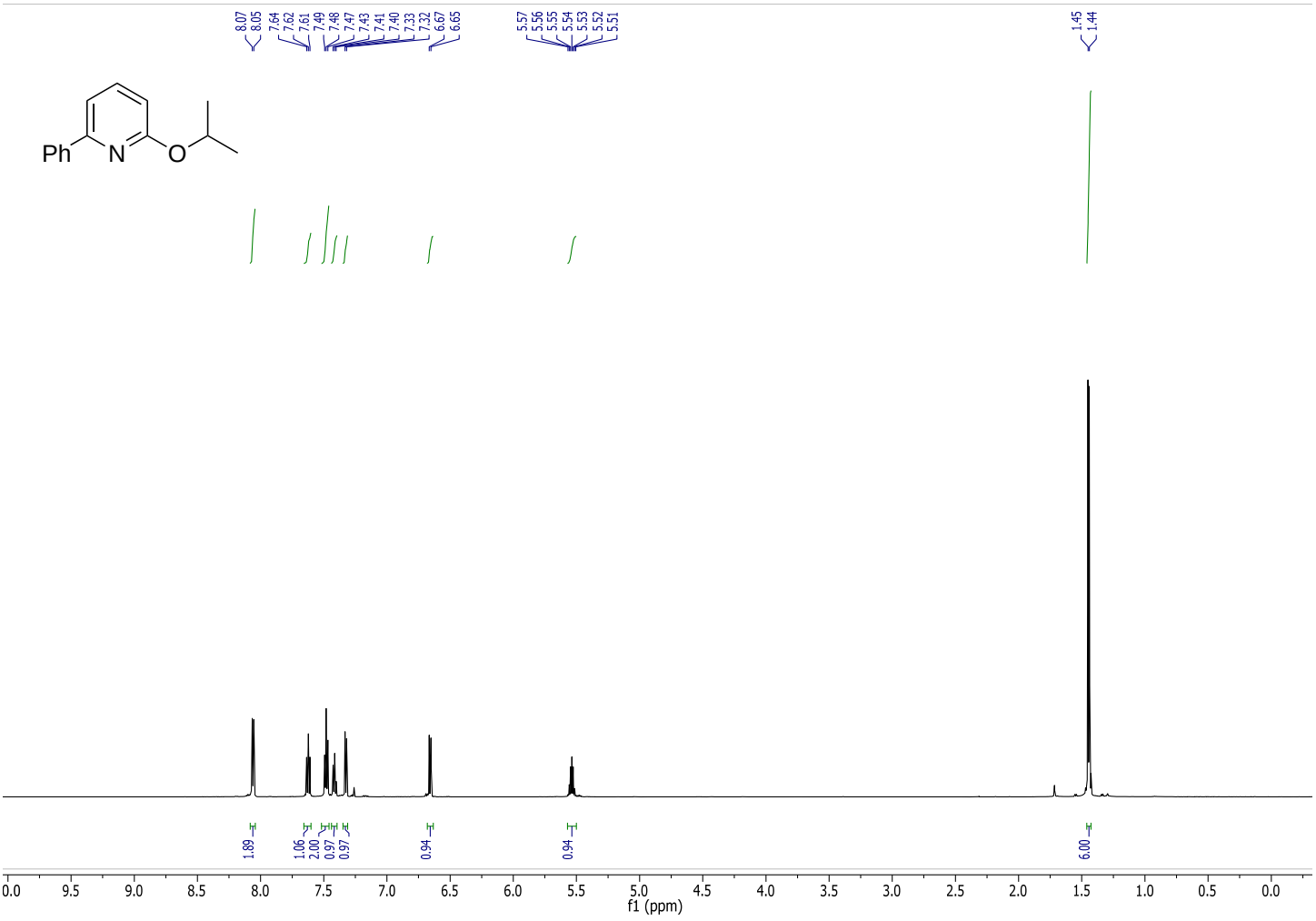
10
0
-10
f1 (ppm)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7.49
7.48
7.47
7.43
7.41
7.40
7.33
7.32
6.67
6.65
5.57
5.56
5.55
5.54
5.53
5.52
5.51
1.45
1.44
Ph
N
O
1.89
1.06
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0.97
0.94
0.94
6.00
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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2.5
2.0
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1.0
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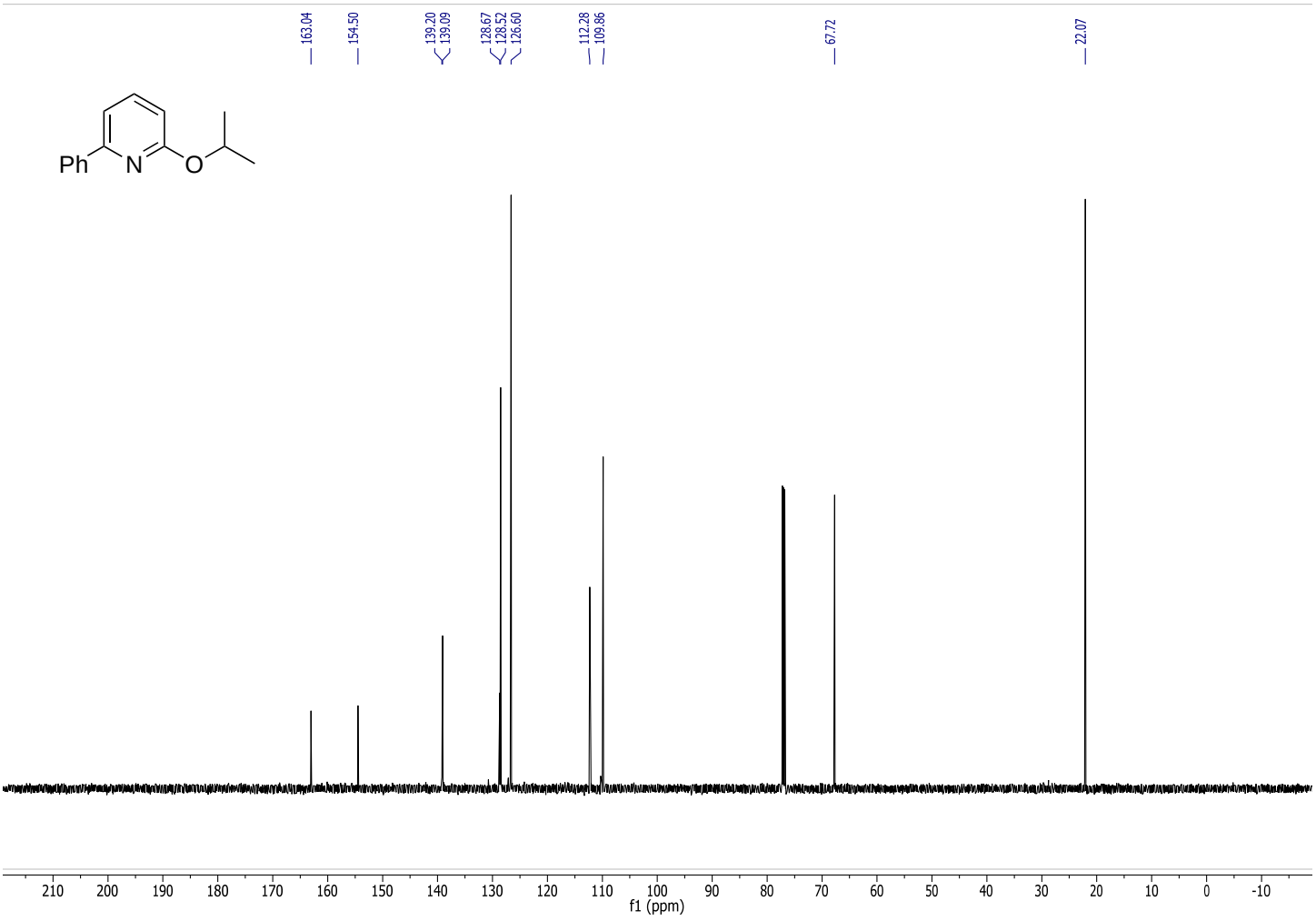
f1 (ppm)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128.52
126.60
112.28
109.86
67.72
22.07
Ph
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O
210
200
190
180
170
160
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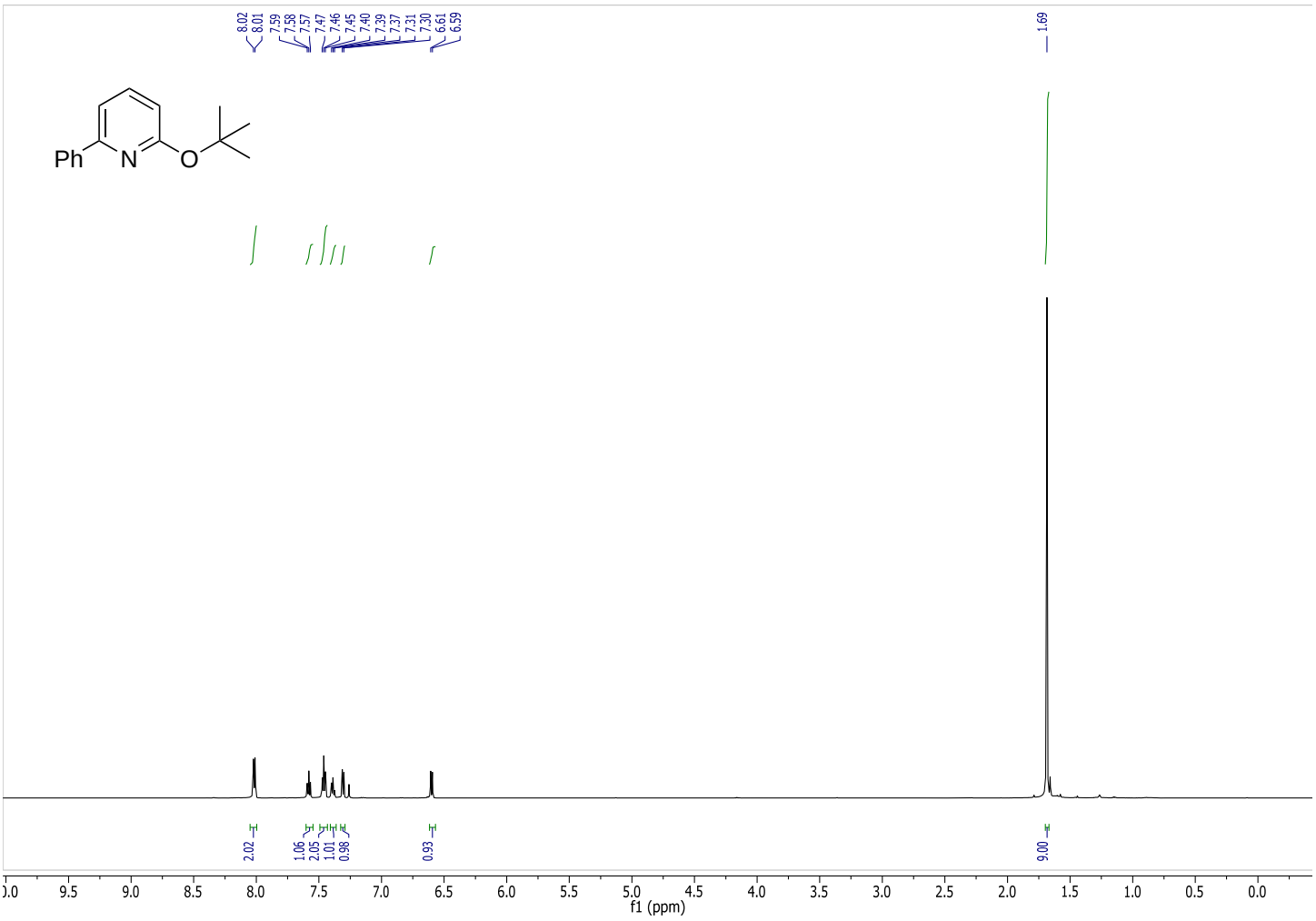
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.47
7.46
7.45
7.40
7.39
7.37
7.31
7.30
6.61
6.59
1.69
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O
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1.06
2.05
1.01
0.98
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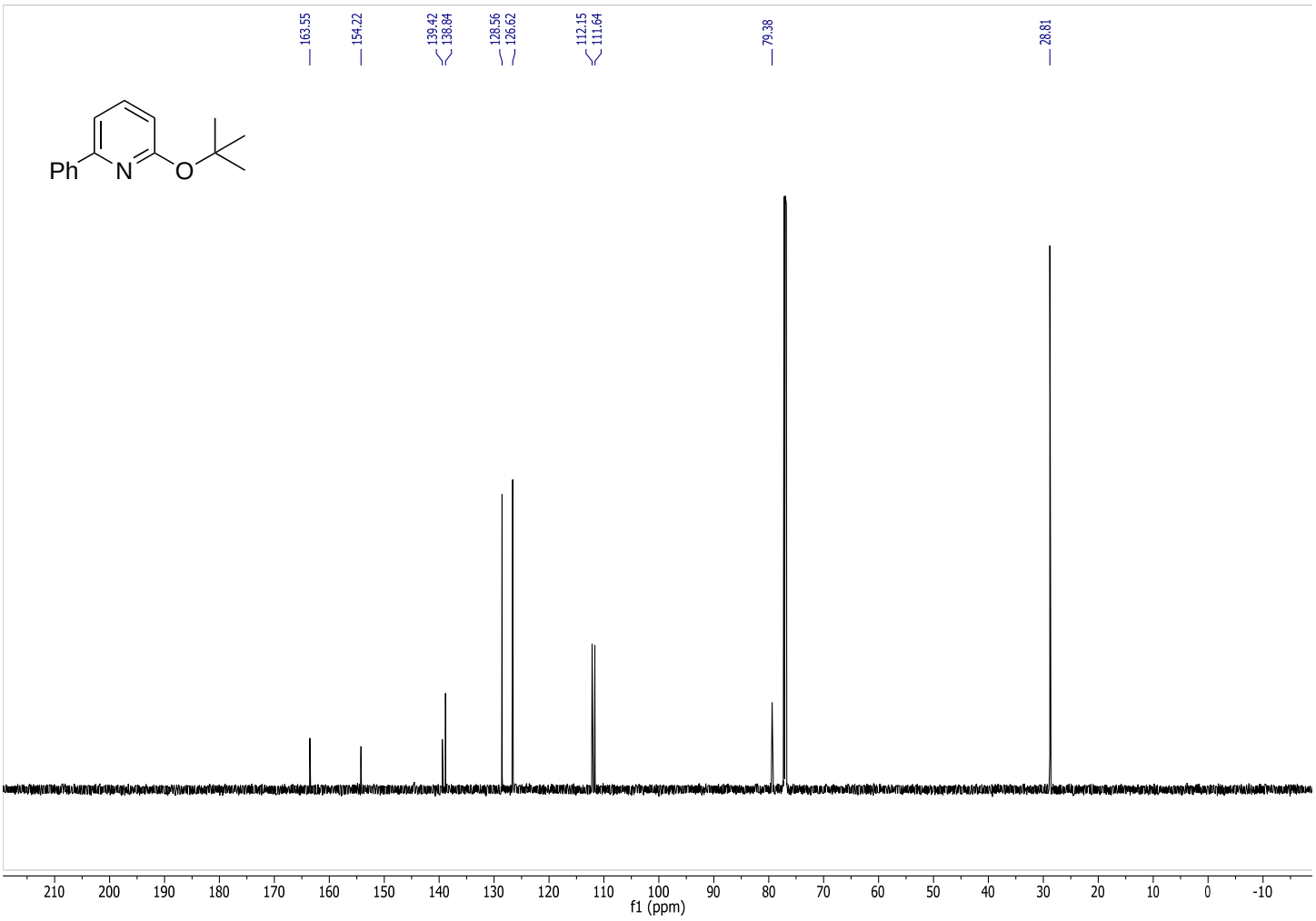
9.00
f1 (ppm)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111.64
79.38
28.81
Ph
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O
210
200
190
180
170
160
150
140
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120
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100
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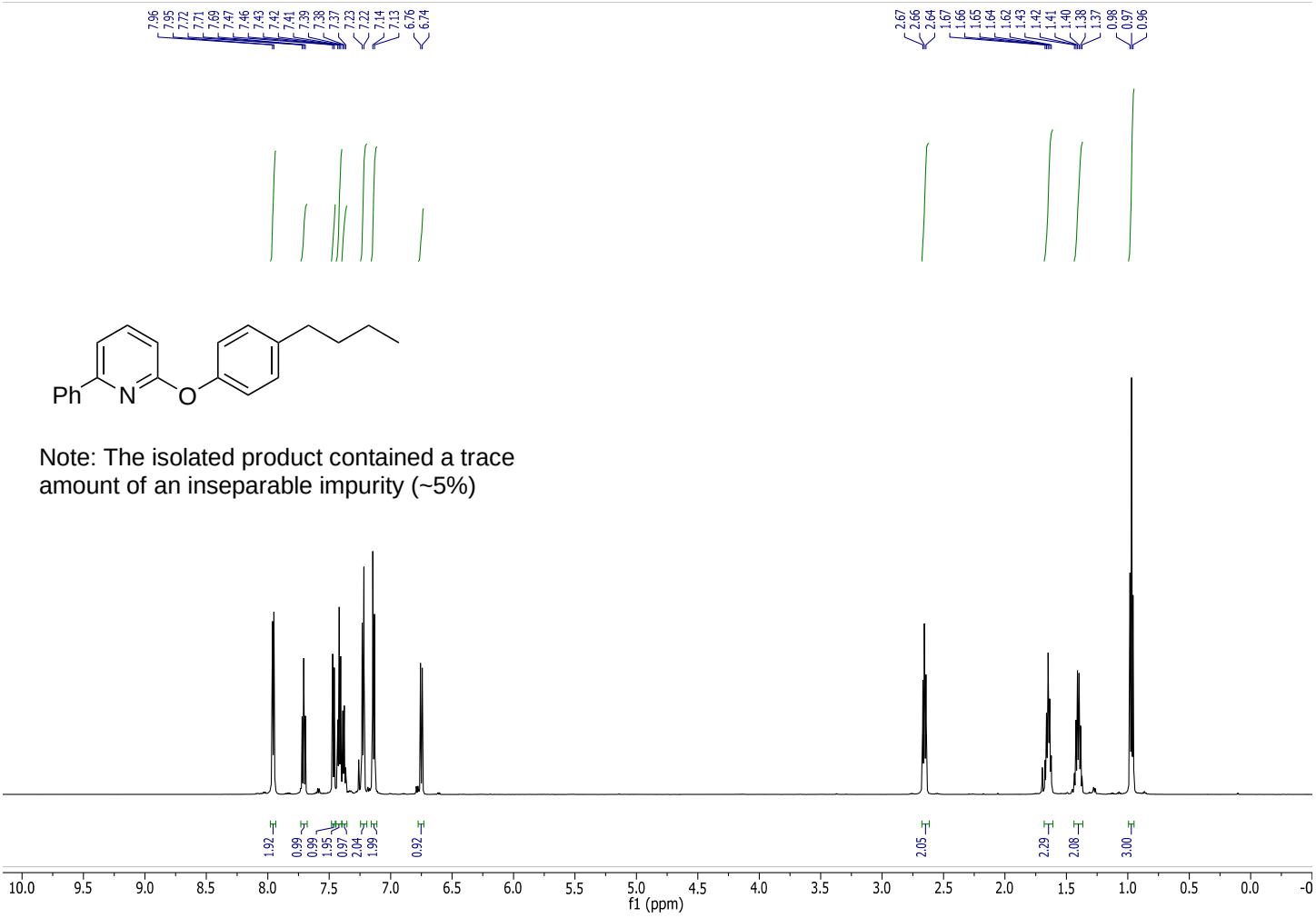
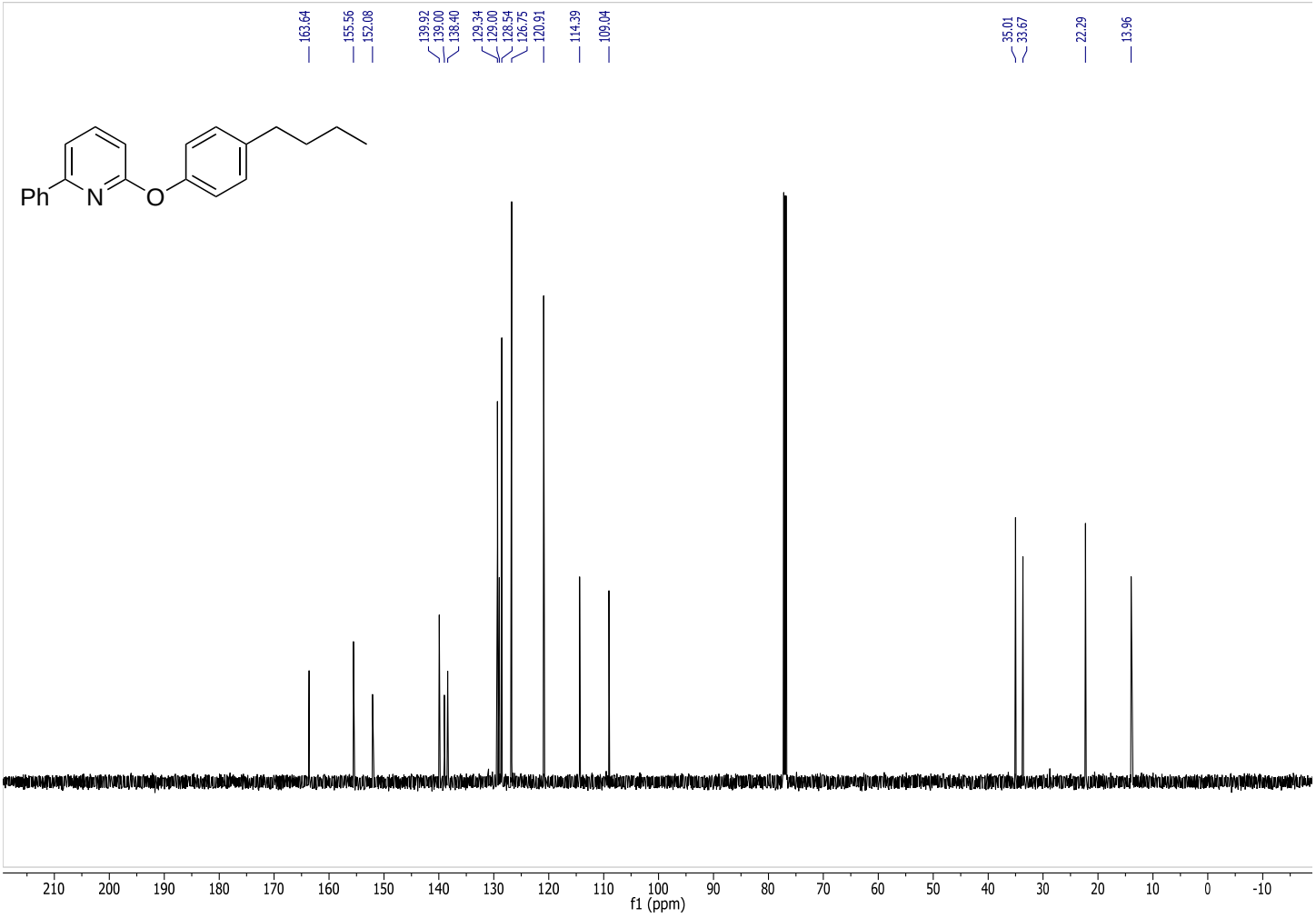
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



Note: The isolated product contained a trace amount of an inseparable impurity (~5%)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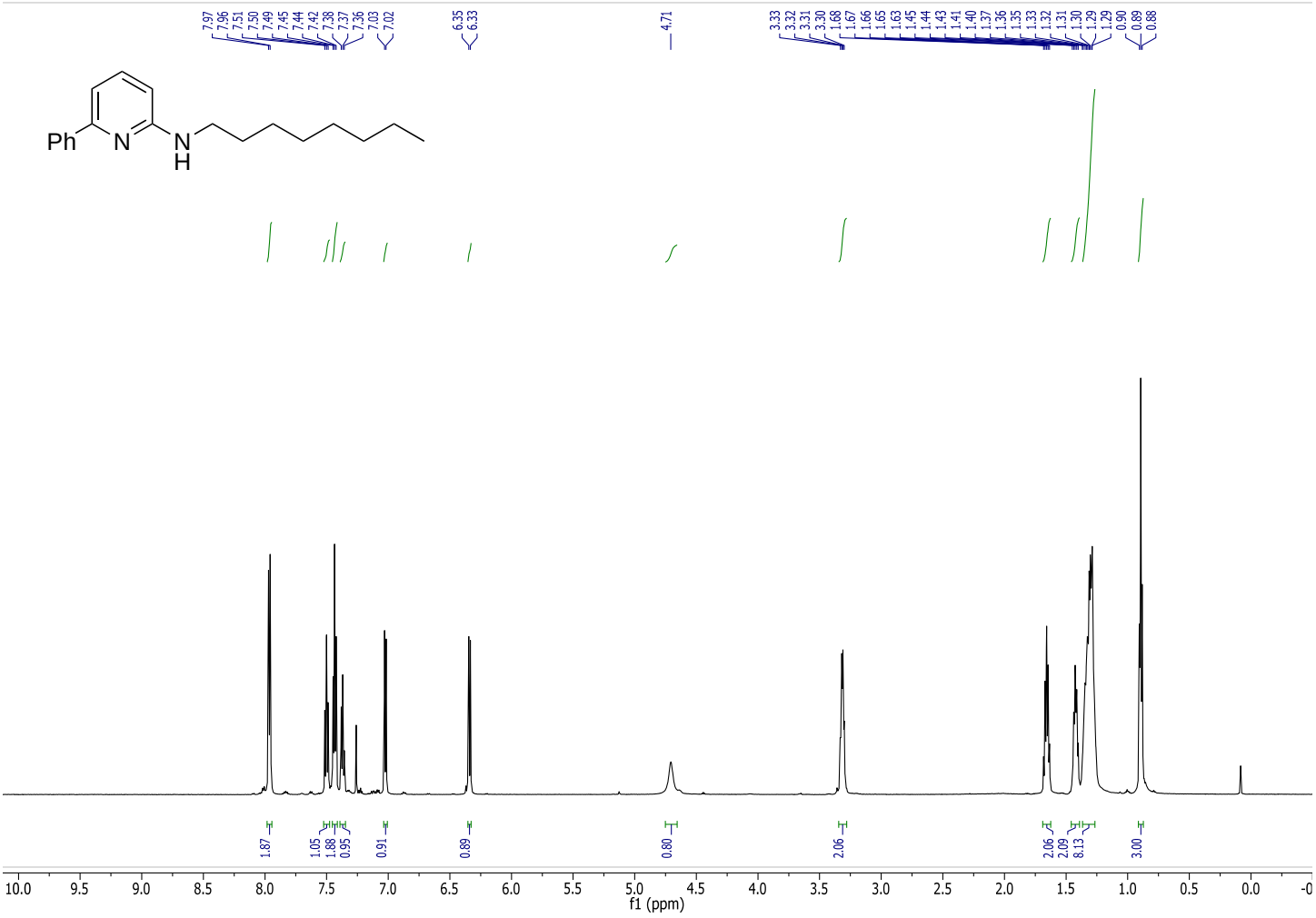
155.56
152.08
139.92
139.00
138.40
129.34
129.00
128.54
126.75
120.91
114.39
109.04
35.01
33.67
22.29
13.96
Ph
N
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.97
7.96
7.51
7.50
7.49
7.45
7.44
7.42
7.38
7.37
7.36
7.03
7.02
6.35
6.33
4.71
3.33
3.32
3.31
3.30
1.68
1.67
1.66
1.65
1.63
1.45
1.44
1.43
1.41
1.40
1.37
1.36
1.35
1.33
1.32
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0.88
Ph
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N
H
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0.91
0.89
0.80
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2.06
2.09
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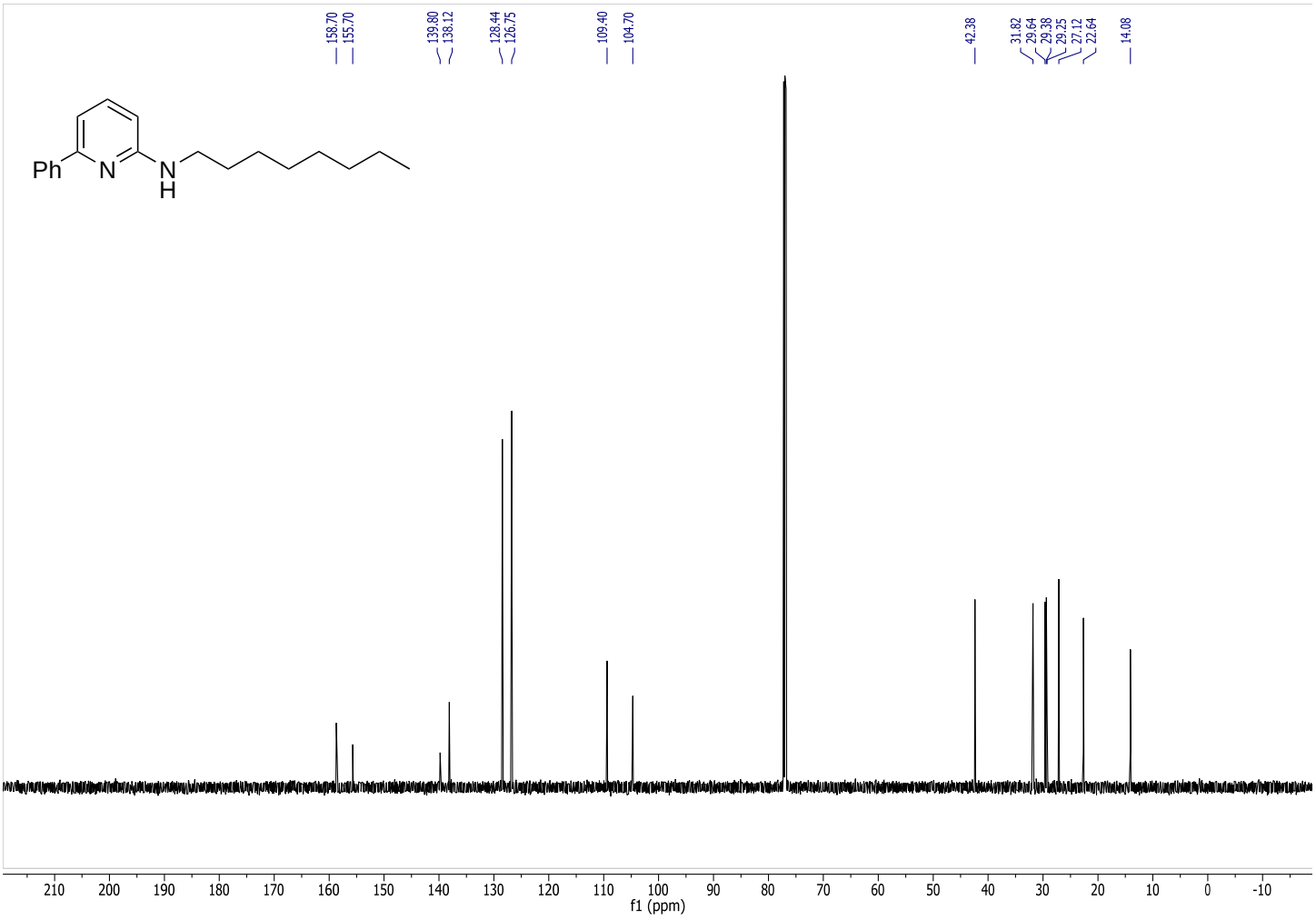
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27.12
22.64
14.08
Ph
N
N
H
210
200
190
180
170
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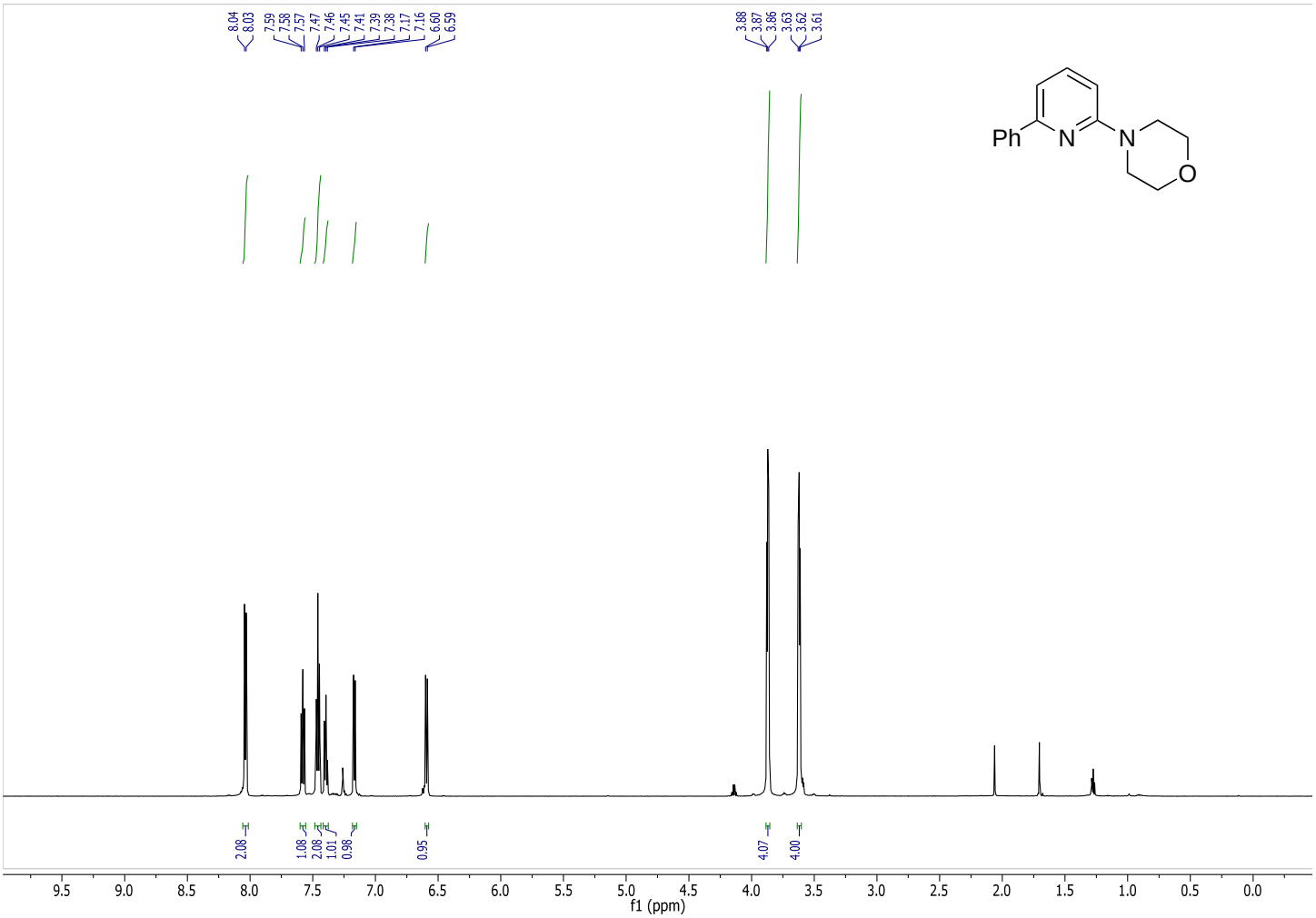
f1 (ppm)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6.59
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3.87
3.86
3.63
3.62
3.61
Ph
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N
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2.08
1.08
2.08
1.01
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0.95
4.07
4.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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1.0
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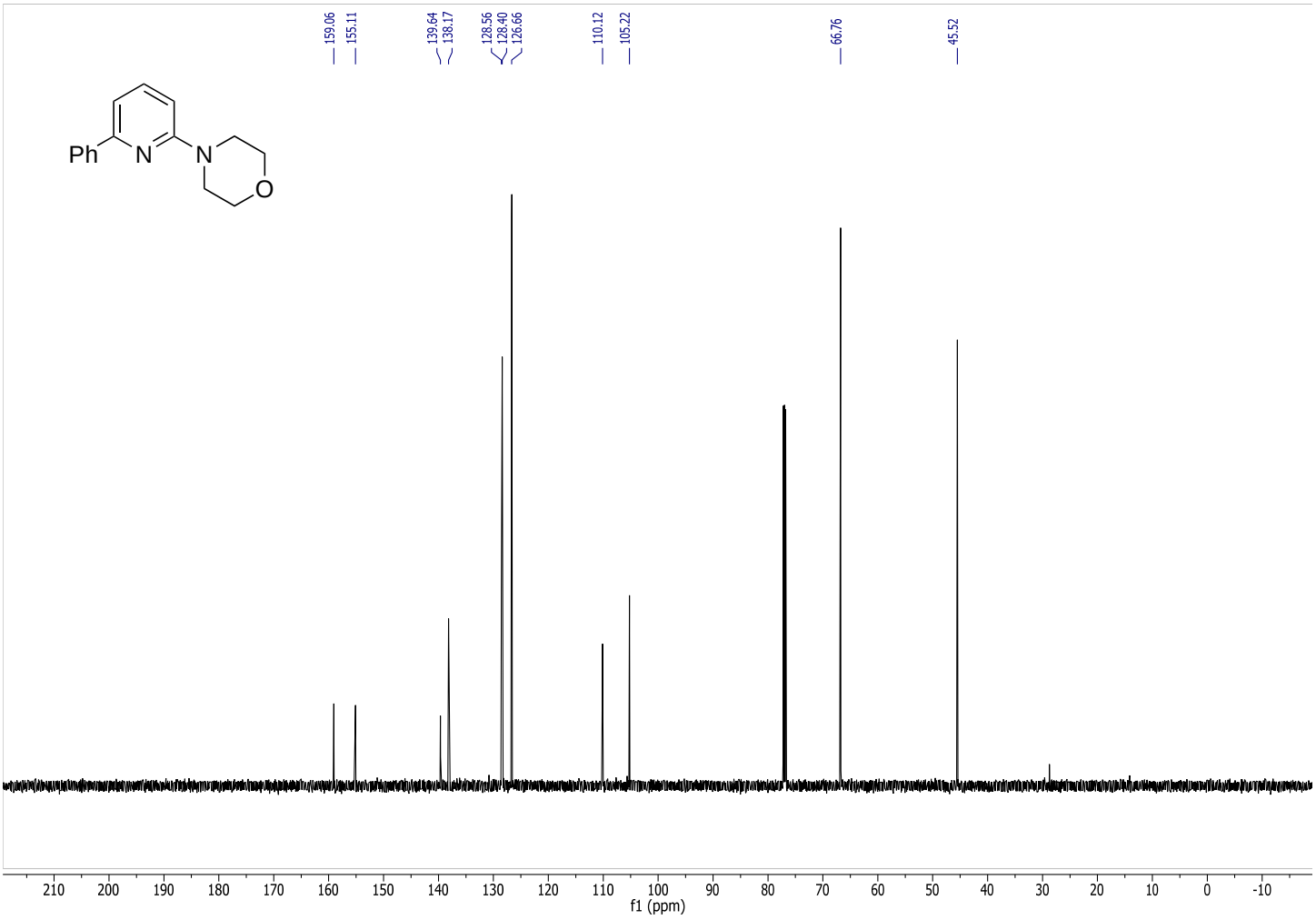
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N
O
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200
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180
170
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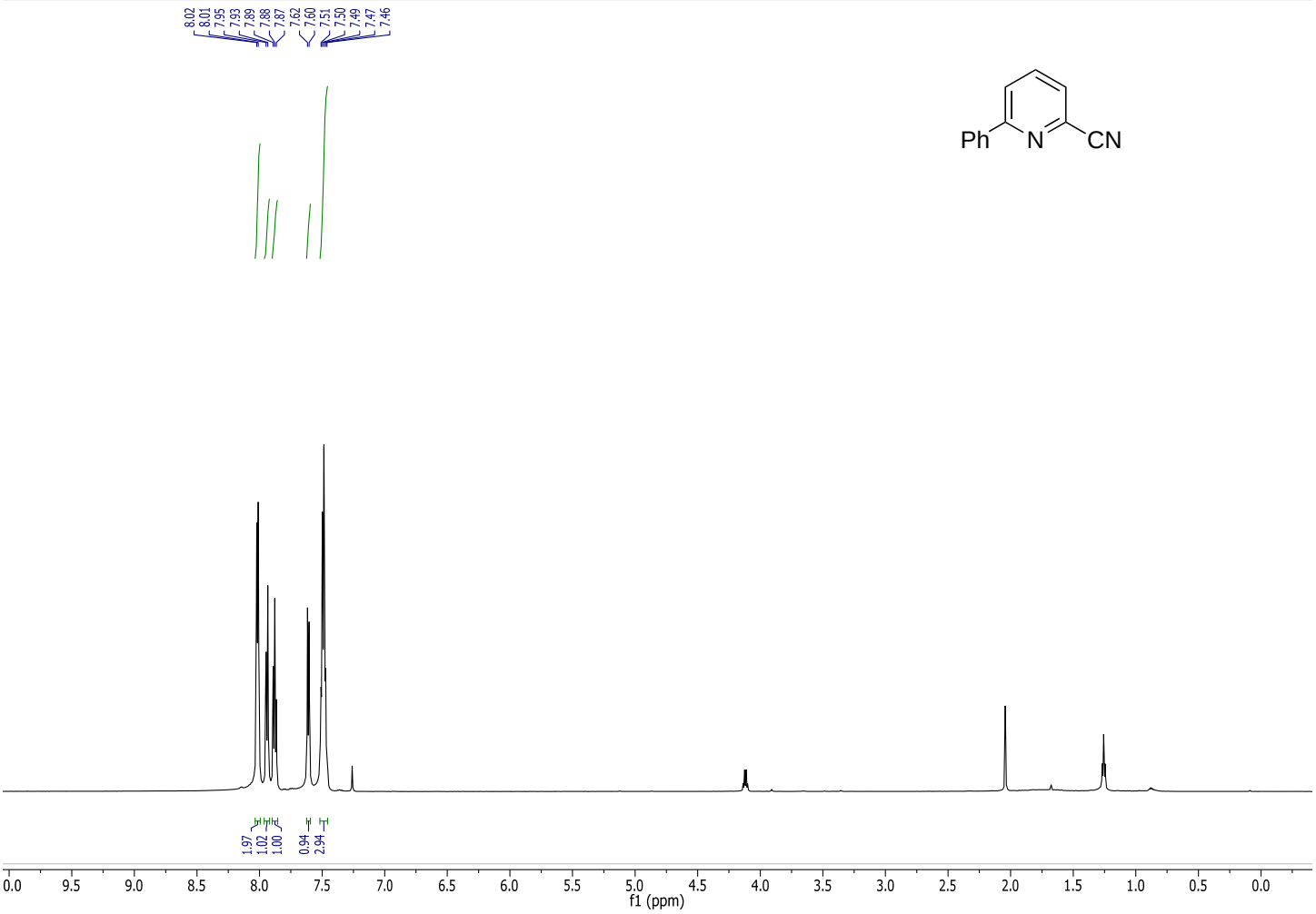
f1 (ppm)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7.50
7.49
7.47
7.46
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CN
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1.00
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2.94
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9.0
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8.0
7.5
7.0
6.5
6.0
5.5
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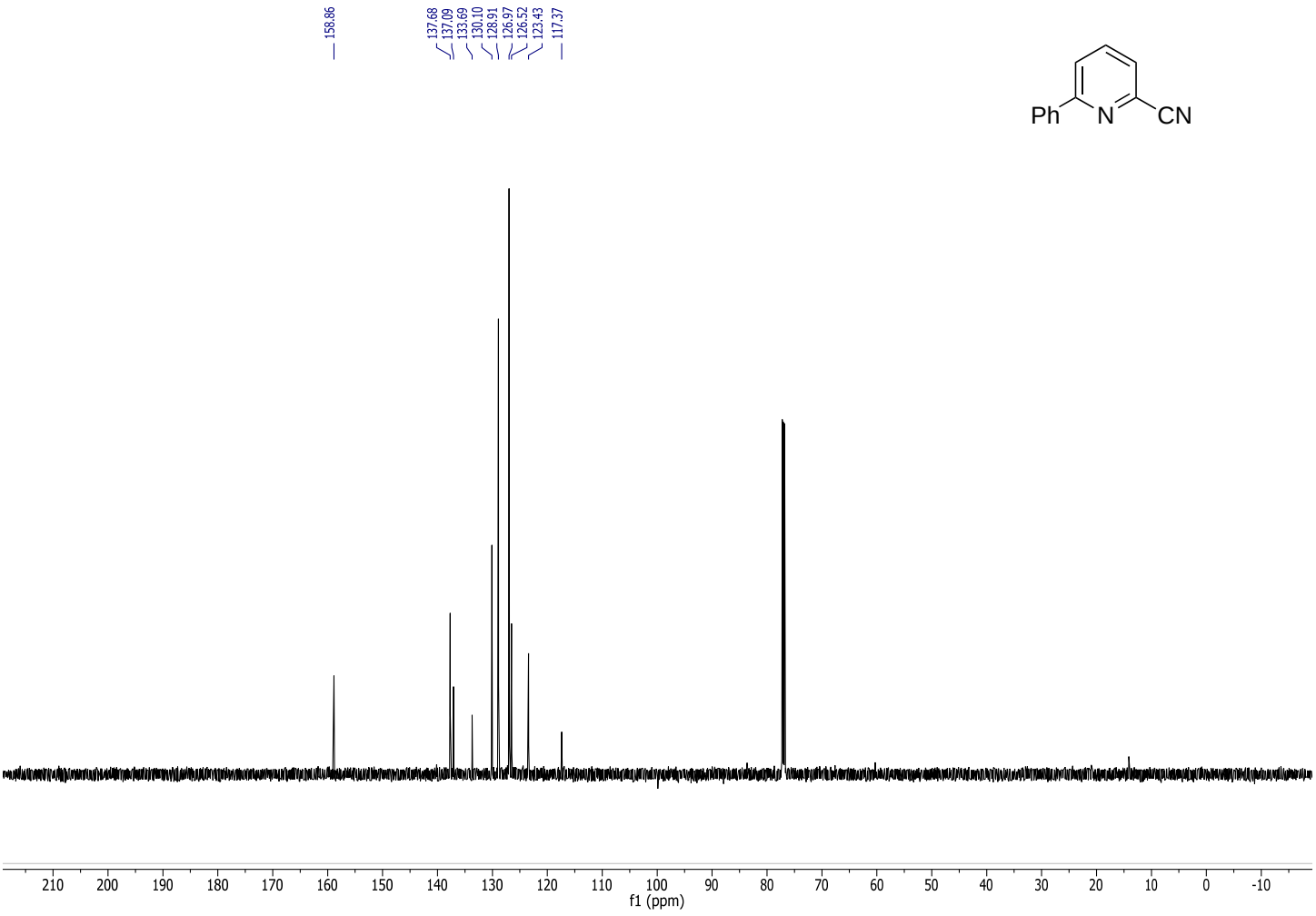
0.0
f1 (ppm)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137.68
137.09
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CN
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200
190
180
170
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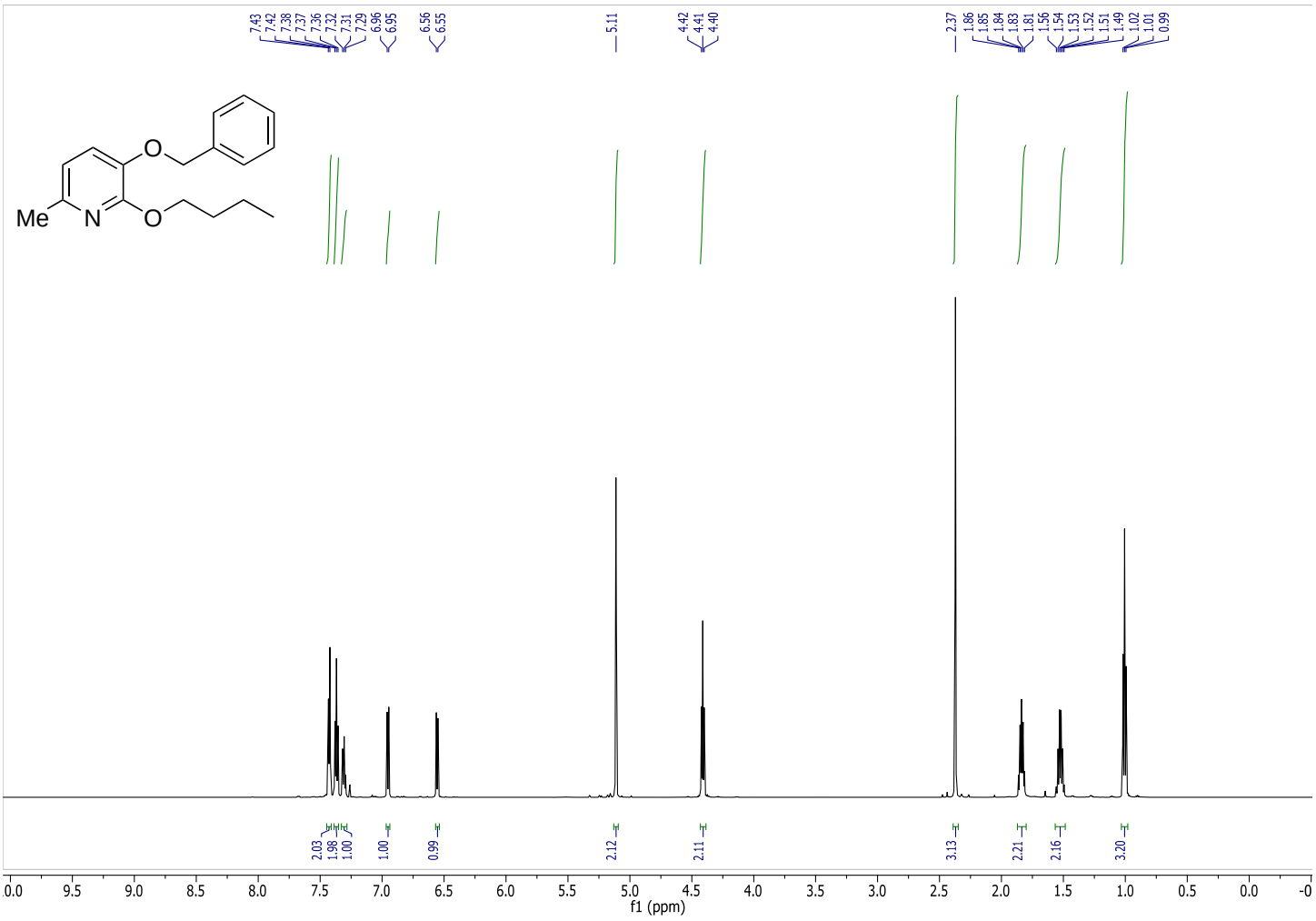
f1 (ppm)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6.95
6.56
6.55
5.11
4.42
4.41
4.40
2.37
1.86
1.85
1.84
1.83
1.81
1.56
1.54
1.53
1.52
1.51
1.49
1.02
1.01
0.99
Me
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O
O
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1.00
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2.21
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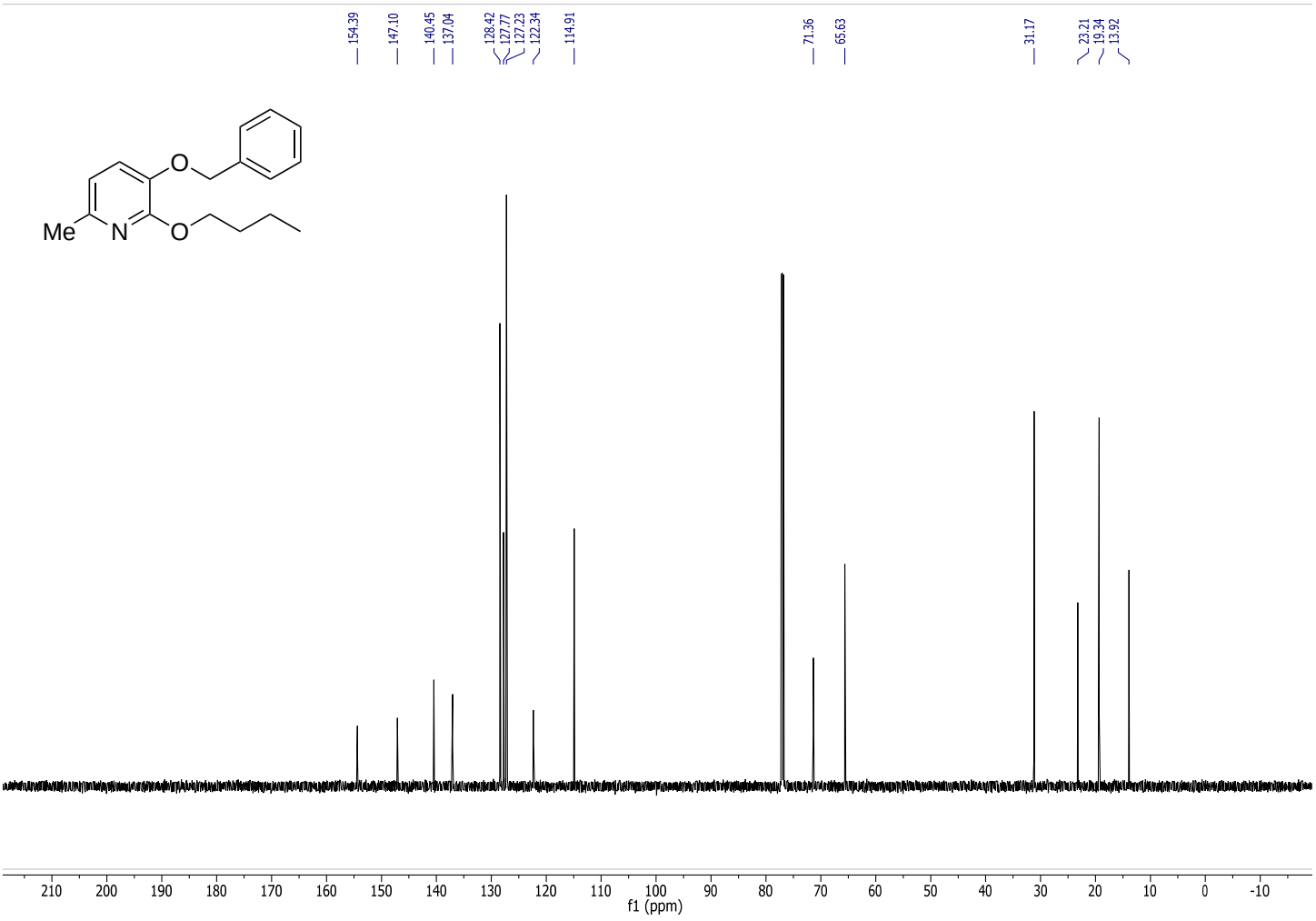
3.20
f1 (ppm)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31.17
23.21
19.34
13.92
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O
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200
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180
170
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140
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100
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80
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40
30
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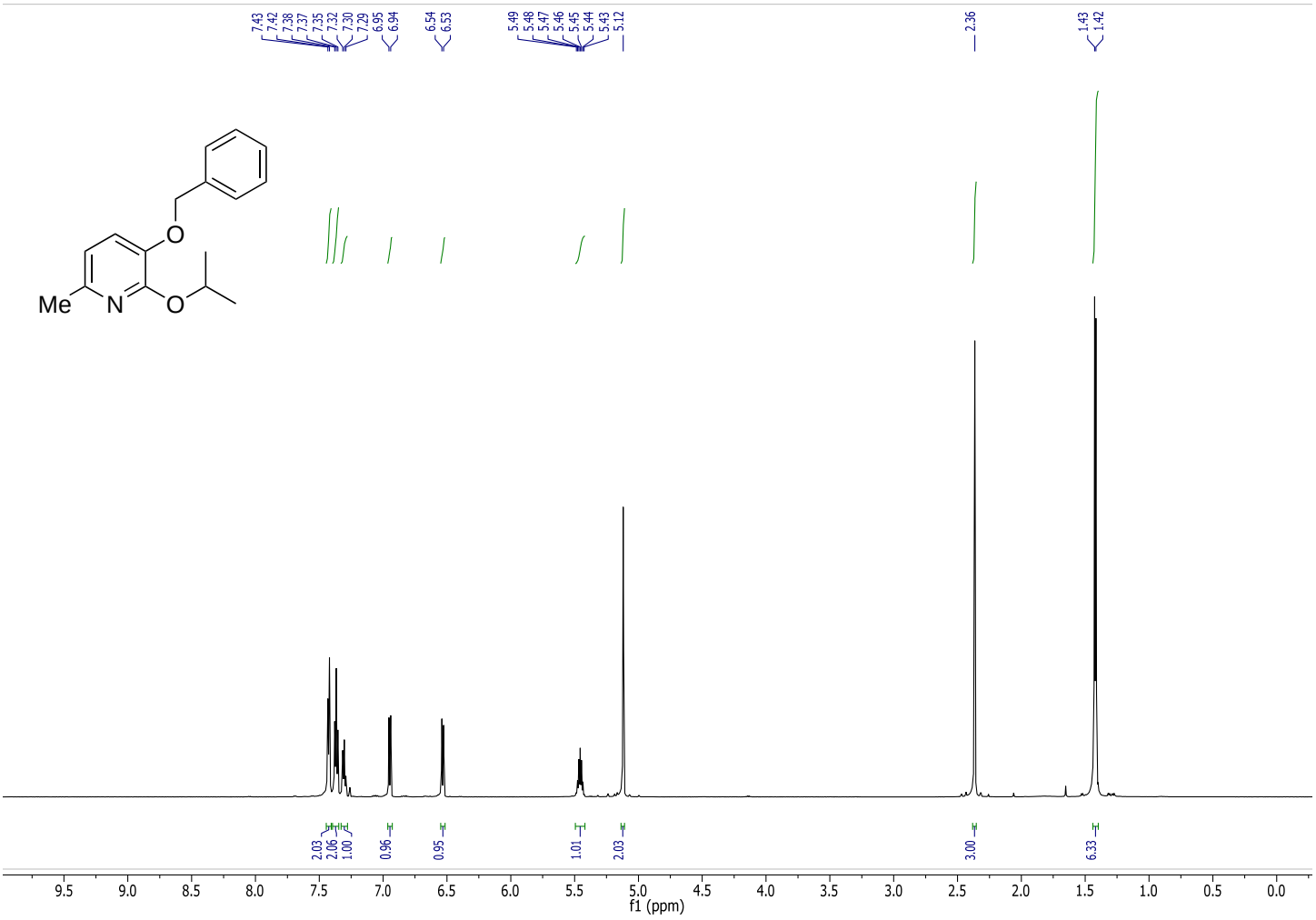
f1 (ppm)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6.54
6.53
5.49
5.48
5.47
5.46
5.45
5.44
5.43
5.12
2.36
1.43
1.42
Me
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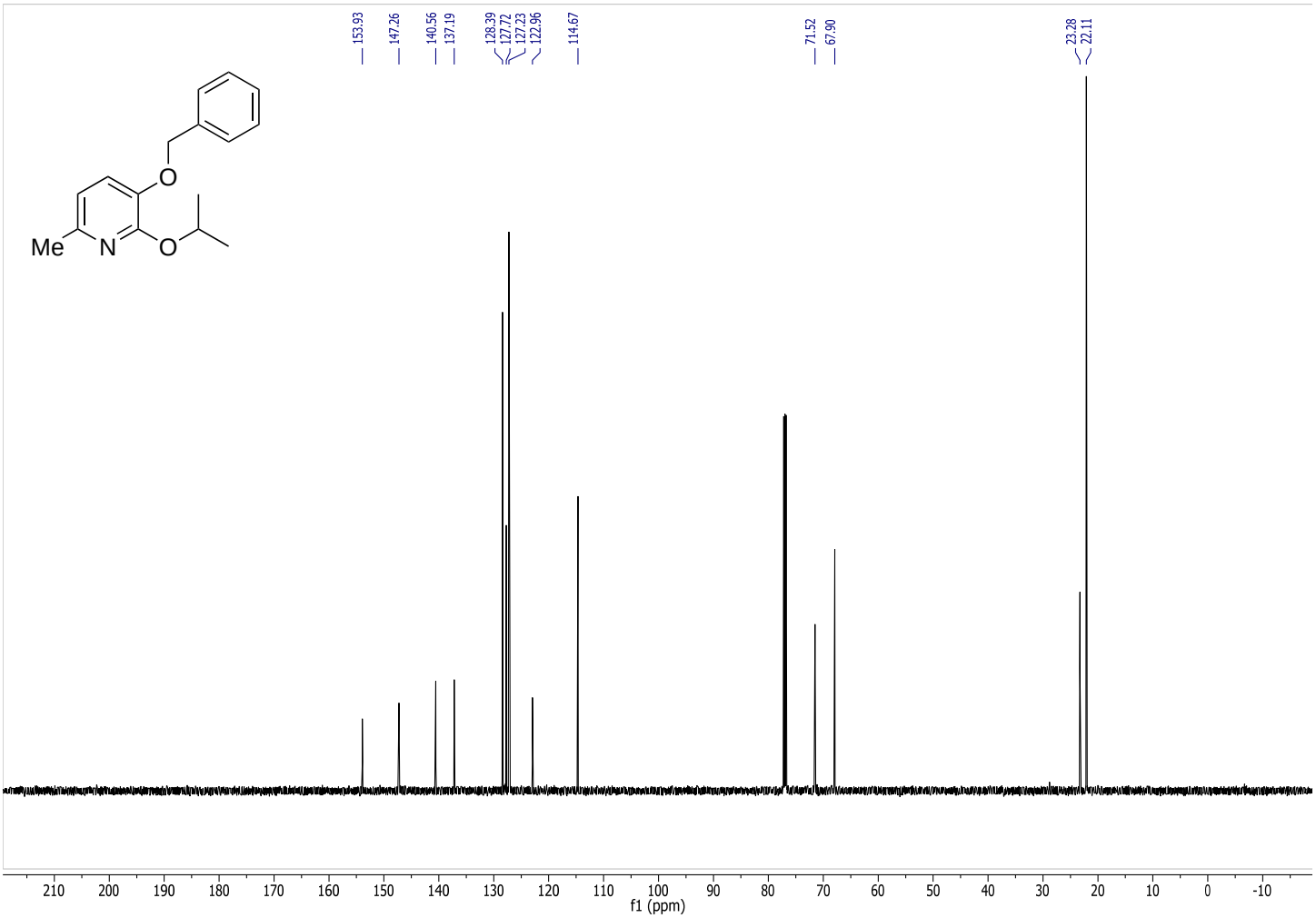
1.01
2.03
3.00
6.33
f1 (ppm)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22.11
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200
190
180
170
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120
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100
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30
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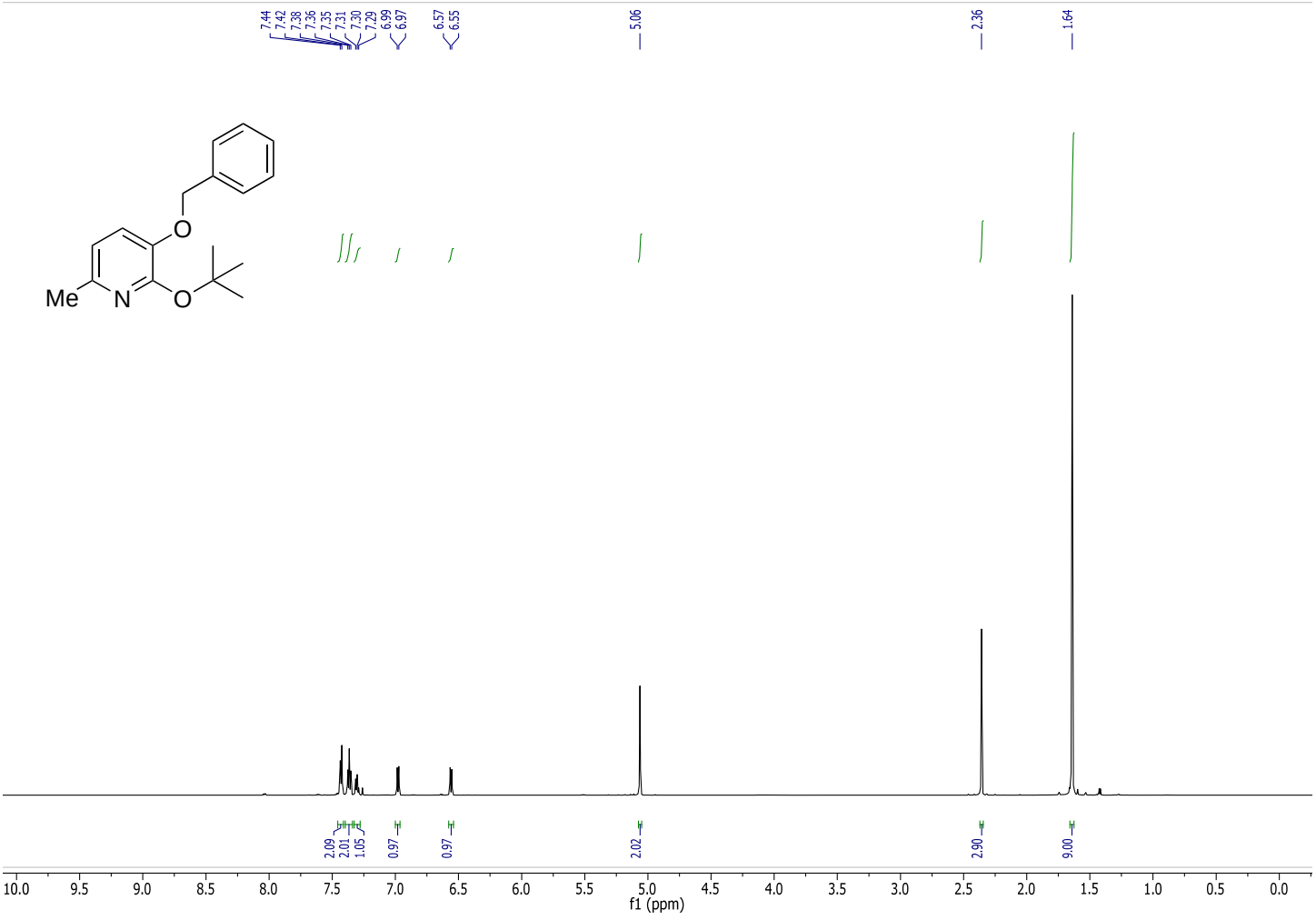
-10
f1 (ppm)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6.57
6.55
5.06
2.36
1.64
Me
N
O
O
2.09
2.01
1.05
0.97
0.97
2.02
2.90
9.00
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8.0
7.5
7.0
6.5
6.0
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1.0
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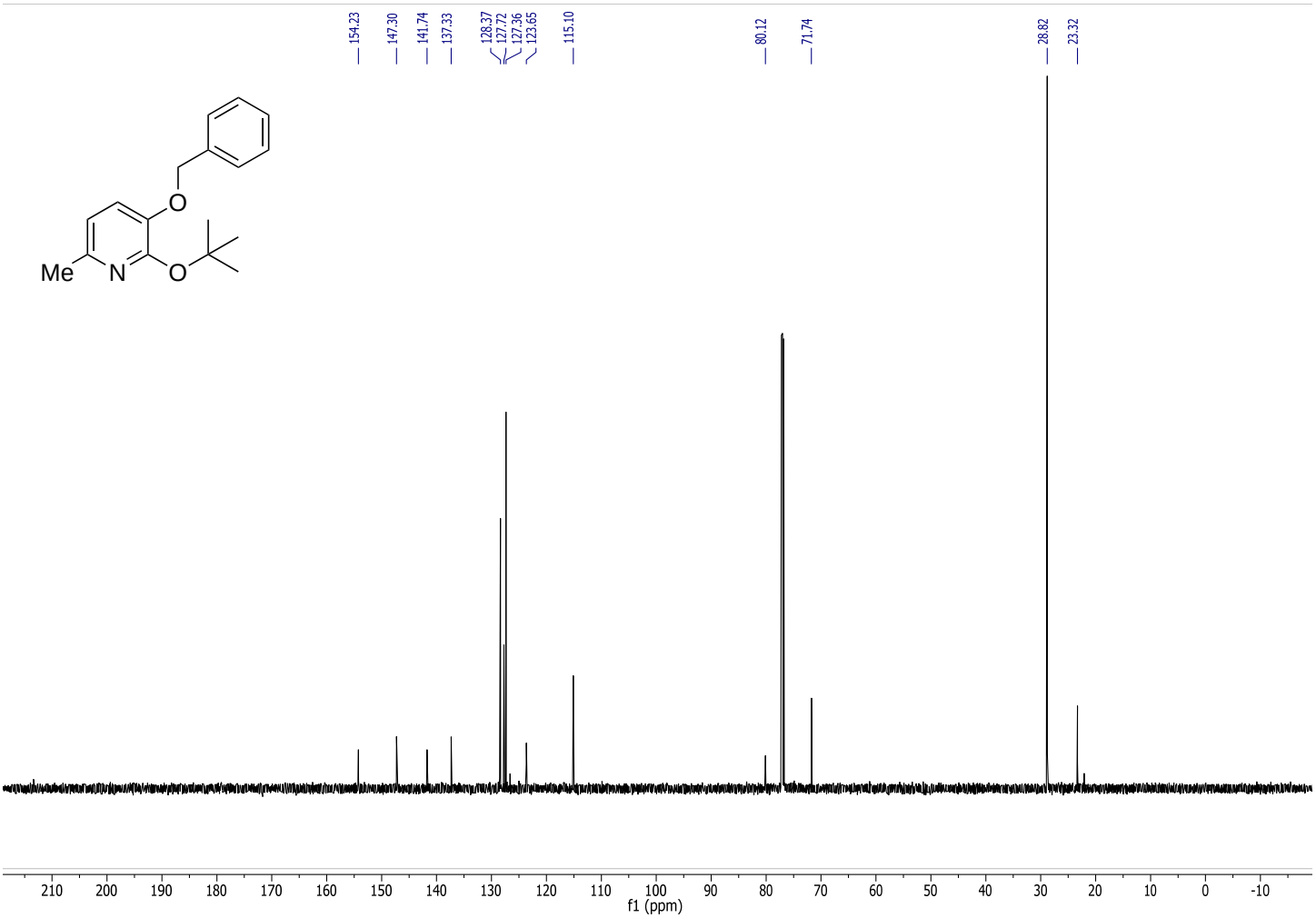
0.0
f1 (ppm)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23.32
Me
N
O
O
210
200
190
180
170
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140
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100
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80
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40
30
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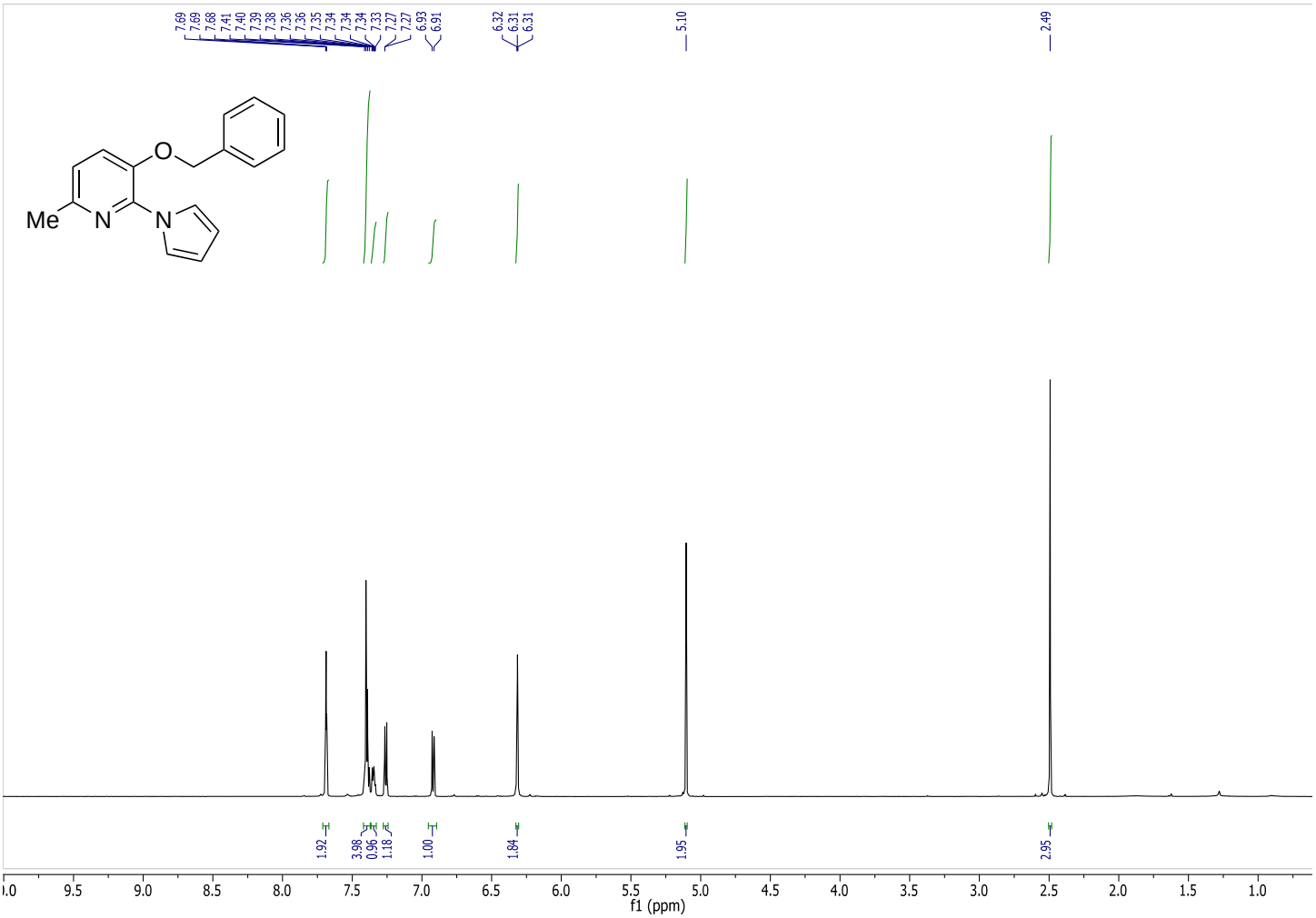
f1 (ppm)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7.27
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6.91
6.32
6.31
6.31
5.10
2.49
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Me
N
N
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0.96
1.18
1.00
1.84
1.95
2.95
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8.0
7.5
7.0
6.5
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3.5
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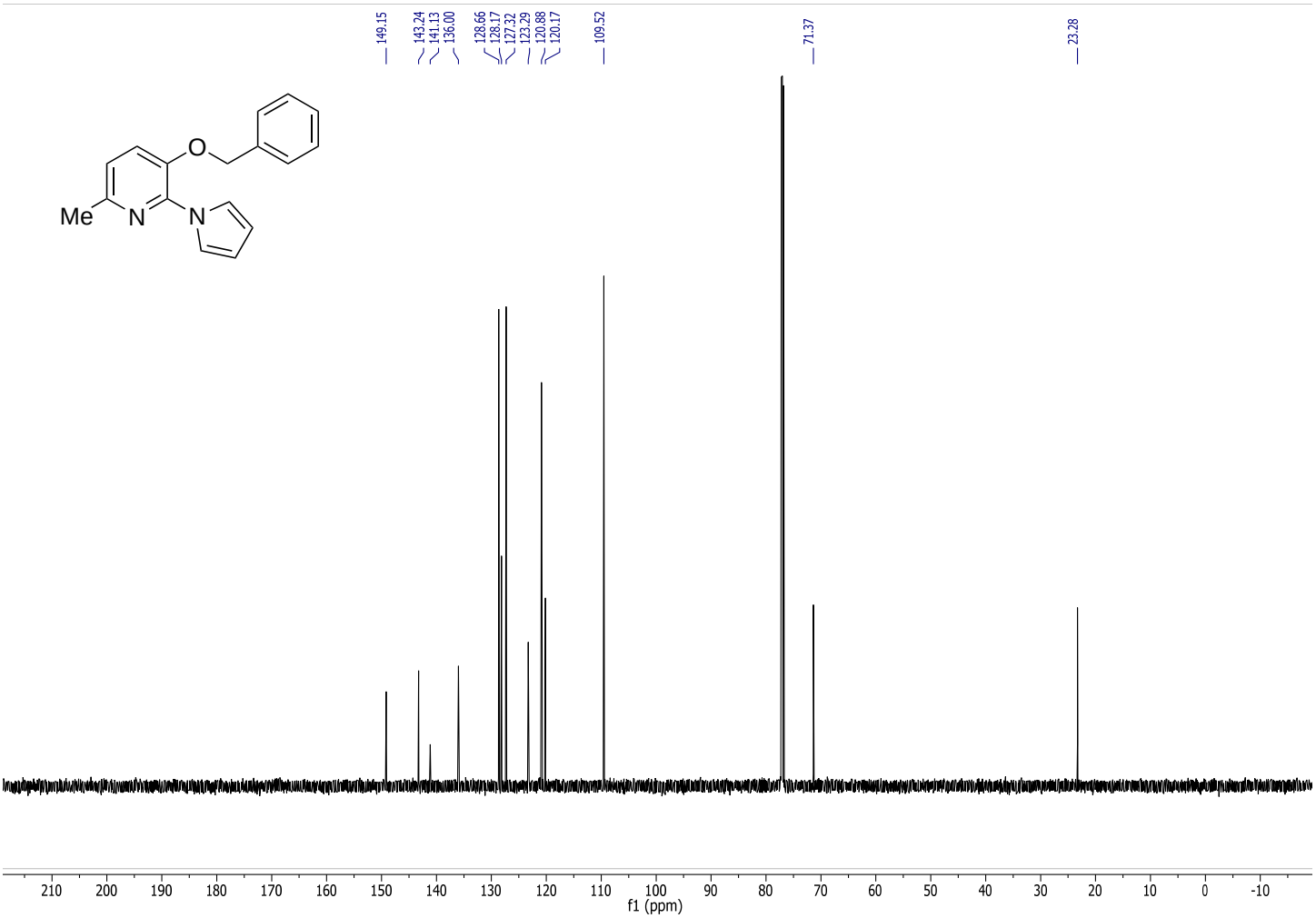
1.0
f1 (ppm)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O
Me
N
N
210
200
190
180
170
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100
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80
70
60
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40
30
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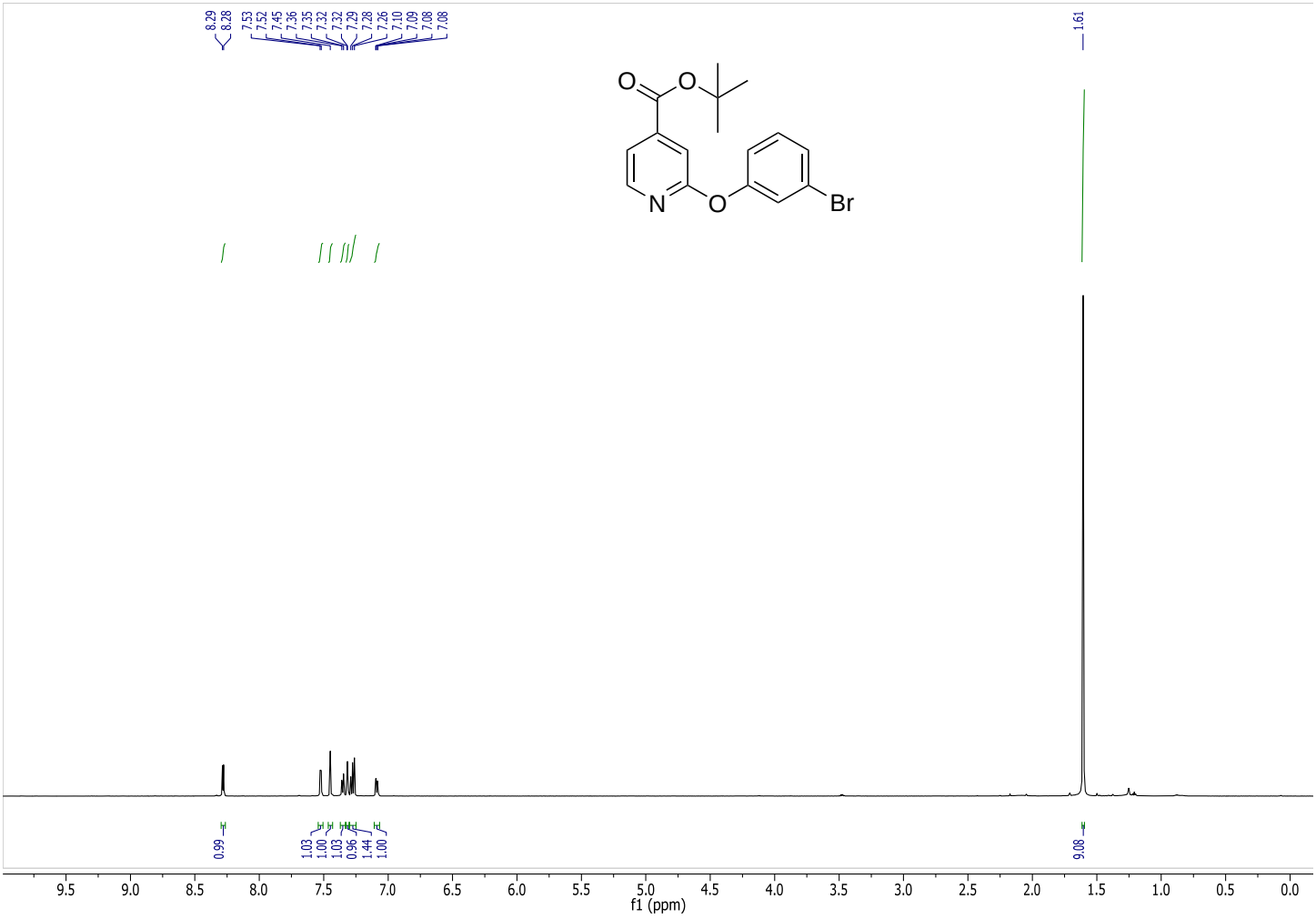
0
-10
f1 (ppm)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7.32
7.32
7.29
7.28
7.26
7.10
7.09
7.08
7.08
1.61
O
O
N
O
Br
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1.03
1.00
1.03
0.96
1.44
1.00
9.08
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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3.0
2.5
2.0
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1.0
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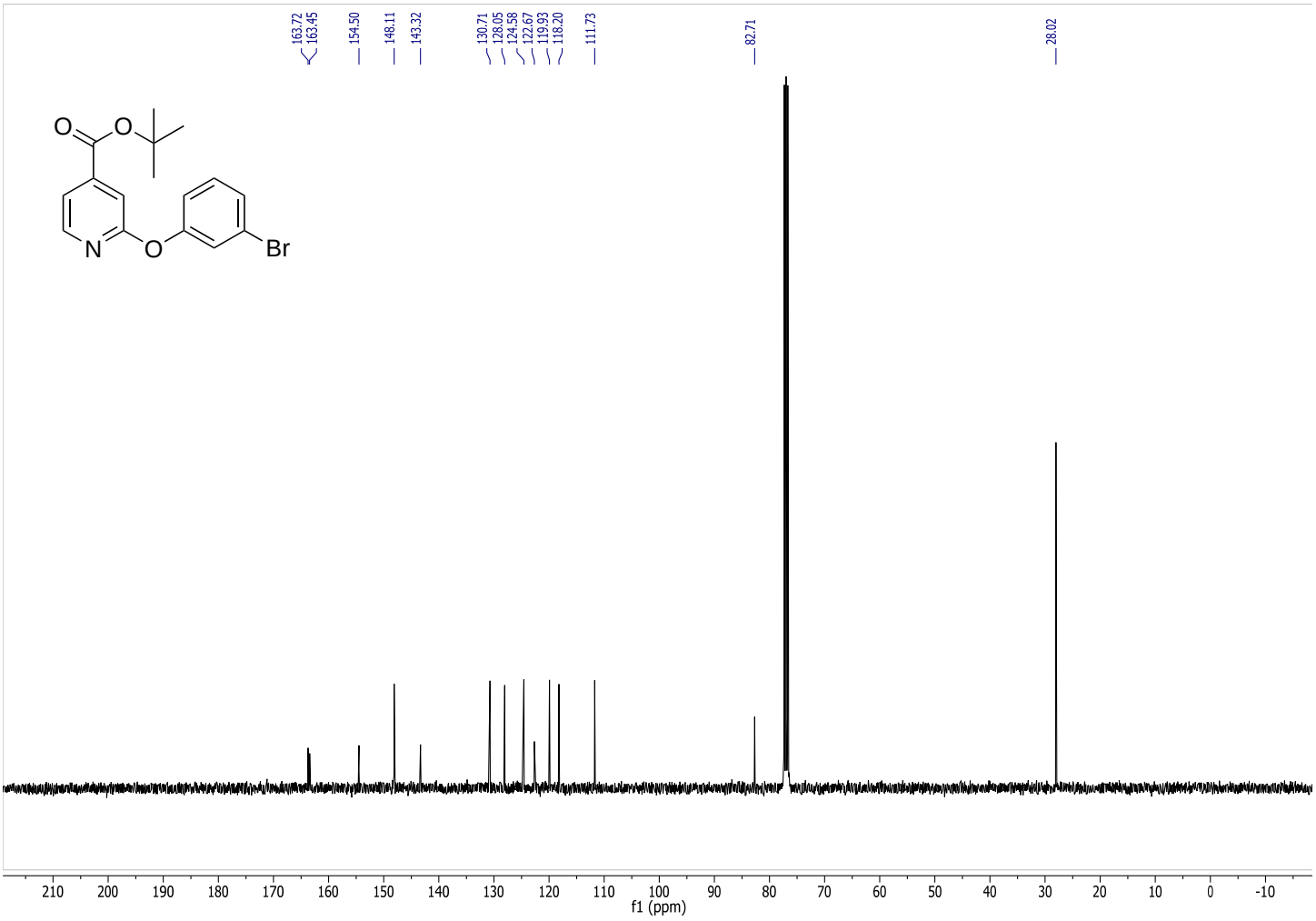
0.0
f1 (ppm)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118.20
111.73
82.71
28.02
O
O
N
O
Br
210
200
190
180
170
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140
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120
110
100
90
80
70
60
50
40
30
20
10
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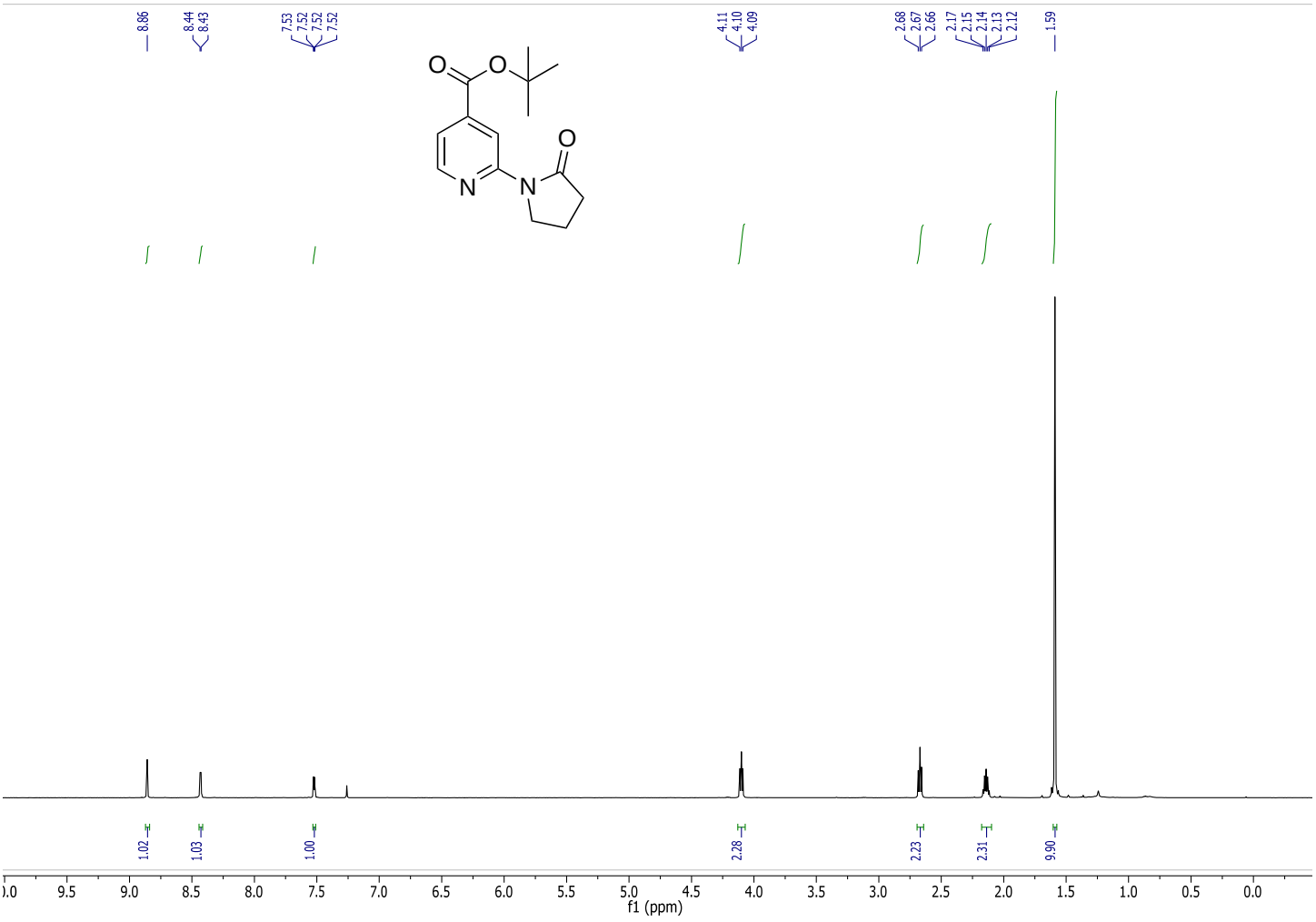
-10
f1 (ppm)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2.66
2.17
2.15
2.14
2.13
2.12
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O
N
N
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1.03
1.00
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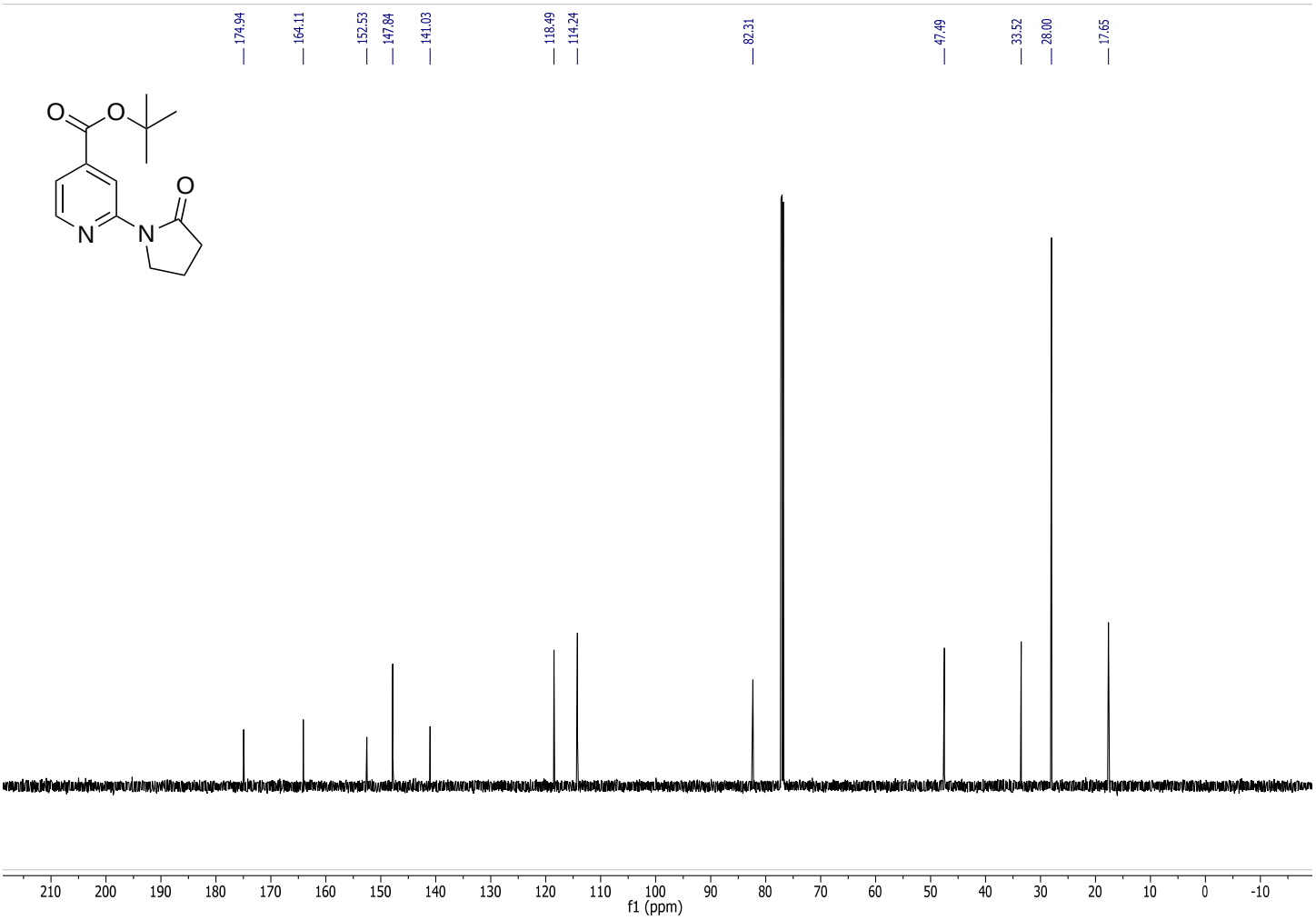
2.23
2.31
9.90
f1 (ppm)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33.52
28.00
17.65
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O
O
N
N
210
200
190
180
170
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120
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100
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80
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60
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40
30
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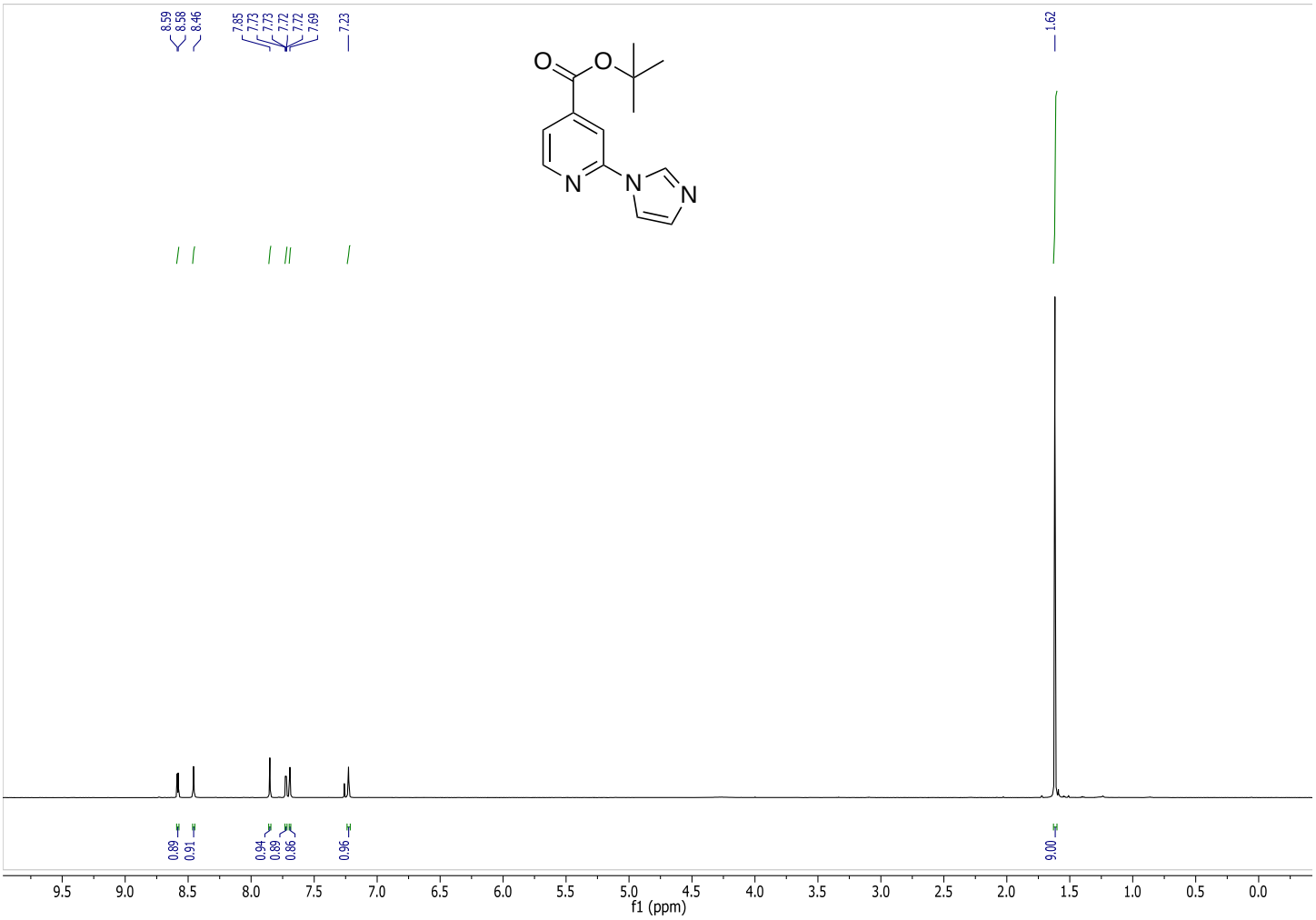
0
-10
f1 (ppm)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7.72
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7.23
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N
N
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0.94
0.89
0.86
0.96
9.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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2.5
2.0
1.5
1.0
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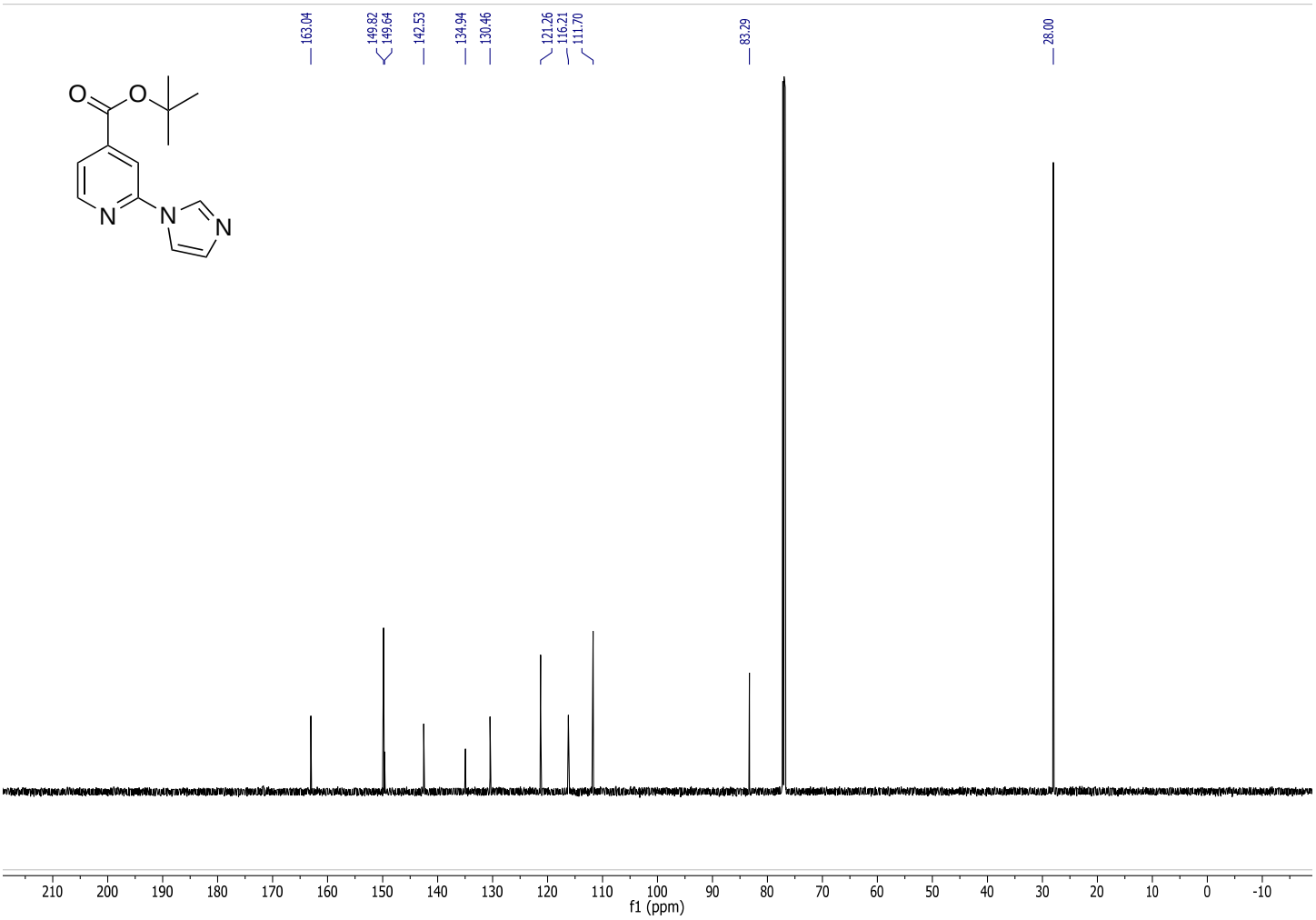
0.0
f1 (ppm)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83.29
28.00
O
O
N
N
N
210
200
190
180
170
160
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140
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120
110
100
90
80
70
60
50
40
30
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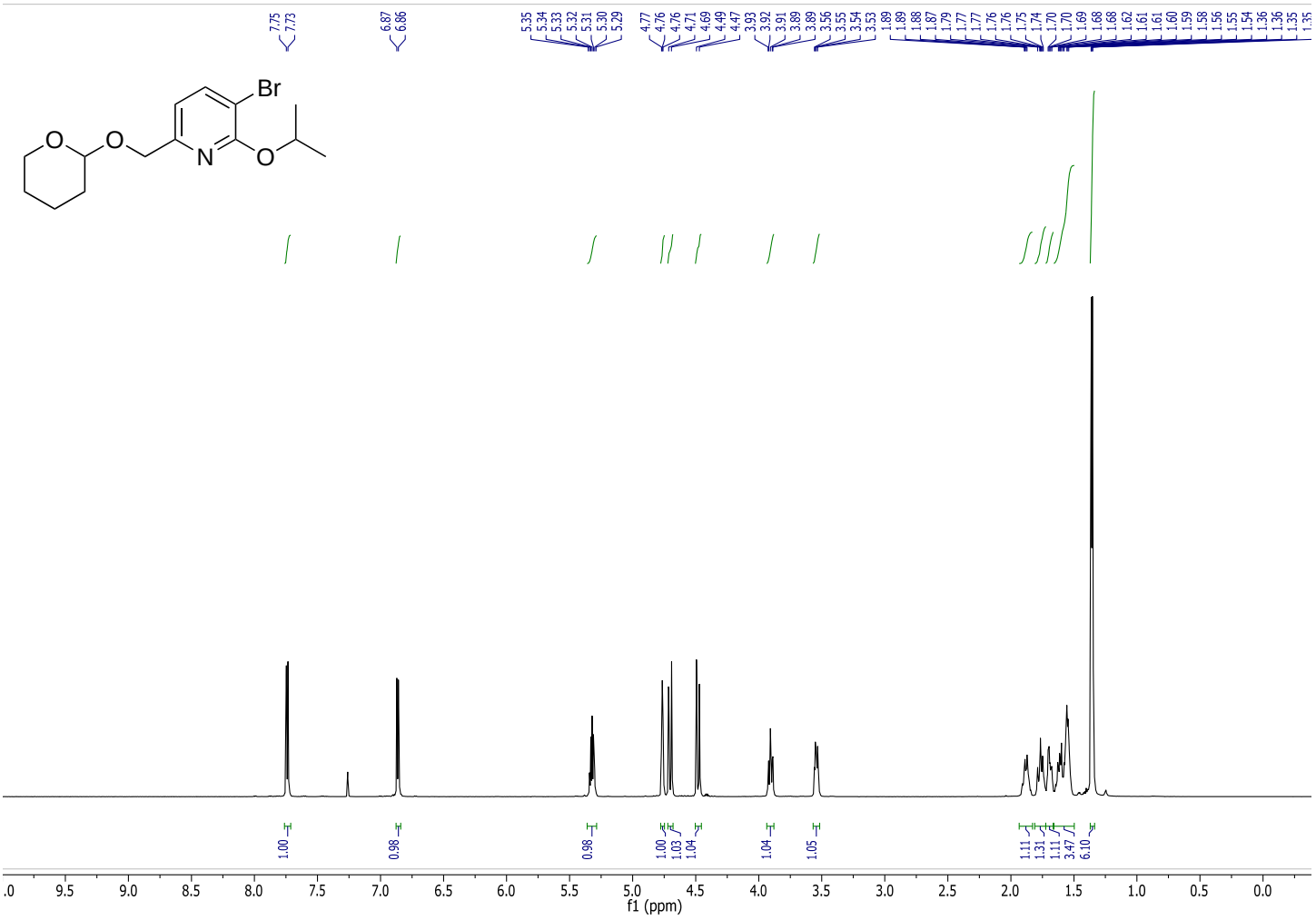
0
-10
f1 (ppm)


Br
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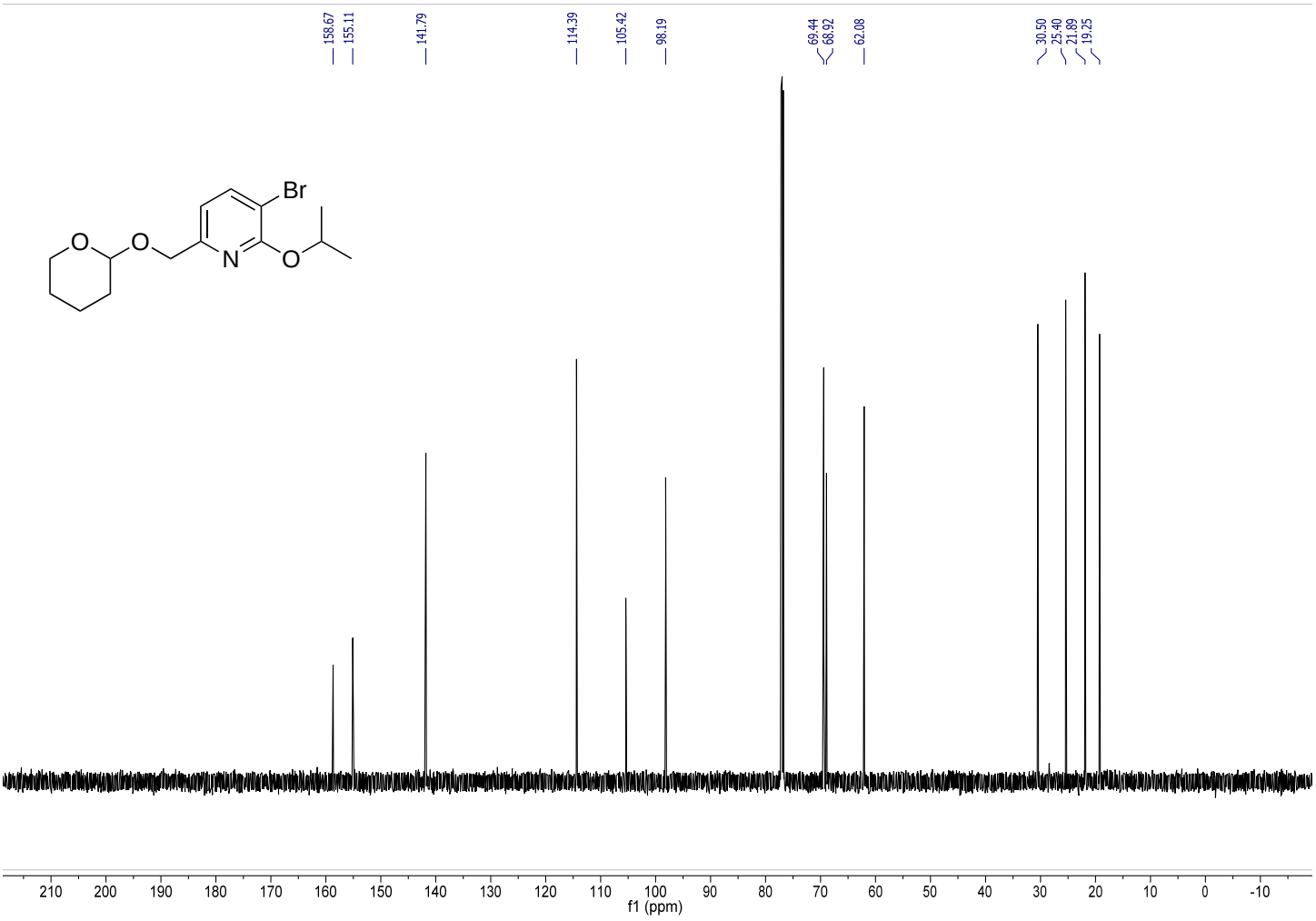
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68.92
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30.50
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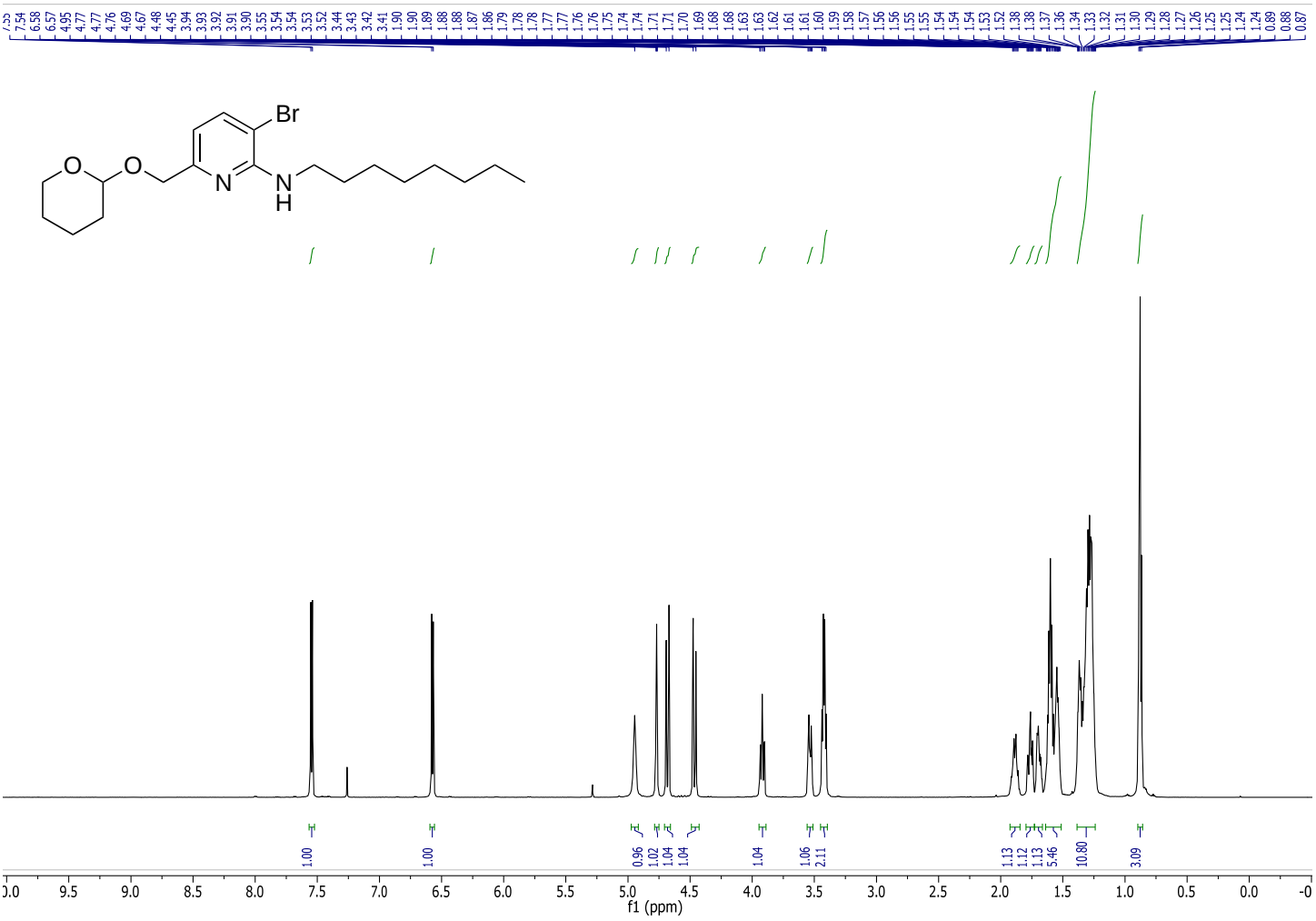
Br
O
O
N
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Br
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O
N
N
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1.00
0.96
1.02
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1.04
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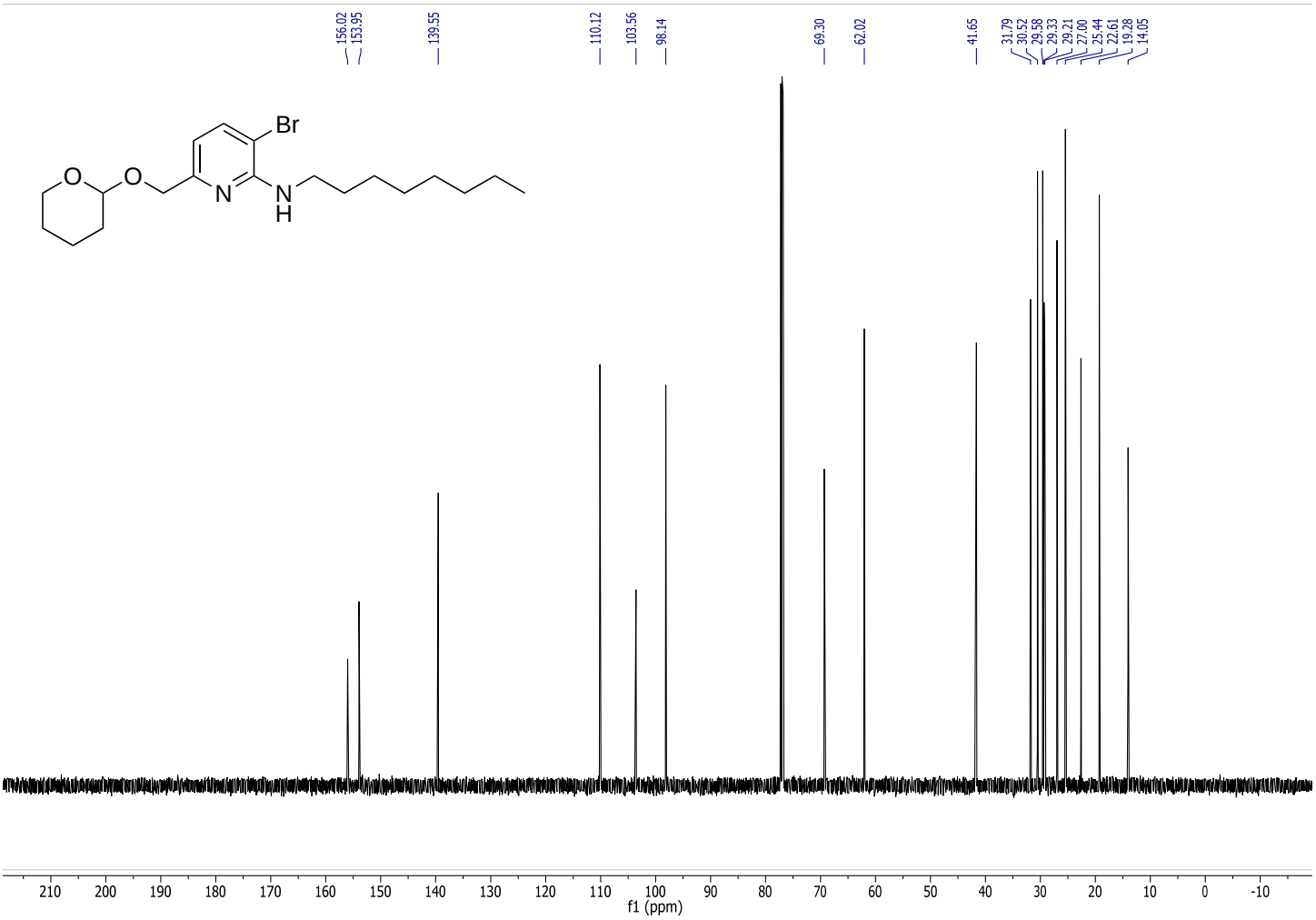
1.13
1.12
1.13
5.46
10.80
3.09
f1 (ppm)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62.02
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29.33
29.21
27.00
25.44
22.61
19.28
14.05
Br
O
O
N
N
H
210
200
190
180
170
160
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140
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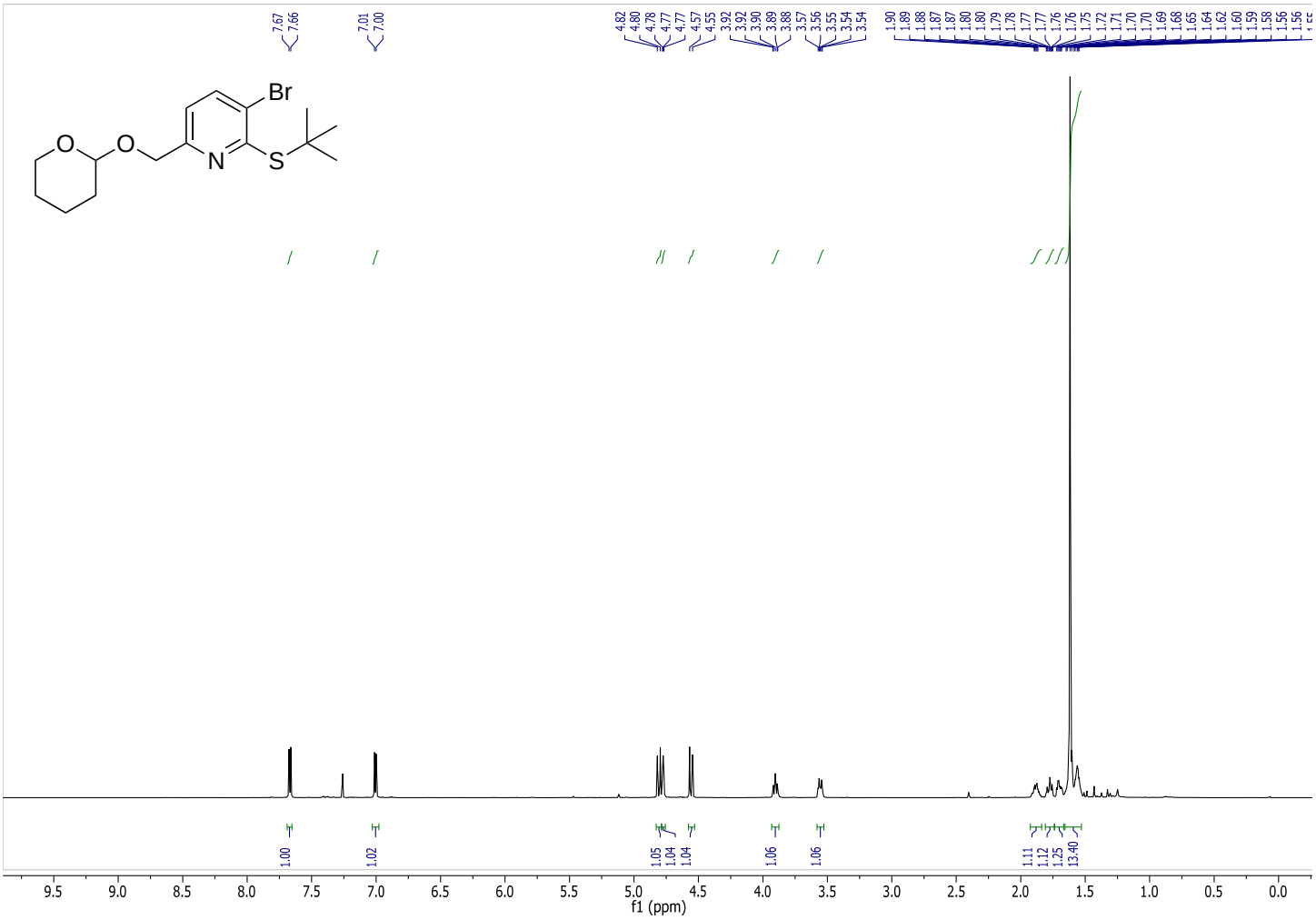
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


Br
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S
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3.92
3.92
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3.89
3.88
3.57
3.56
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3.54
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1.58
1.56
1.56
1.00
1.02
1.05
1.04
1.04
1.06
1.06
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1.12
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7.5
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6.5
6.0
5.5
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2.5
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1.0
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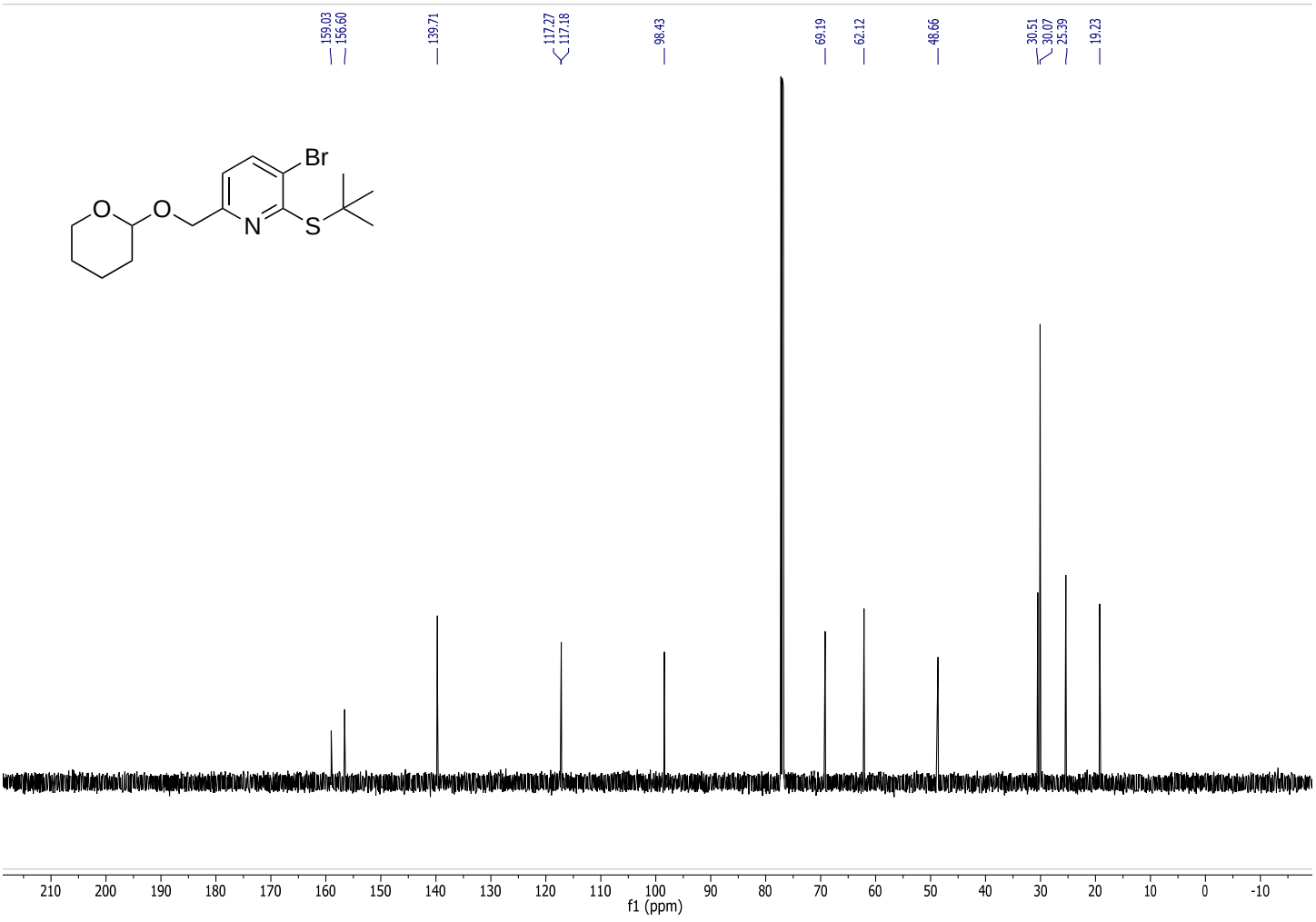
0.0
f1 (ppm)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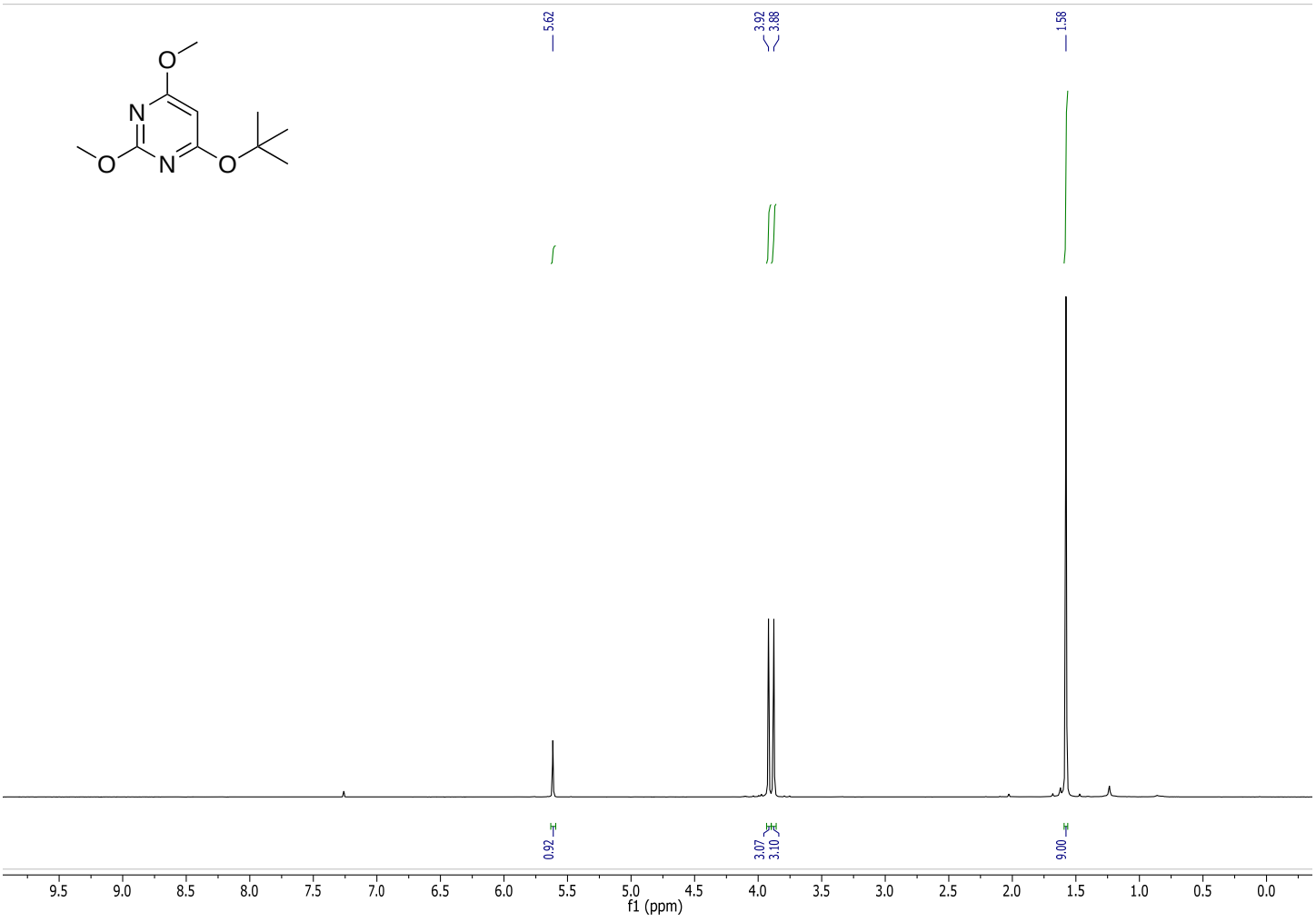
30.07
25.39
19.23
Br
O
O
N
S
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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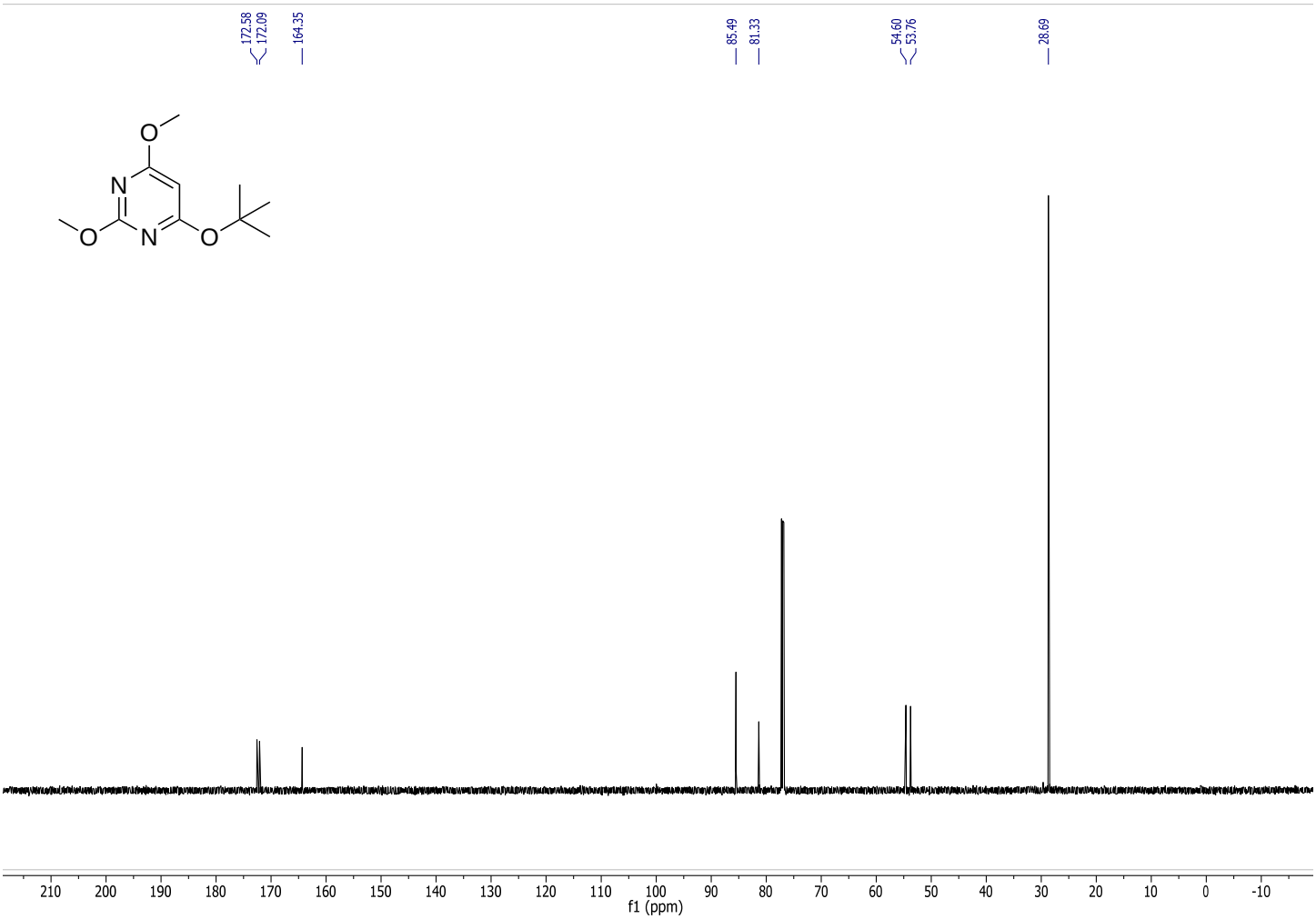
3.88
1.58
0.92
3.07
3.10
9.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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172.09
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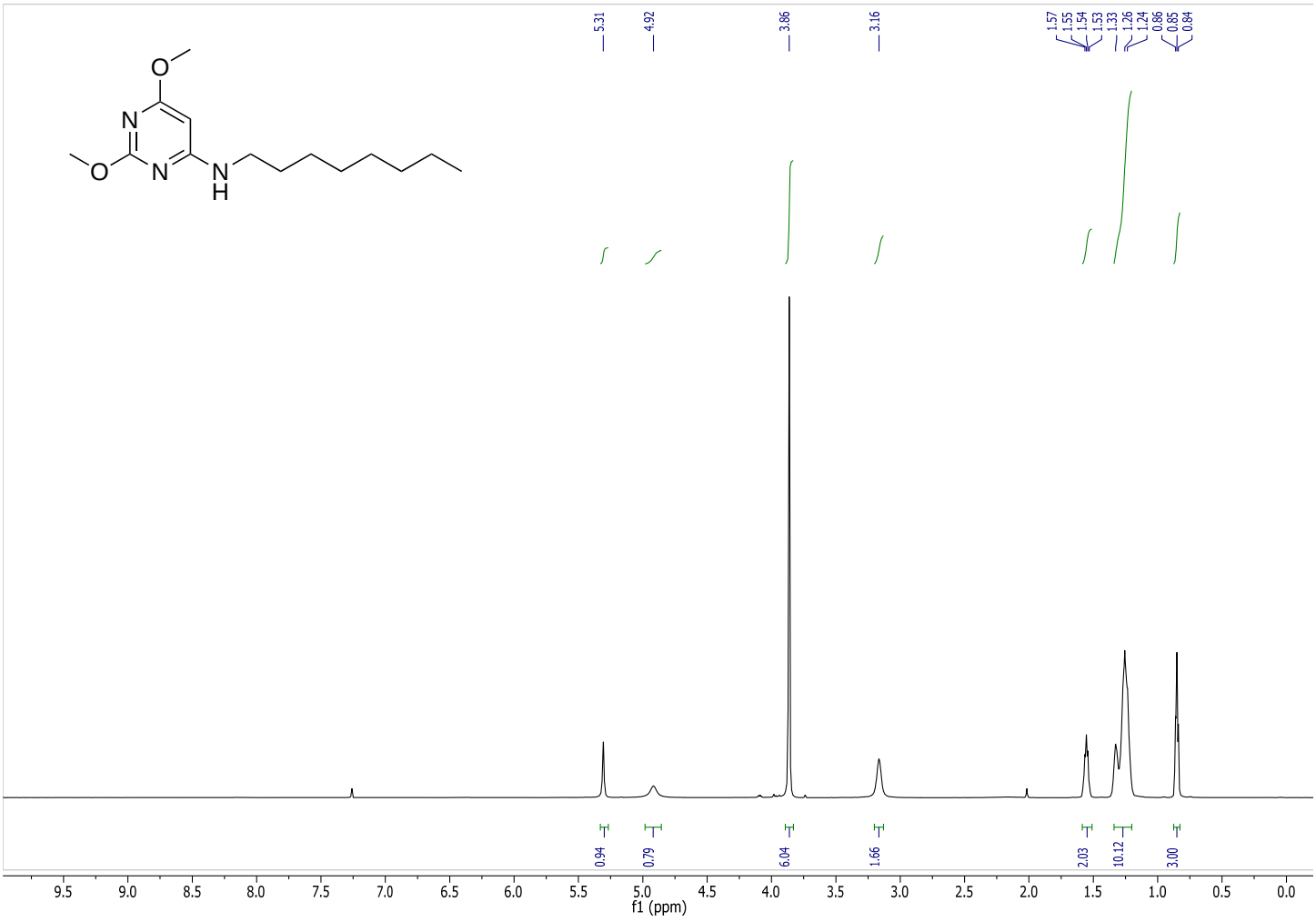
85.49
81.33
54.60
53.76
28.69
O
N
O
N
O
f1 (ppm)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4.92
3.86
3.16
1.57
1.55
1.54
1.53
1.33
1.26
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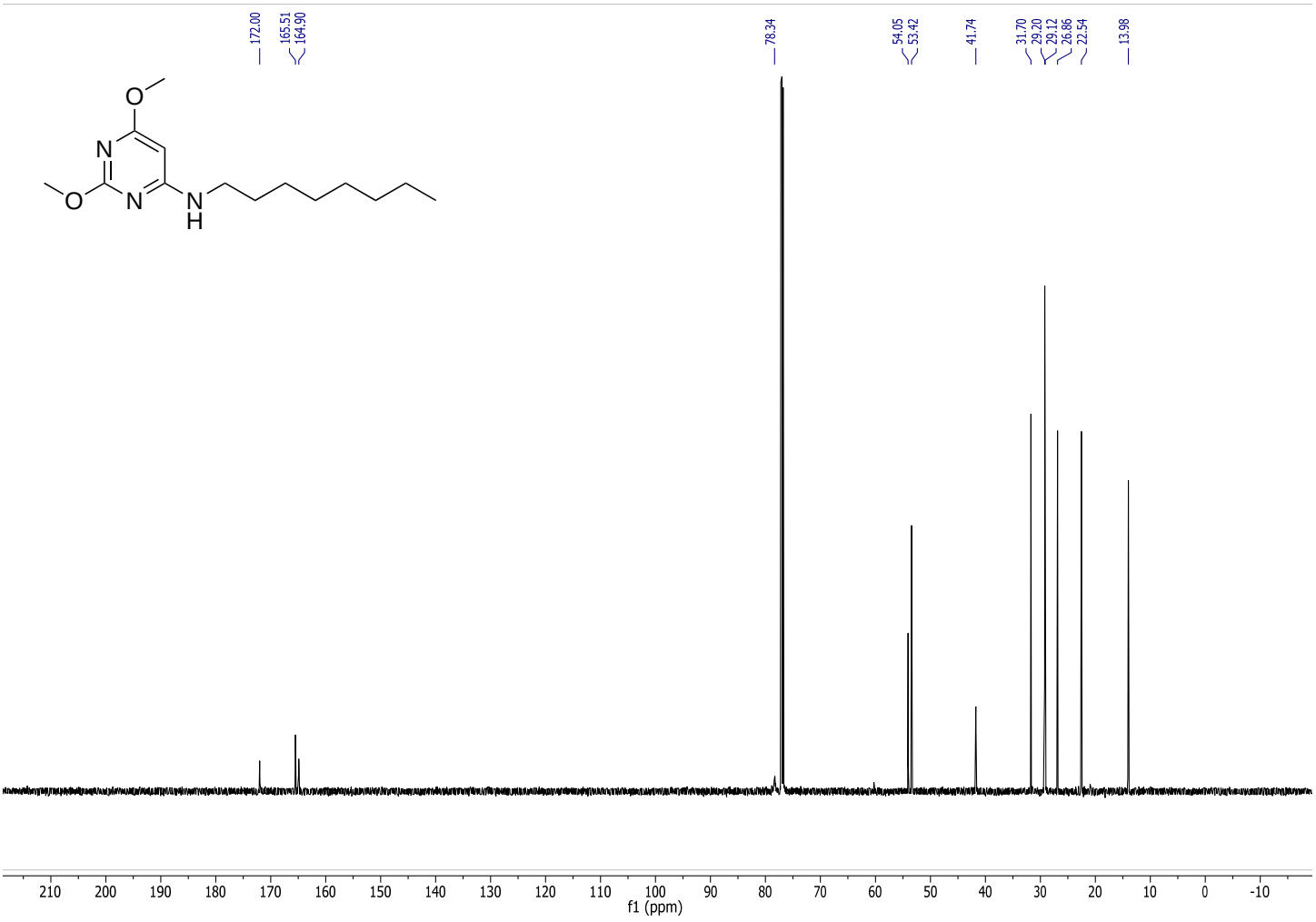
0.84
0.94
0.79
6.04
1.66
2.03
10.12
3.00
f1 (ppm)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164.90
78.34
54.05
53.42
41.74
31.70
29.20
29.12
26.86
22.54
13.98
O
N
O
N
N
H
210
200
190
180
170
160
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140
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120
110
100
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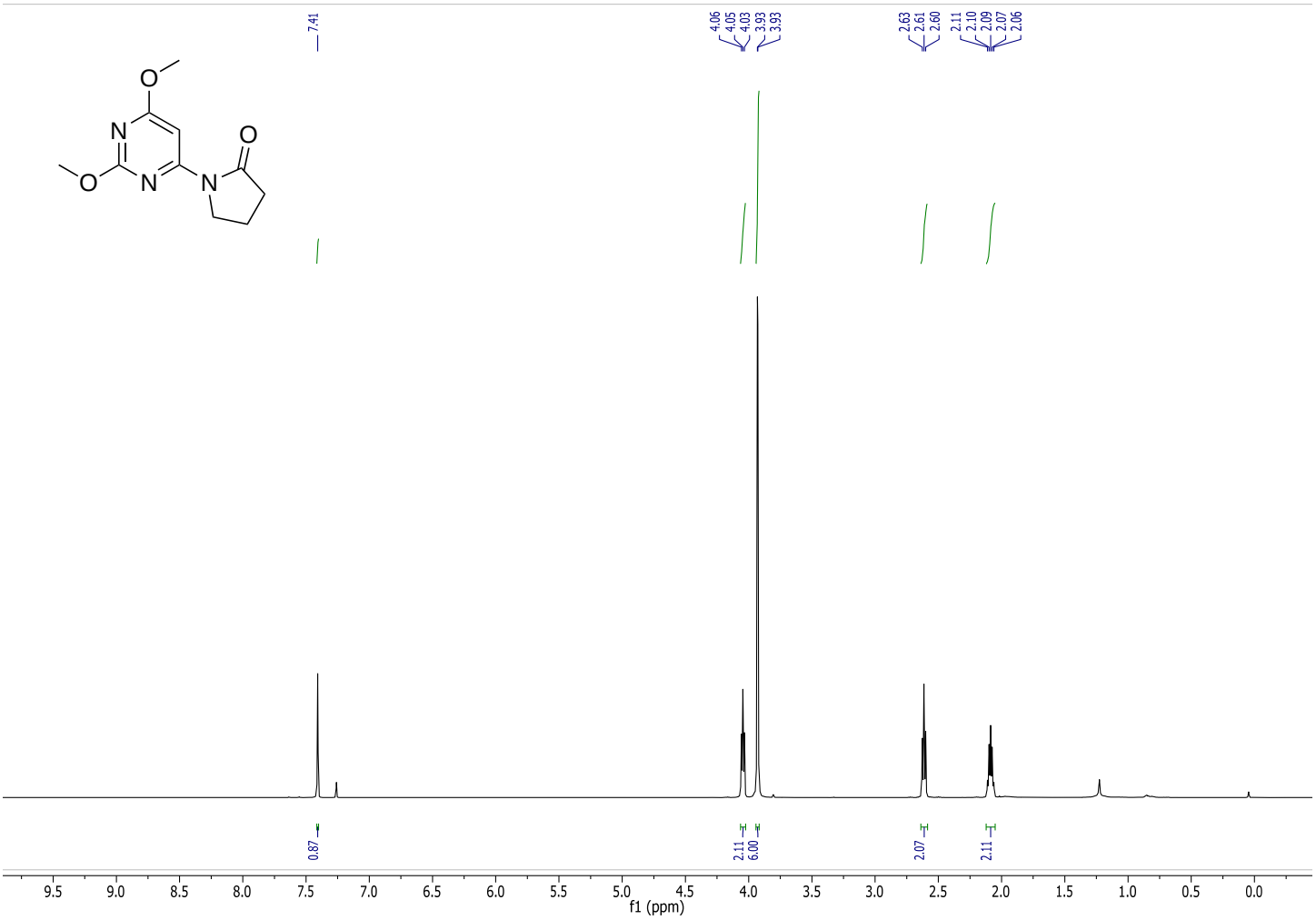
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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4.06
4.05
4.03
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3.93
2.63
2.61
2.60
2.11
2.10
2.09
2.07
2.06
O
N
O
N
N
O
0.87
2.11
6.00
2.07
2.11
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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3.5
3.0
2.5
2.0
1.5
1.0
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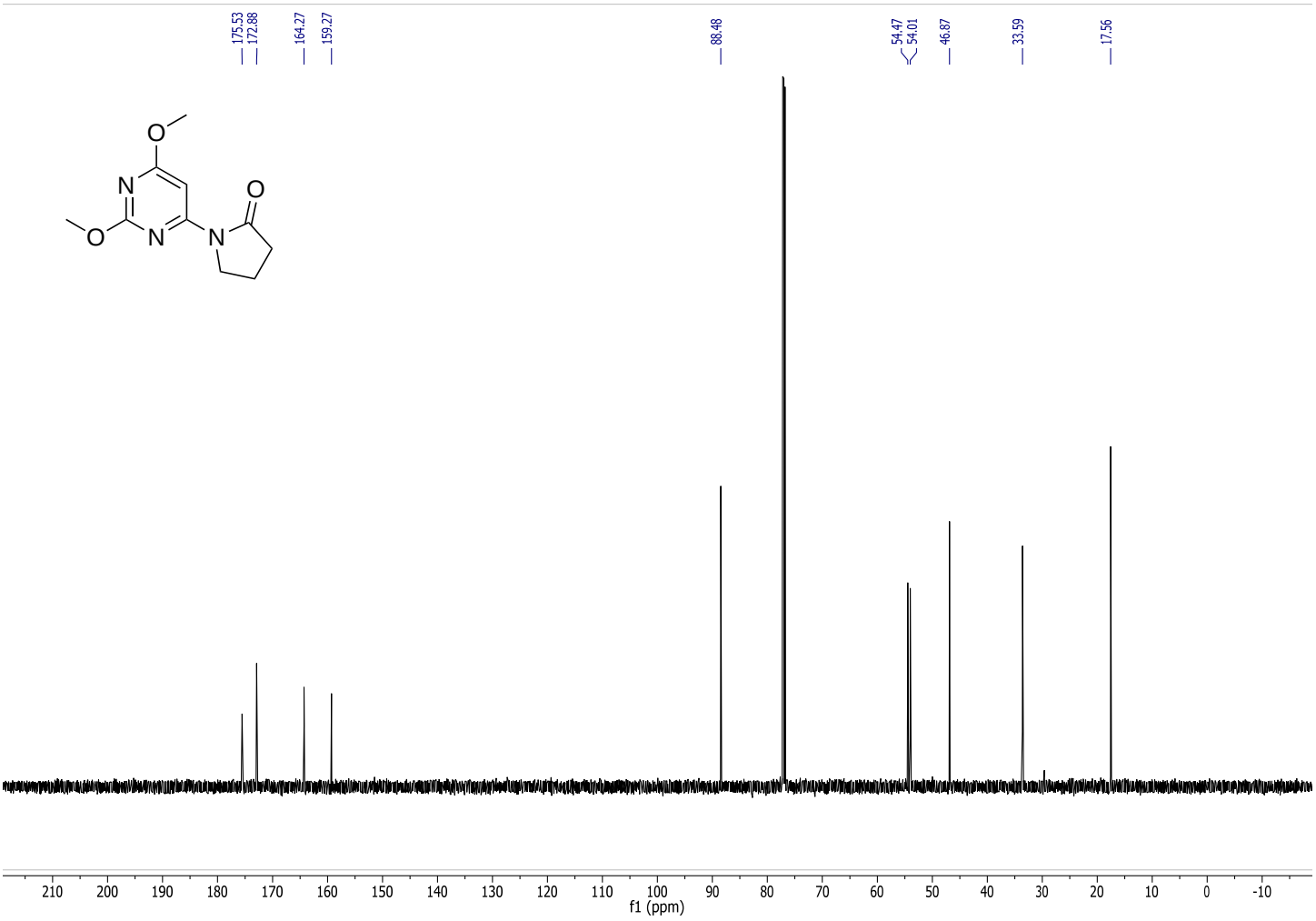
f1 (ppm)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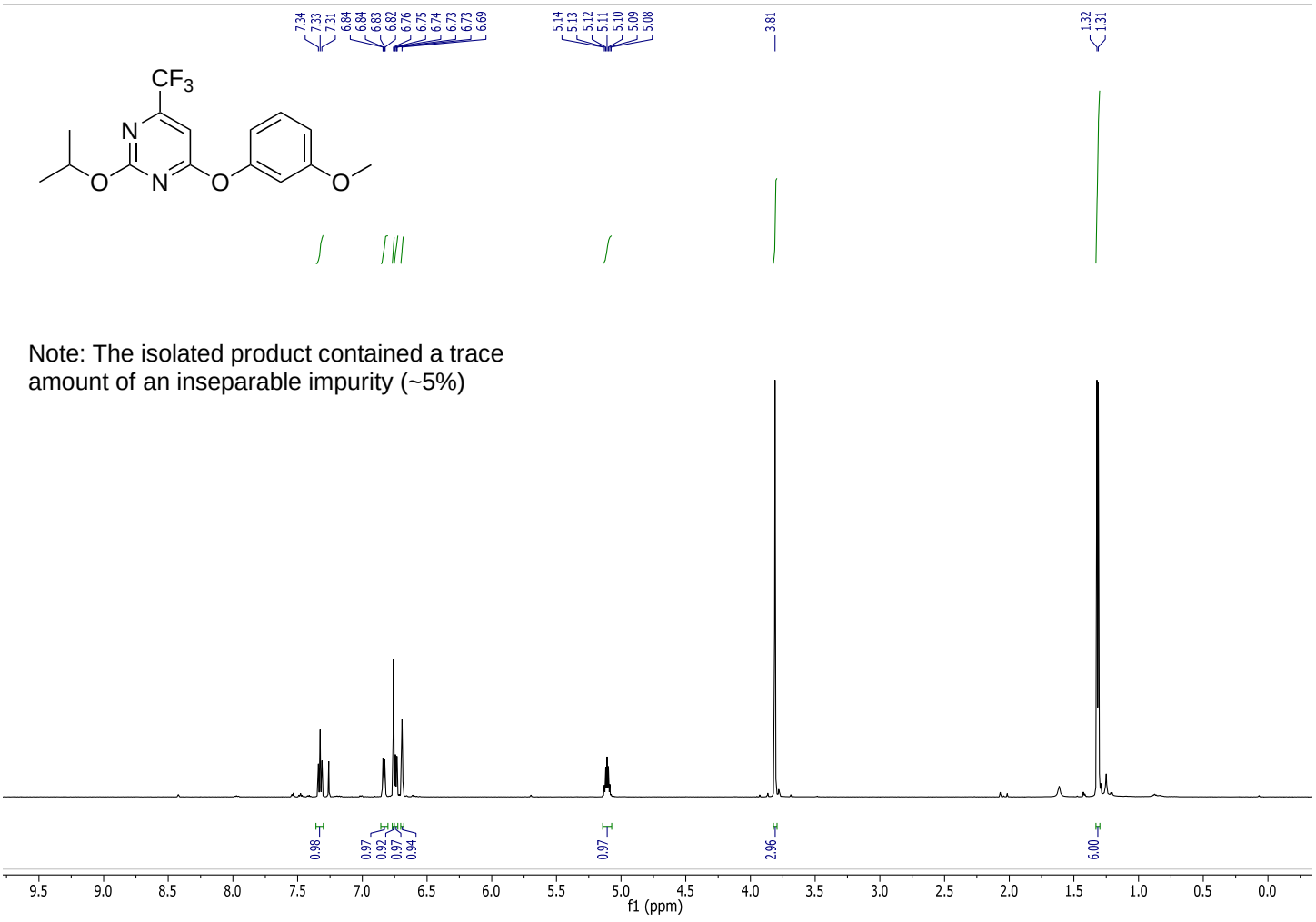
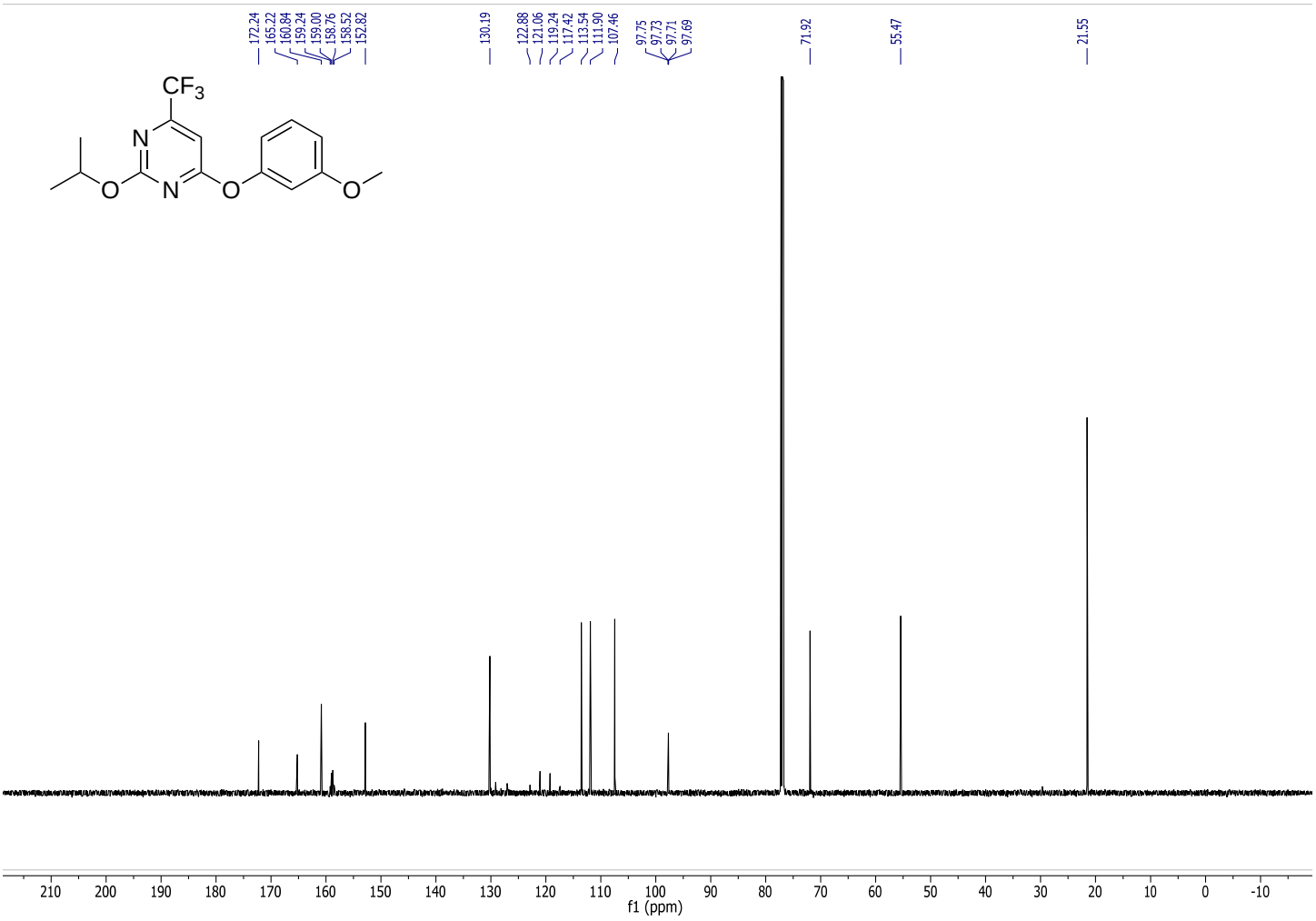
172.88
164.27
159.27
88.48
54.47
54.01
46.87
33.59
17.56
O
N
O
N
N
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



Note: The isolated product contained a trace amount of an inseparable impurity (~5%)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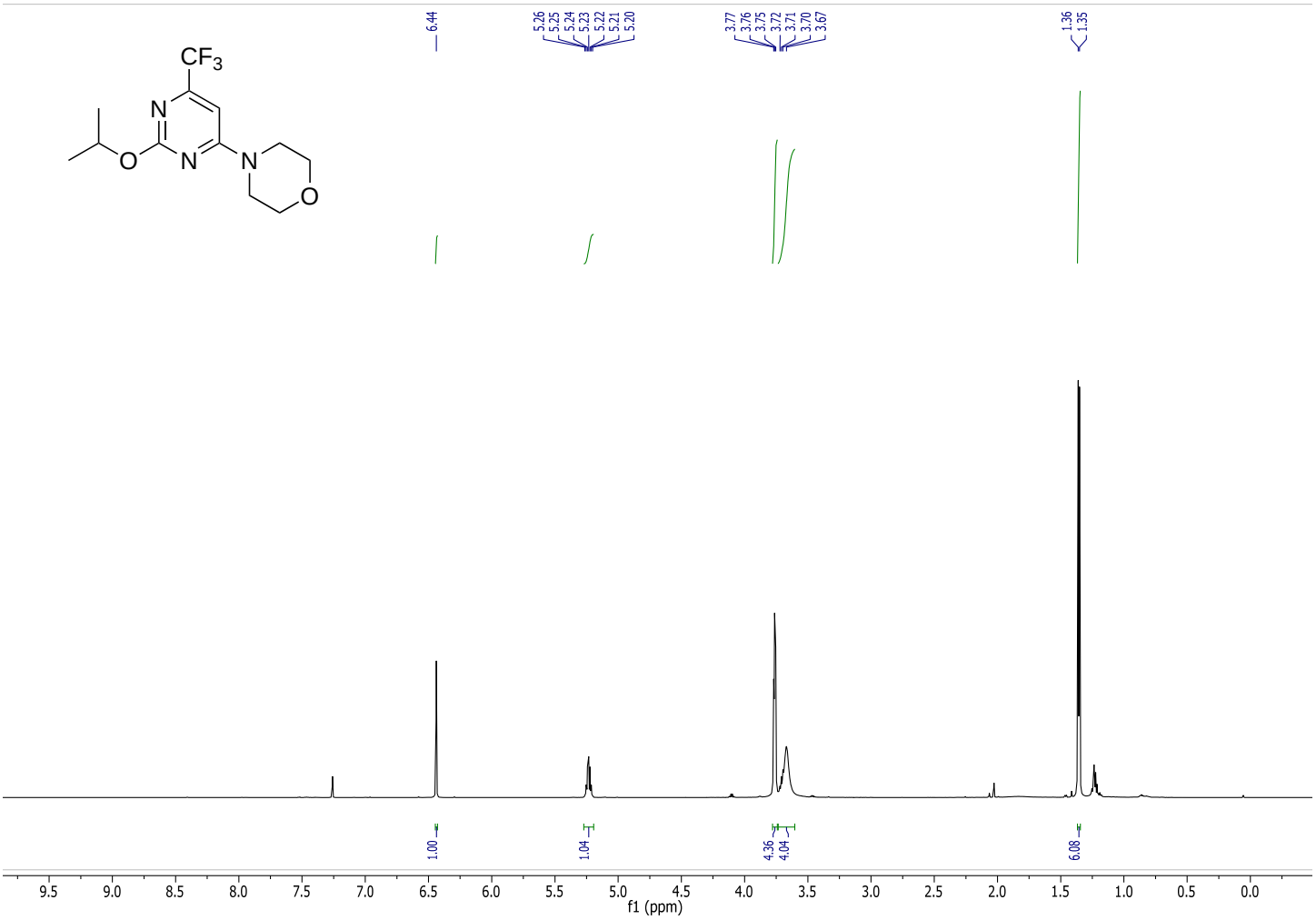
165.22
160.84
159.24
159.00
158.76
158.52
152.82
130.19
122.88
121.06
119.24
117.42
113.54
111.90
107.46
97.75
97.73
97.71
97.69
71.92
55.47
21.55
CF3
N
O
N
O
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


CF3
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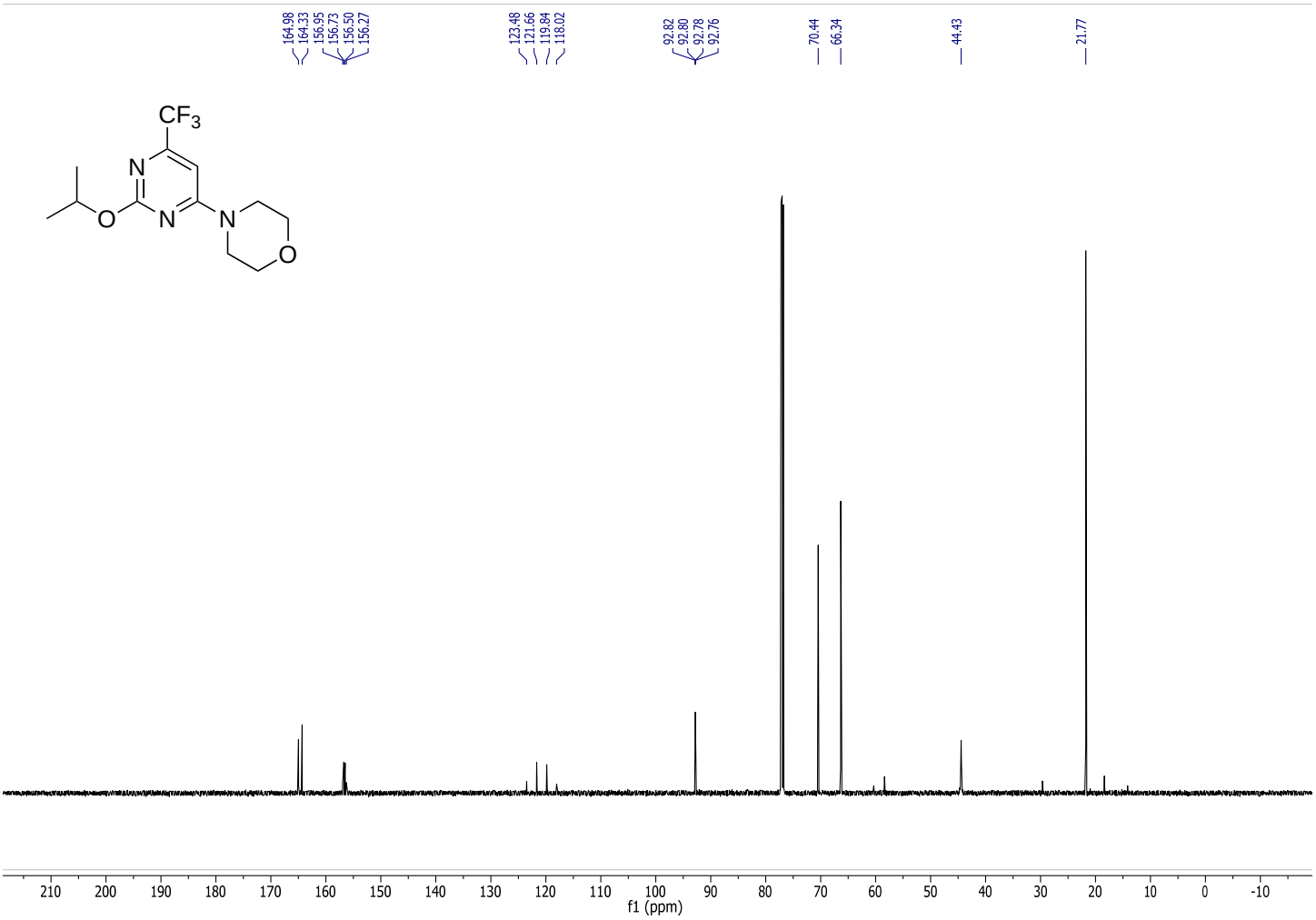
N
N
O
6.44
5.26
5.25
5.24
5.23
5.22
5.21
5.20
3.77
3.76
3.75
3.72
3.71
3.70
3.67
1.36
1.35
1.00
1.04
4.36
4.04
6.08
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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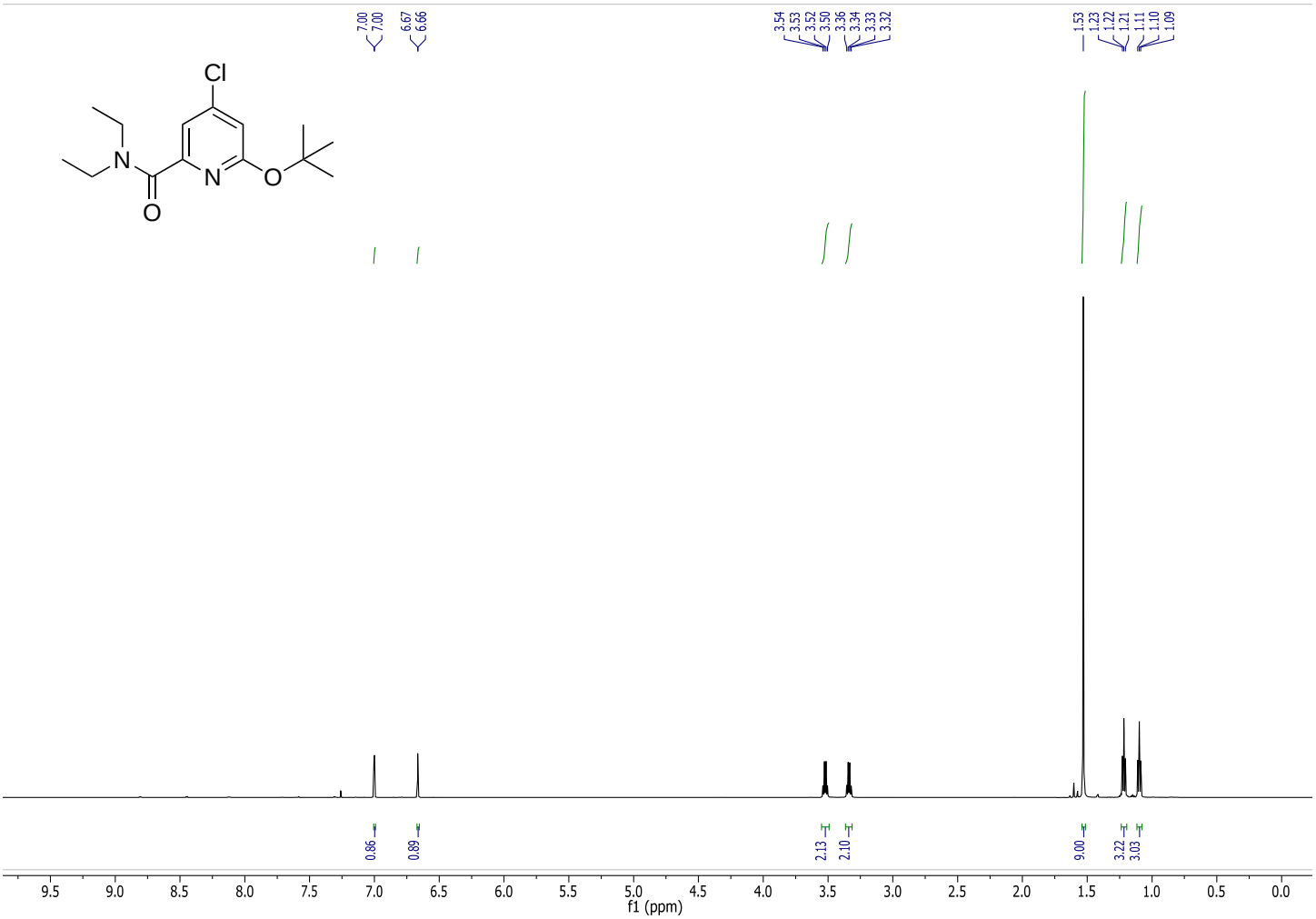
164.33
156.95
156.73
156.50
156.27
123.48
121.66
119.84
118.02
92.82
92.80
92.78
92.76
70.44
66.34
44.43
21.77
CF3
N
O
N
N
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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O
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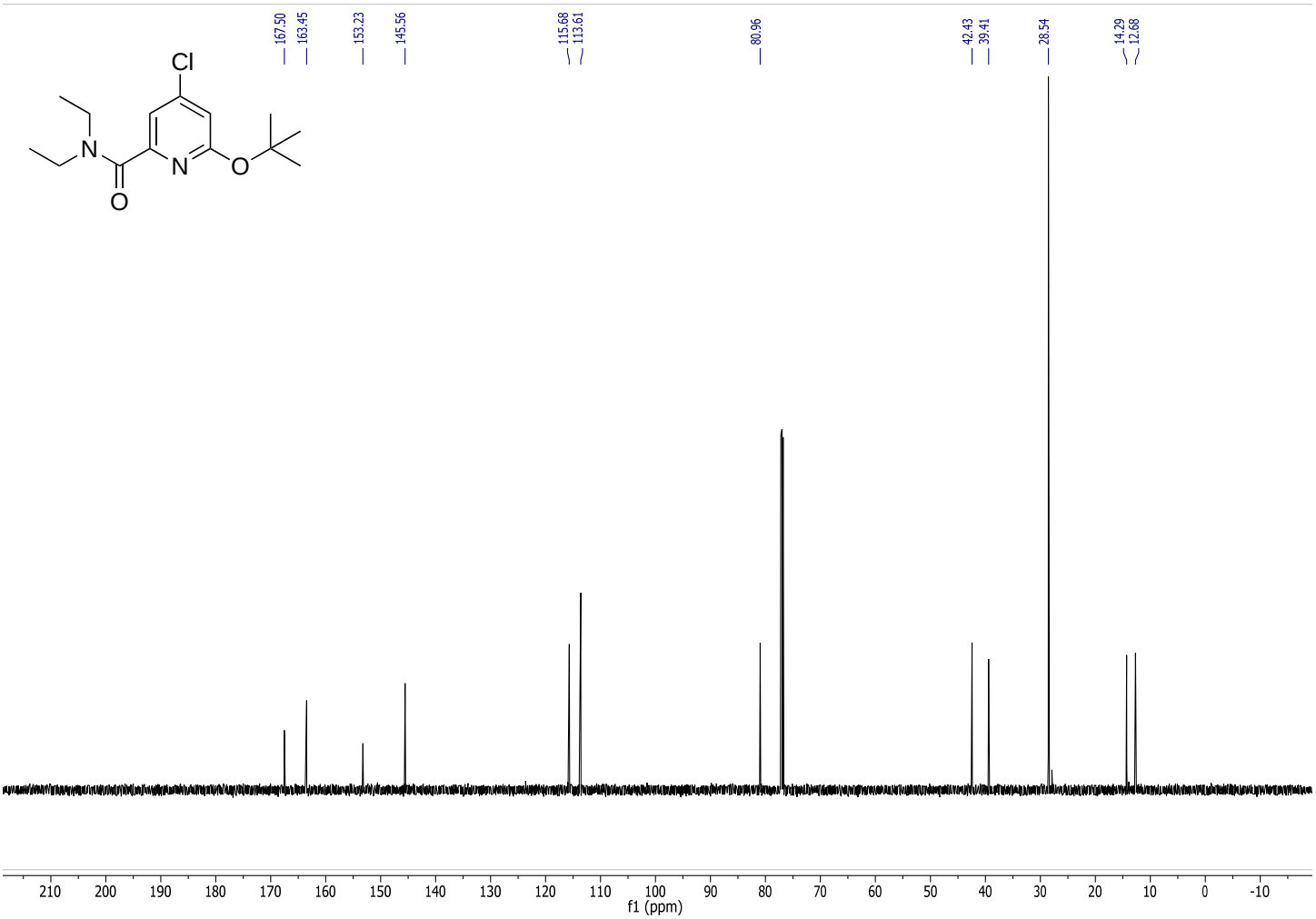
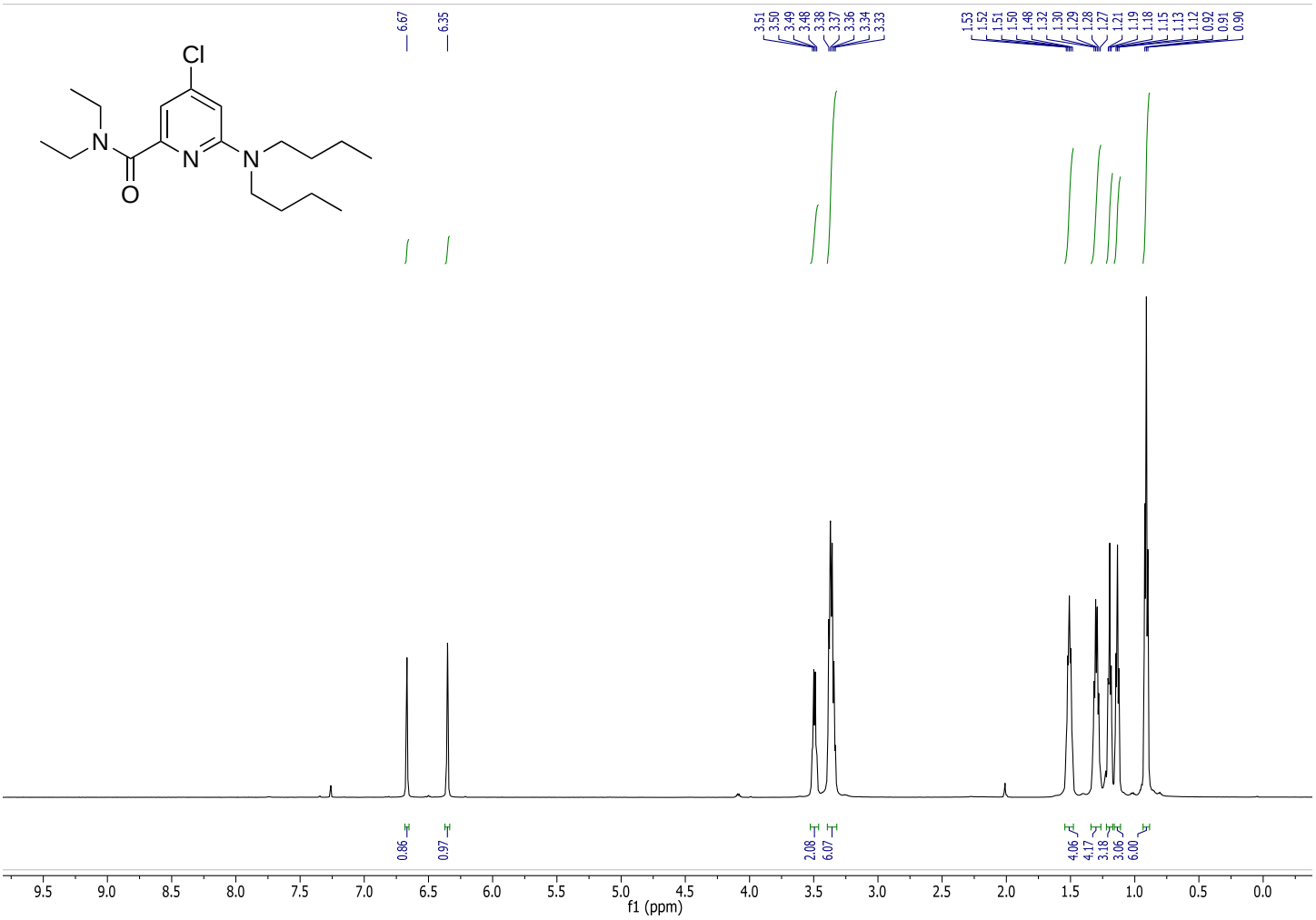
6.67
6.66
3.54
3.53
3.52
3.50
3.36
3.34
3.33
3.32
1.53
1.23
1.22
1.21
1.11
1.10
1.09
0.86
0.89
2.13
2.10
9.00
3.22
3.03
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


167.50
163.45
153.23
145.56
115.68
113.61
80.96
42.43
39.41
28.54
14.29
12.68
Cl
N
N
O
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


Cl
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N
N
O
6.67
6.35
3.51
3.50
3.49
3.48
3.38
3.37
3.36
3.34
3.33
1.53
1.52
1.51
1.50
1.48
1.32
1.30
1.29
1.28
1.27
1.21
1.19
1.18
1.15
1.13
1.12
0.92
0.91
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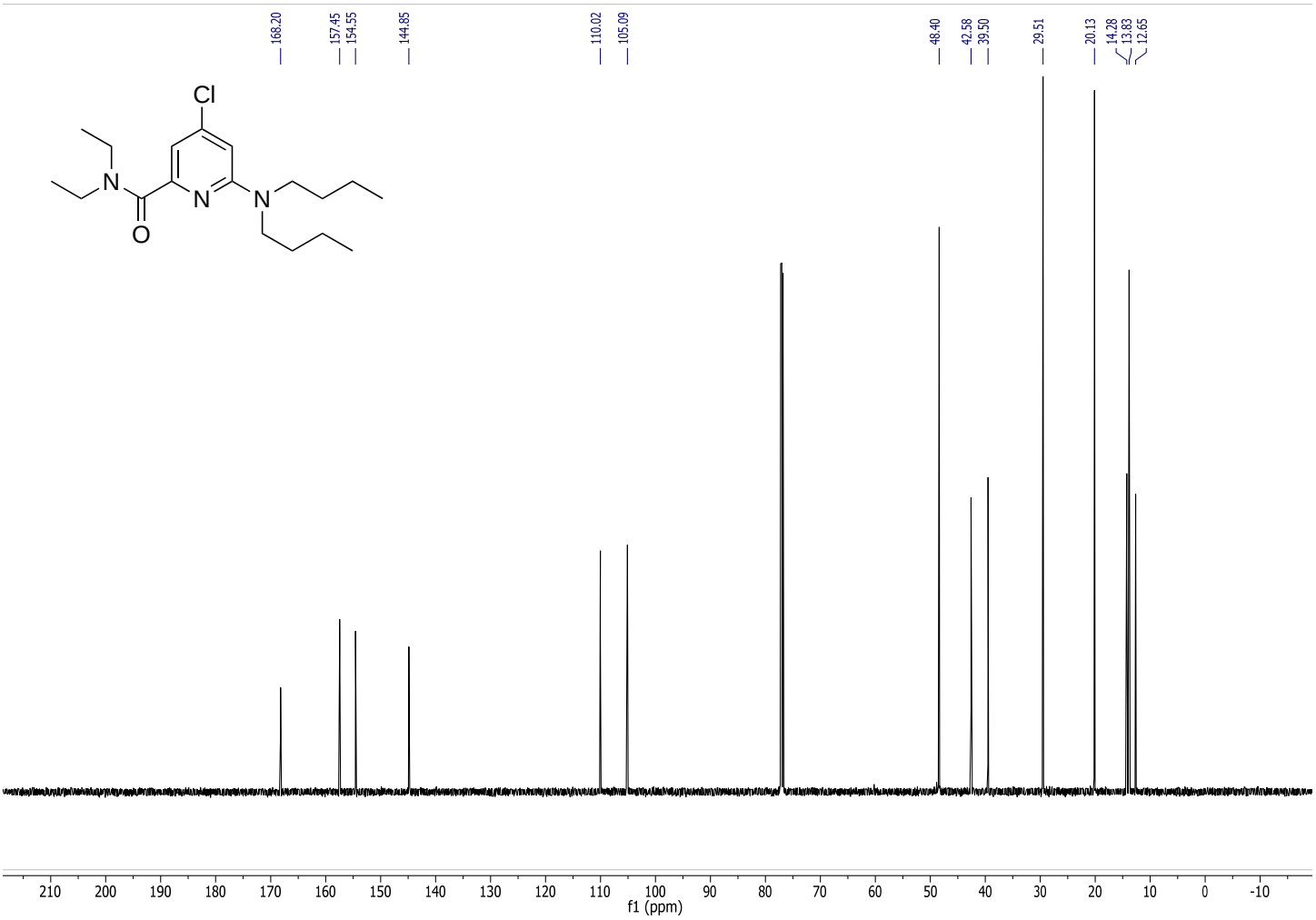
0.97
2.08
6.07
4.06
4.17
3.18
3.06
6.00
f1 (ppm)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157.45
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144.85
110.02
105.09
48.40
42.58
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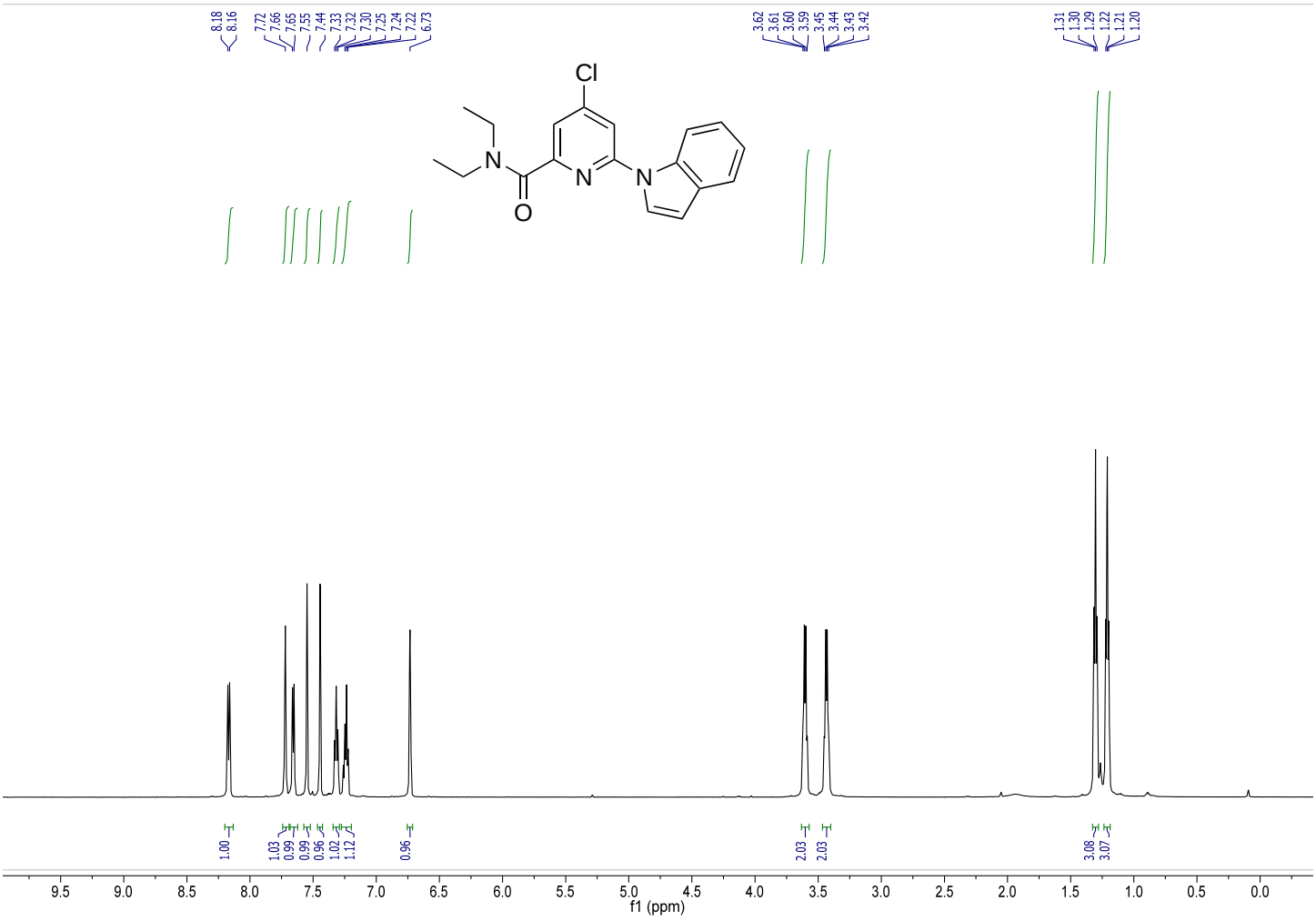
29.51
20.13
14.28
13.83
12.65
Cl
N
N
N
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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8.16
7.72
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7.65
7.55
7.44
7.33
7.32
7.30
7.25
7.24
7.22
6.73
3.62
3.61
3.60
3.59
3.45
3.44
3.43
3.42
1.31
1.30
1.29
1.22
1.21
1.20
Cl
N
O
N
N
1.00
1.03
0.99
0.99
0.96
1.02
1.12
0.96
2.03
2.03
3.08
3.07
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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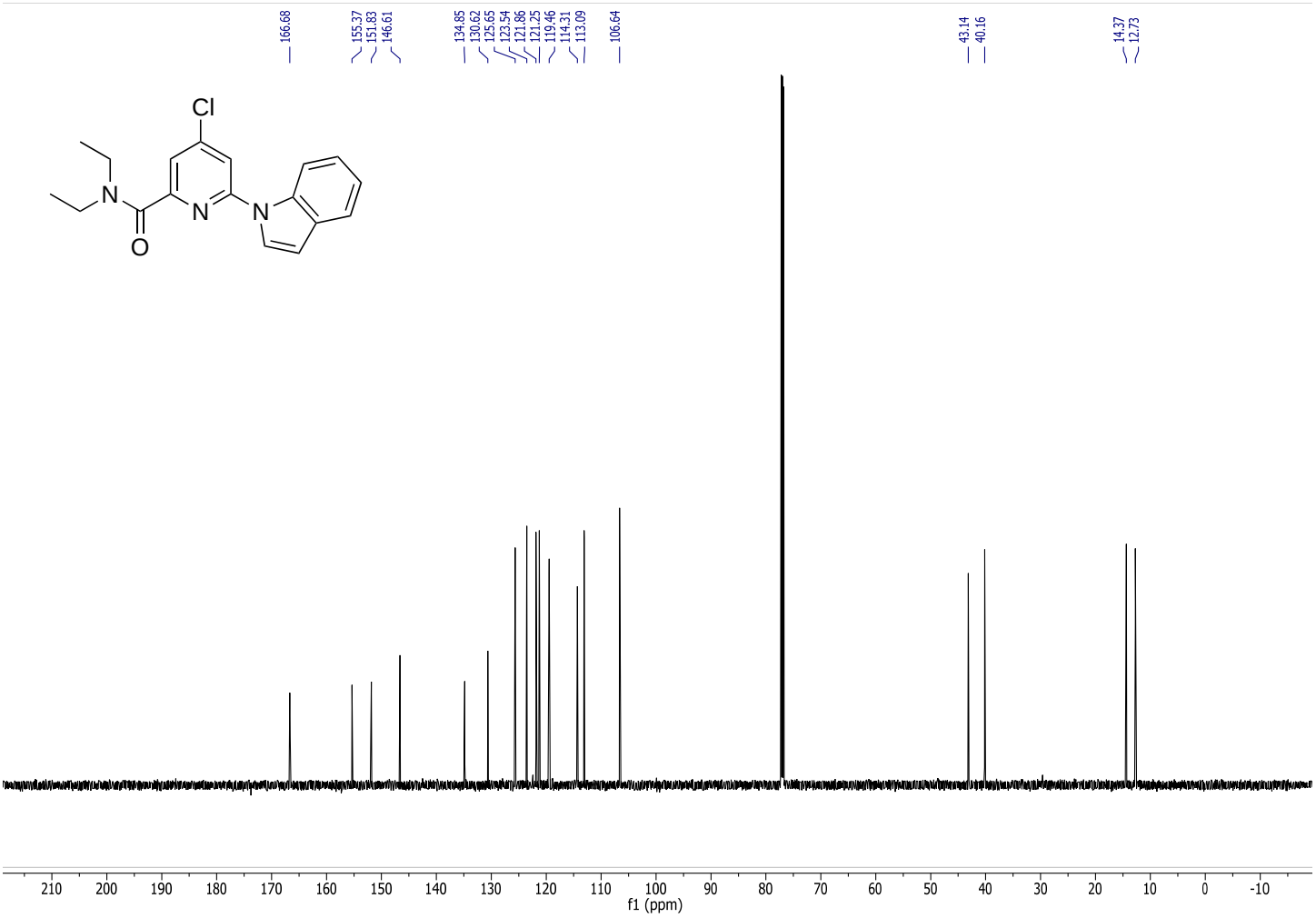
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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123.54
121.86
121.25
119.46
114.31
113.09
106.64
43.14
40.16
14.37
12.73
Cl
N
O
N
N
210
200
190
180
170
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150
140
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110
100
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80
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60
50
40
30
20
10
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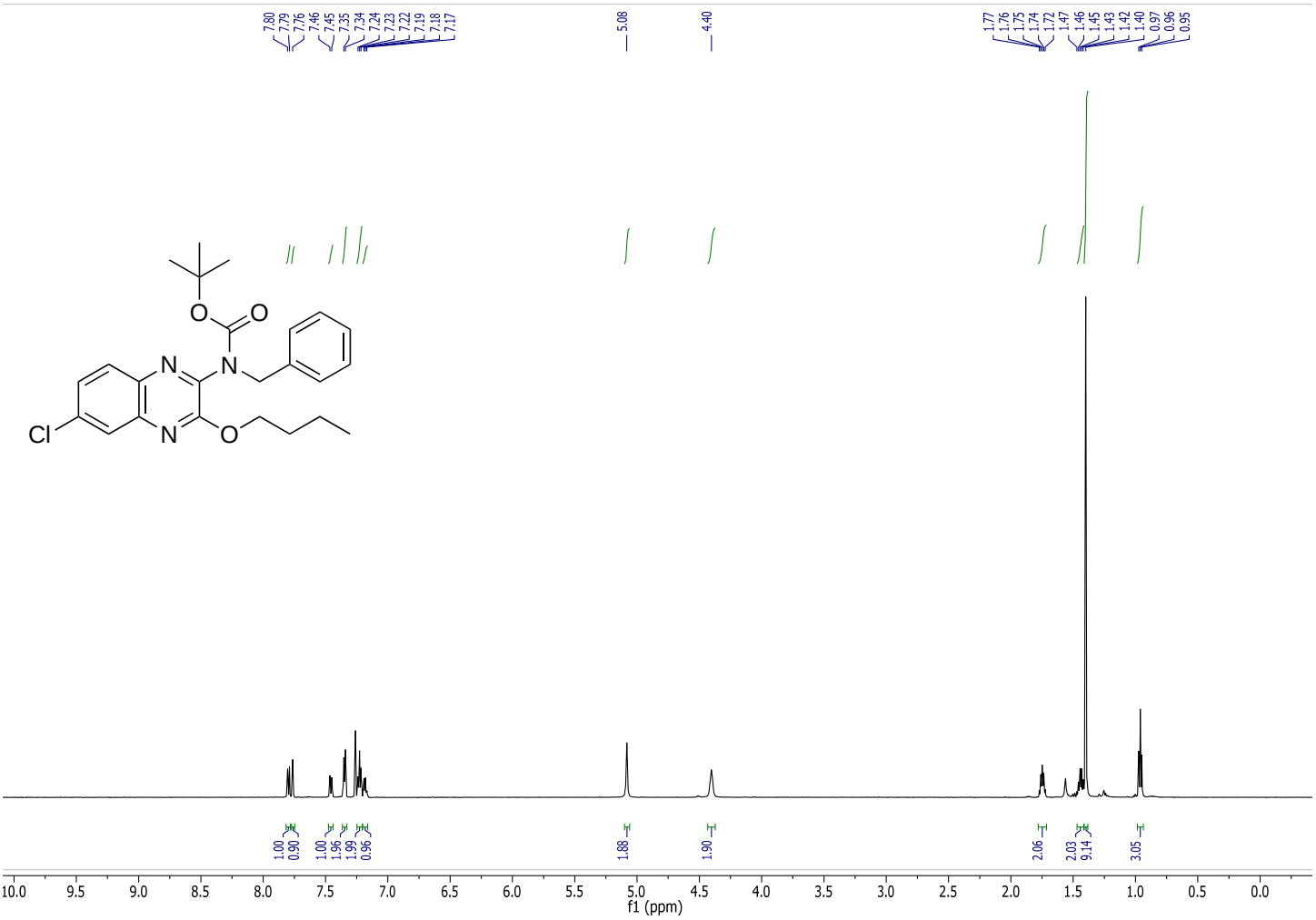
-10
f1 (ppm)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7.19
7.18
7.17
5.08
4.40
1.77
1.76
1.75
1.74
1.72
1.47
1.46
1.45
1.43
1.42
1.40
0.97
0.96
0.95
Cl
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N
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O
O
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1.00
1.96
1.99
0.96
1.88
1.90
2.06
2.03
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3.05
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9.5
9.0
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8.0
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7.0
6.5
6.0
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1.0
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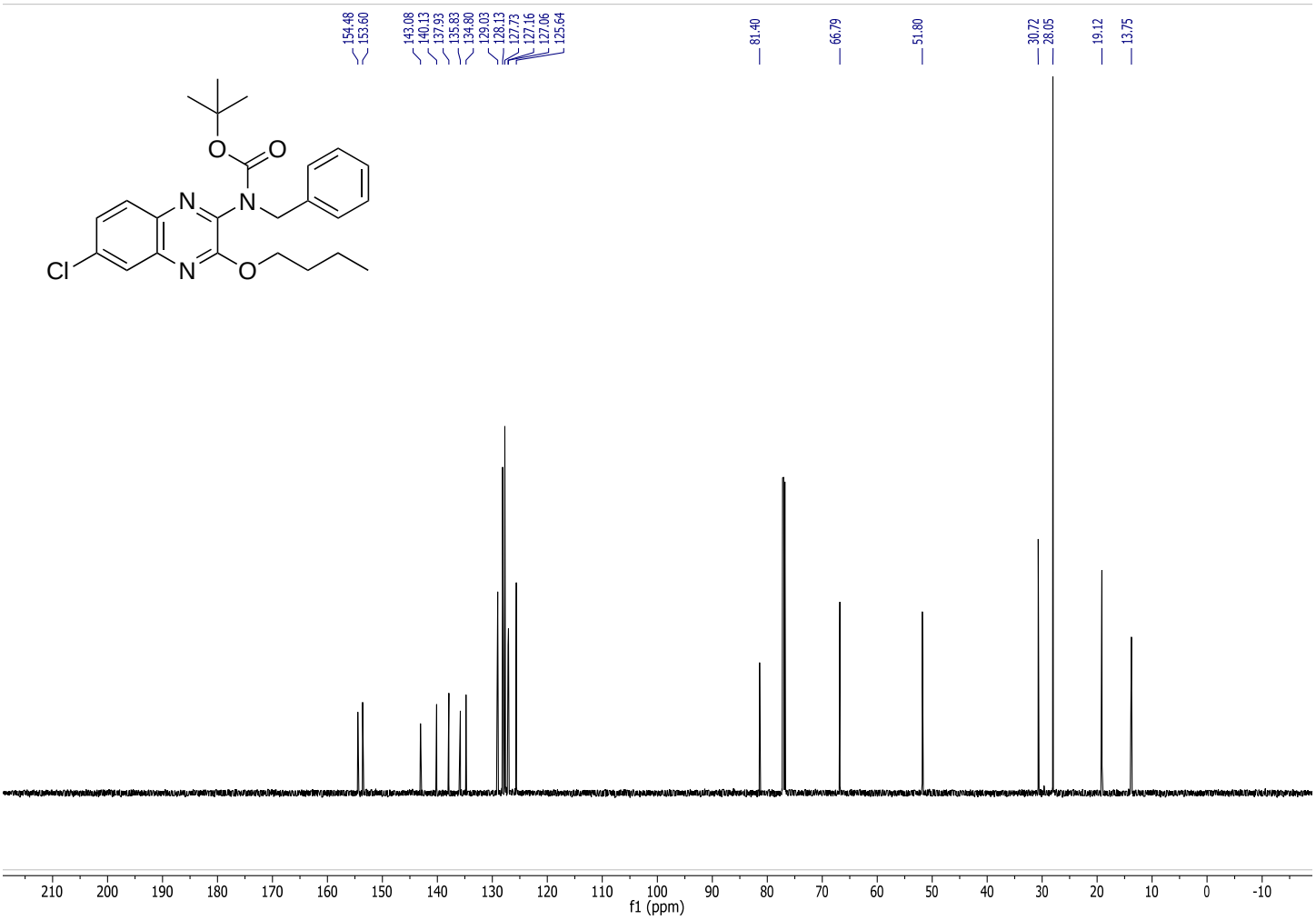
f1 (ppm)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135.83
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129.03
128.13
127.73
127.16
127.06
125.64
81.40
66.79
51.80
30.72
28.05
19.12
13.75
O
O
N
N
Cl
N
O
210
200
190
180
170
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140
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110
100
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80
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60
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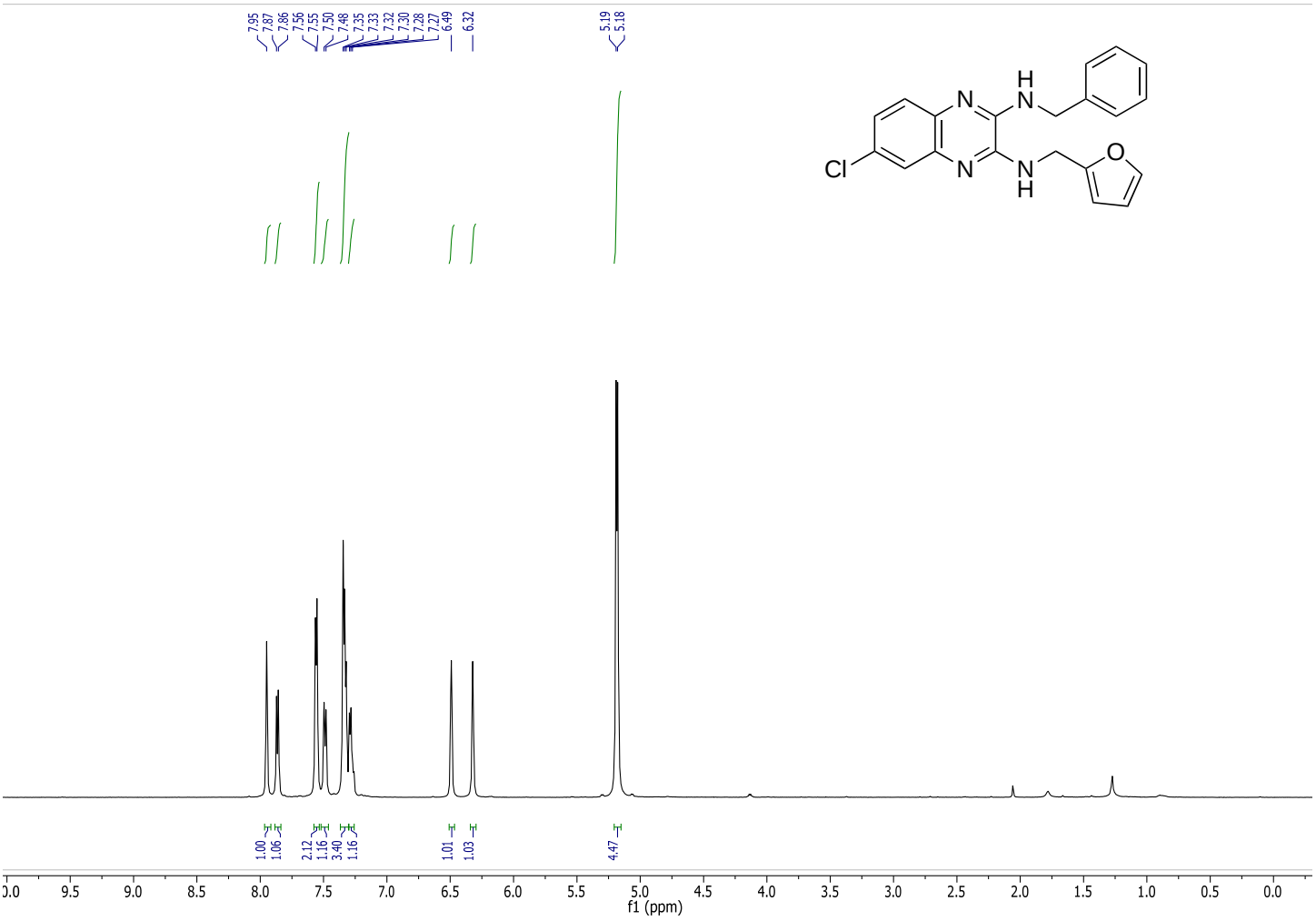
40
30
20
10
0
-10
f1 (ppm)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7.35
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7.32
7.30
7.28
7.27
6.49
6.32
5.19
5.18
Cl
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H
N
N
H
N
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1.16
3.40
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1.01
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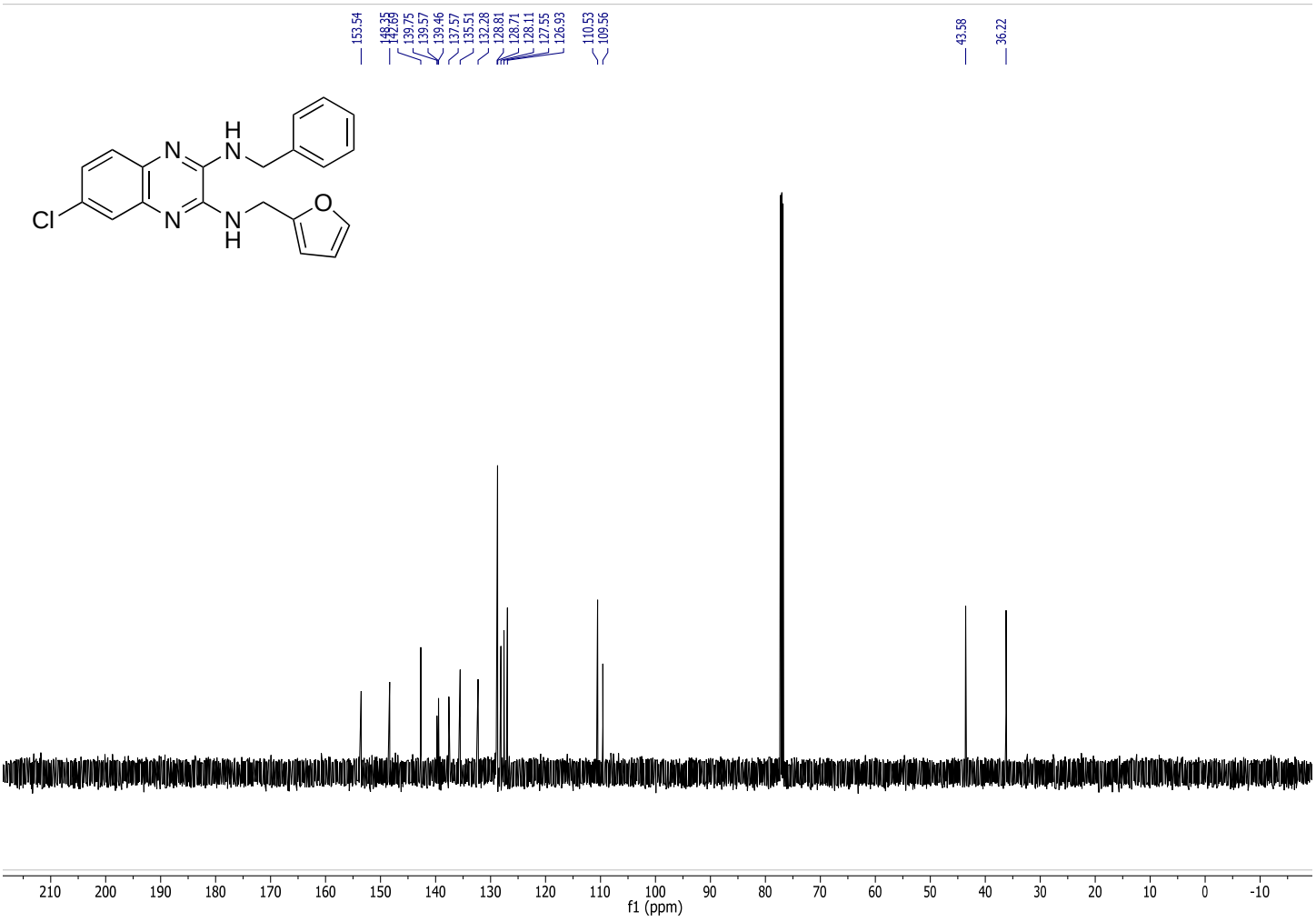
4.47
f1 (ppm)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127.55
126.93
110.53
109.56
43.58
36.22
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H
N
N
N
H
O
210
200
190
180
170
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100
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80
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40
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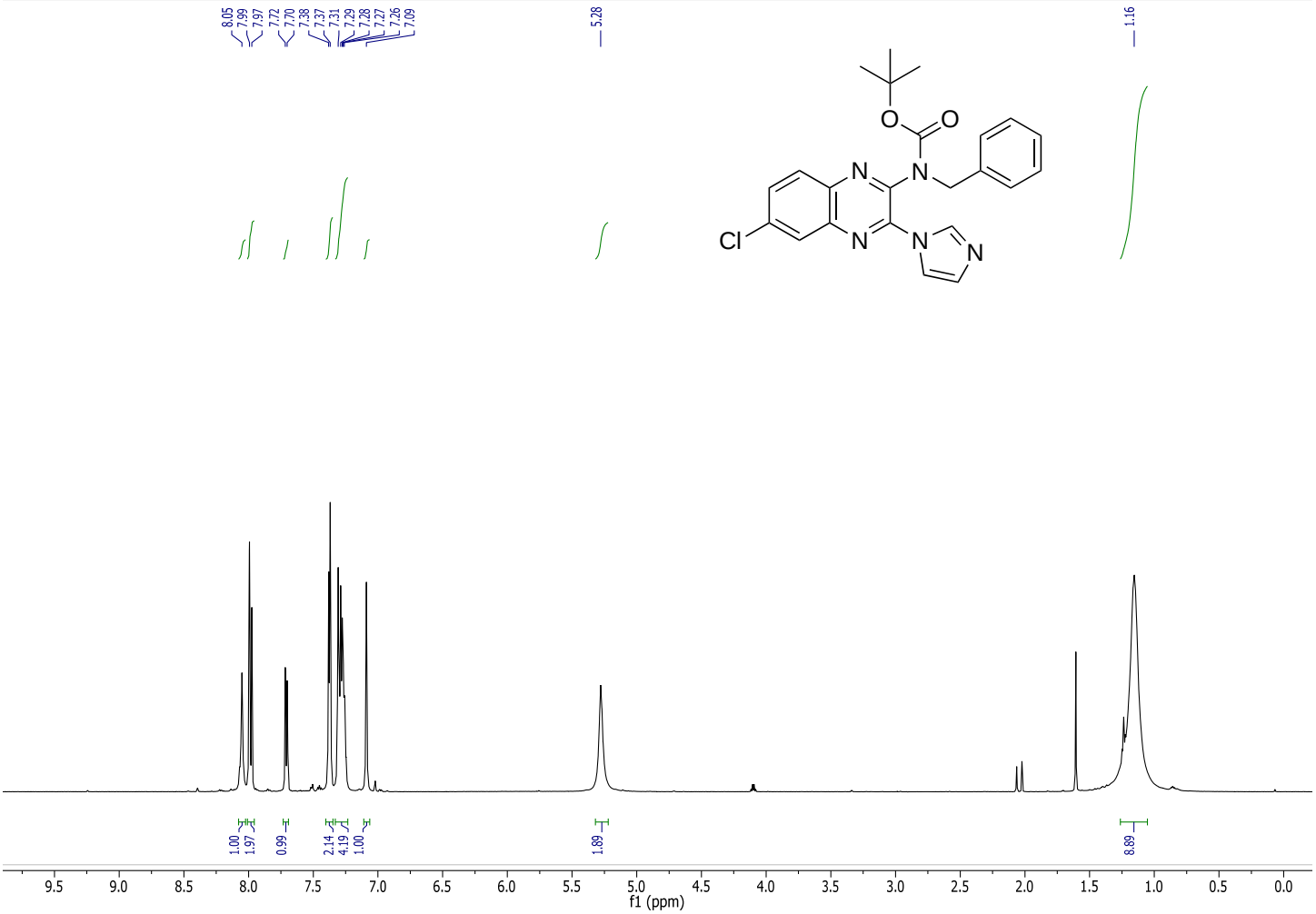
-10
f1 (ppm)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7.28
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7.26
7.09
5.28
1.16
O
O
N
N
Cl
N
N
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1.00
1.97
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2.14
4.19
1.00
1.89
8.89
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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2.5
2.0
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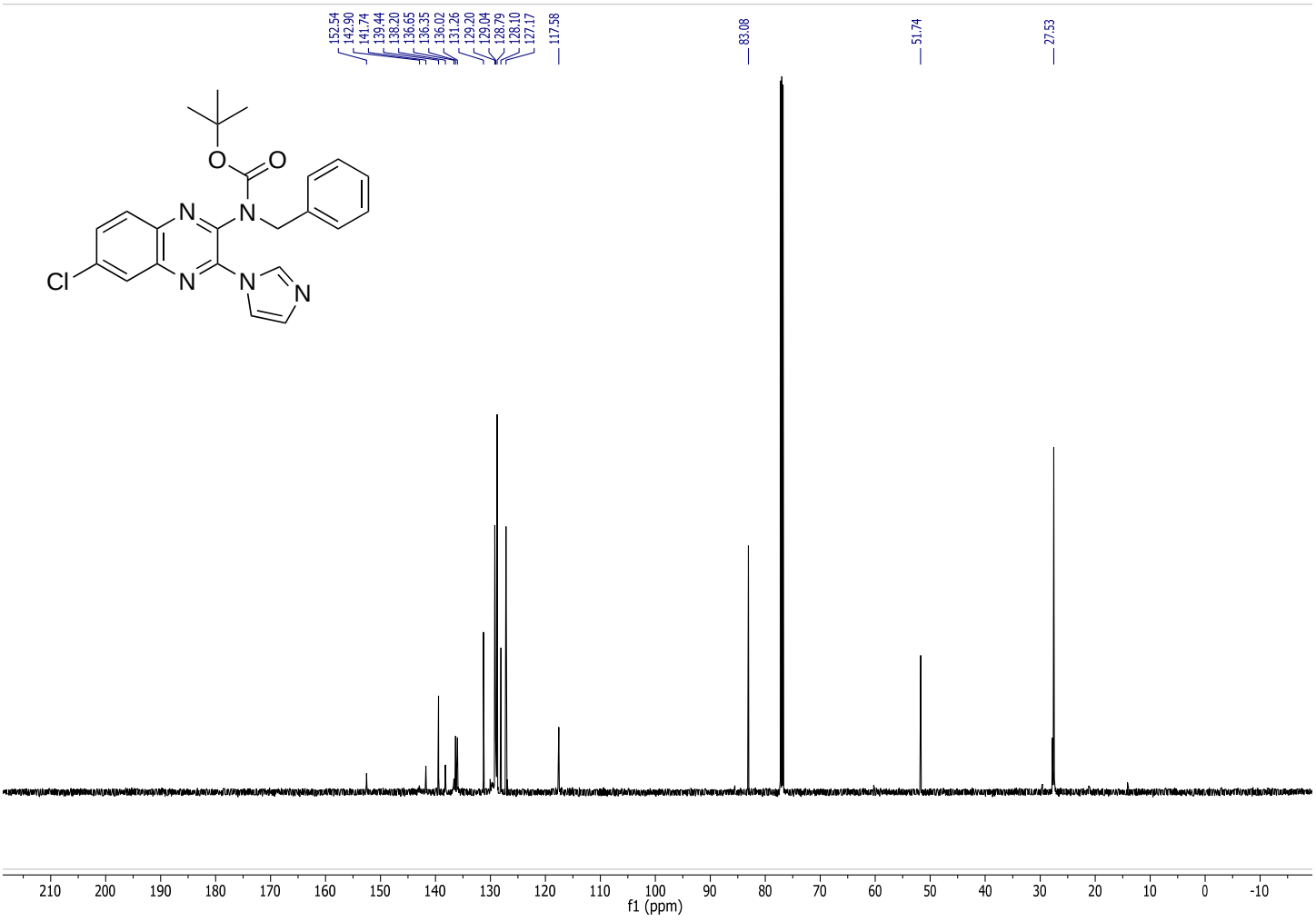
0.0
f1 (ppm)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141.74
139.44
138.20
136.65
136.35
136.02
131.26
129.20
129.04
128.79
128.10
127.17
117.58
83.08
51.74
27.53
O
O
N
N
Cl
N
N
N
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200
190
180
170
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100
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30
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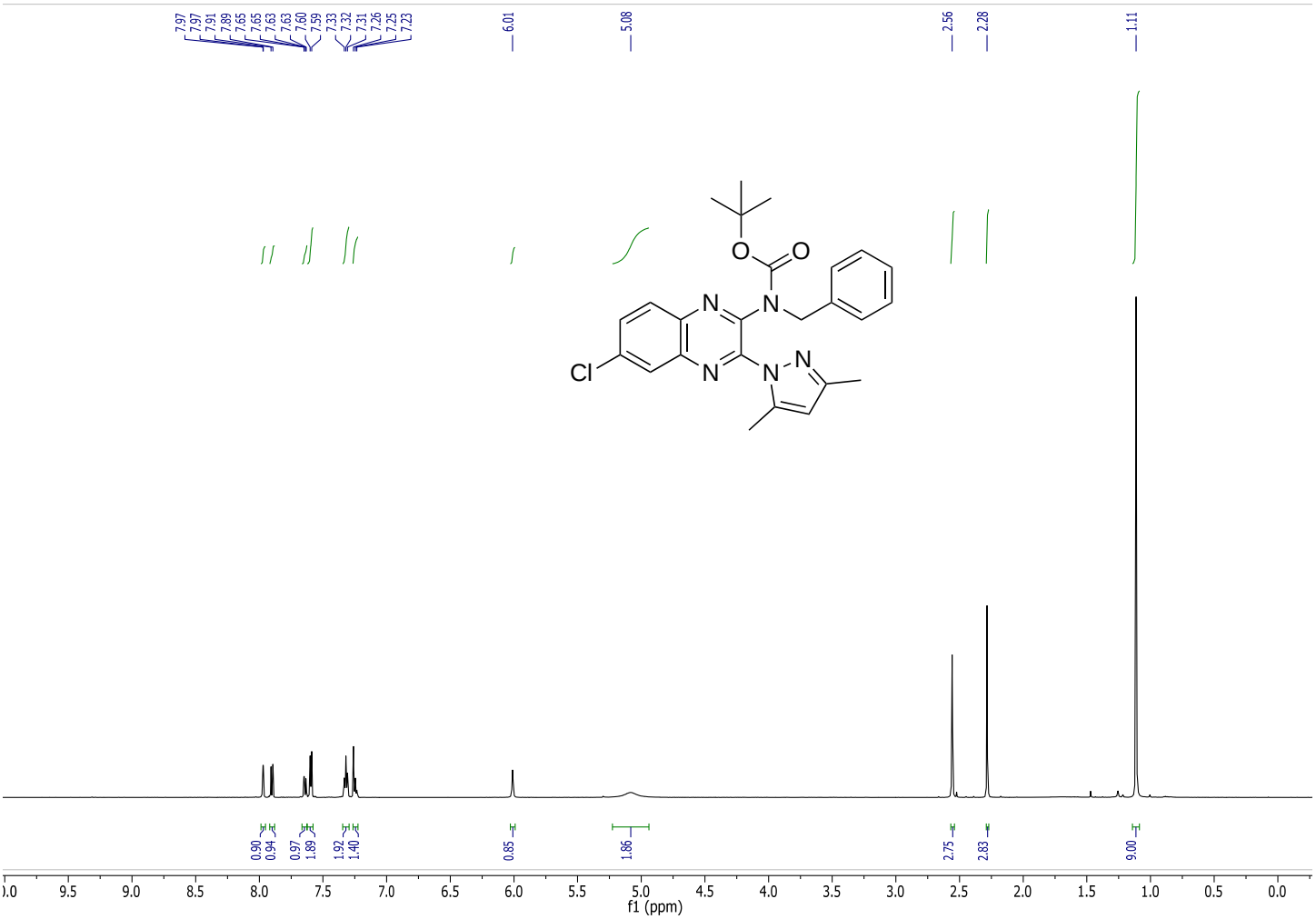
f1 (ppm)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7.63
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7.59
7.33
7.32
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7.26
7.25
7.23
6.01
5.08
2.56
2.28
1.11
O
O
N
N
Cl
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N
N
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0.94
0.97
1.89
1.92
1.40
0.85
1.86
2.75
2.83
9.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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2.5
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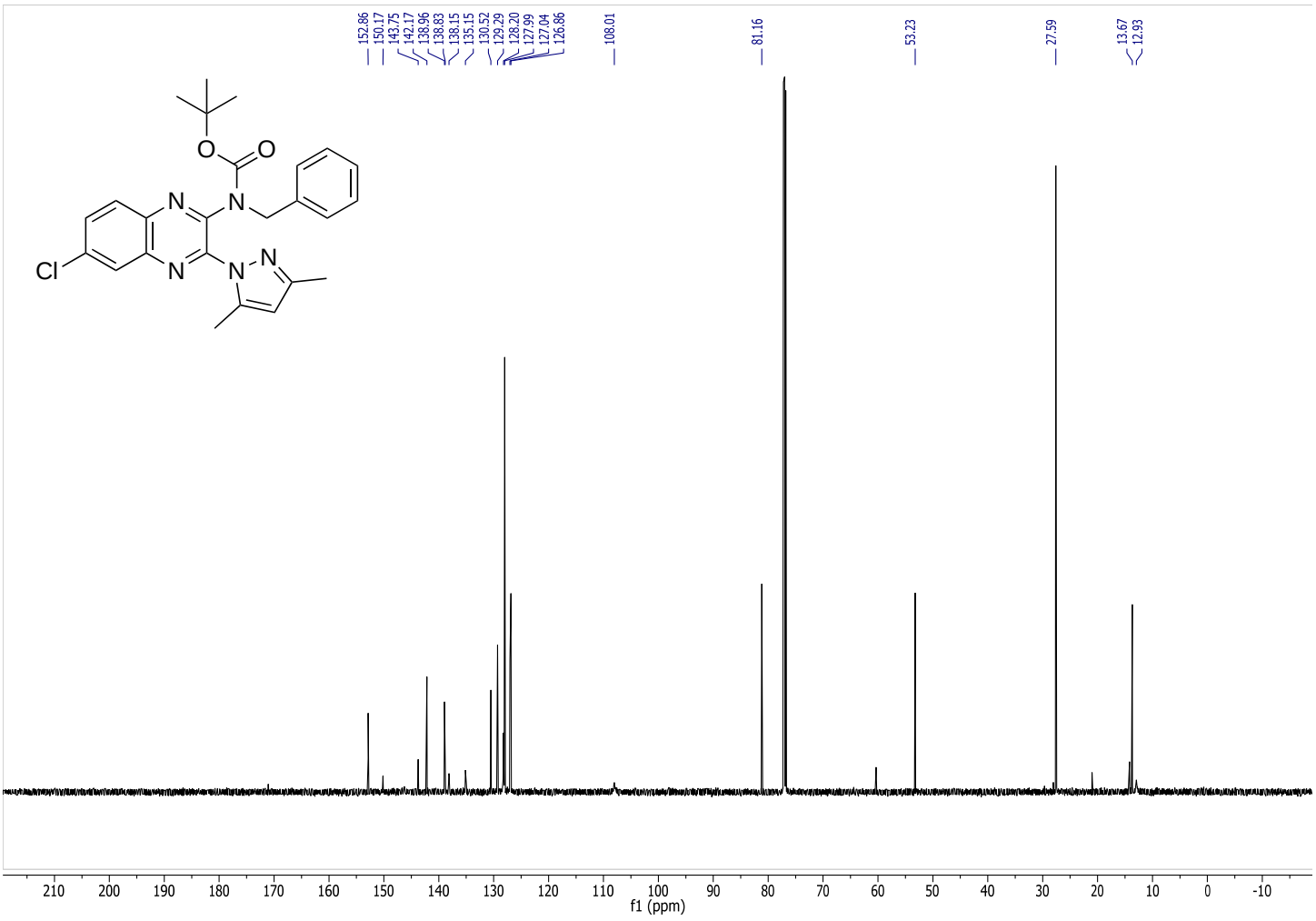
f1 (ppm)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135.15
130.52
129.29
128.20
127.99
127.04
126.86
108.01
81.16
53.23
27.59
13.67
12.93
O
O
N
N
Cl
N
N
N
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200
190
180
170
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80
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50
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30
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10
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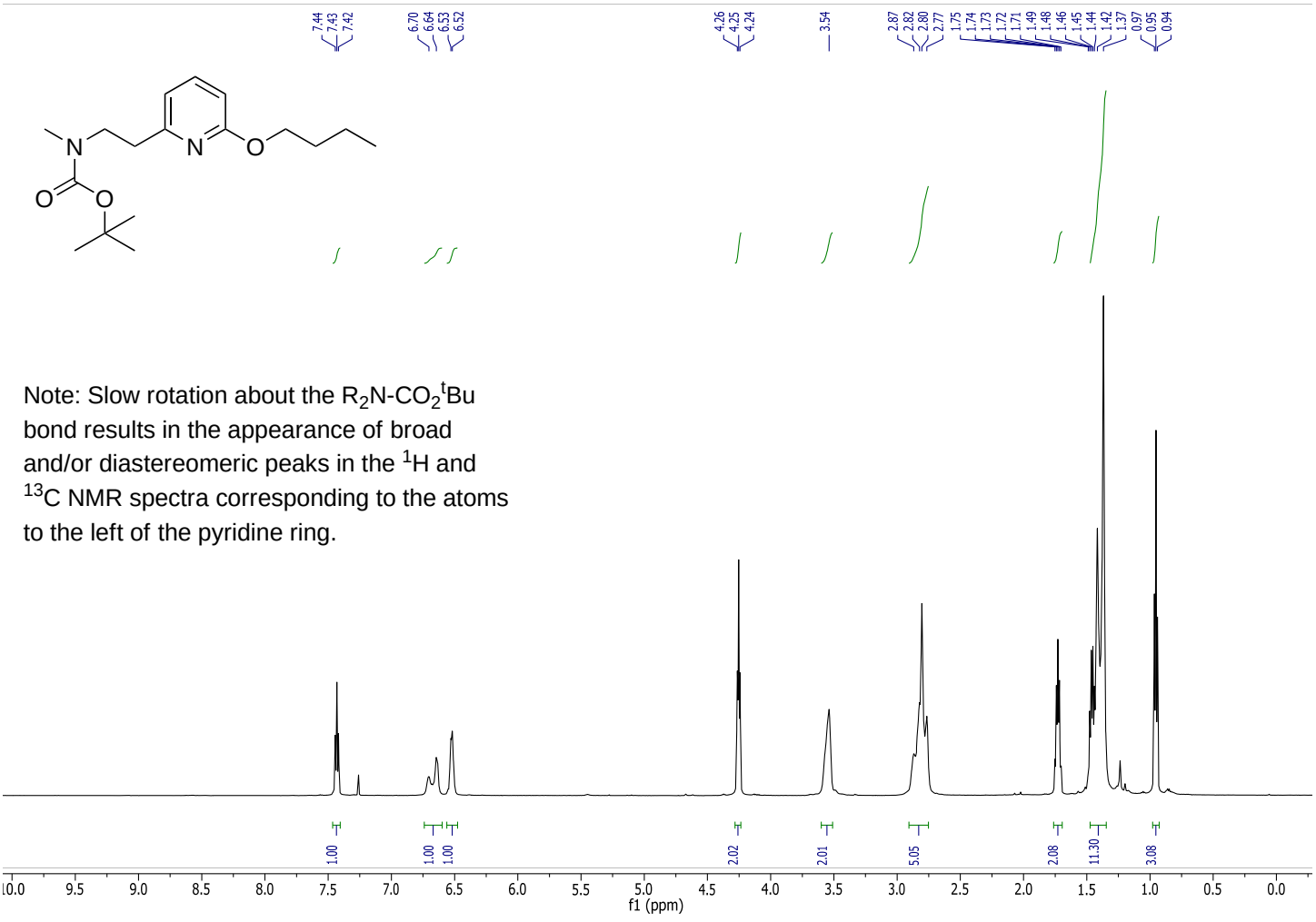
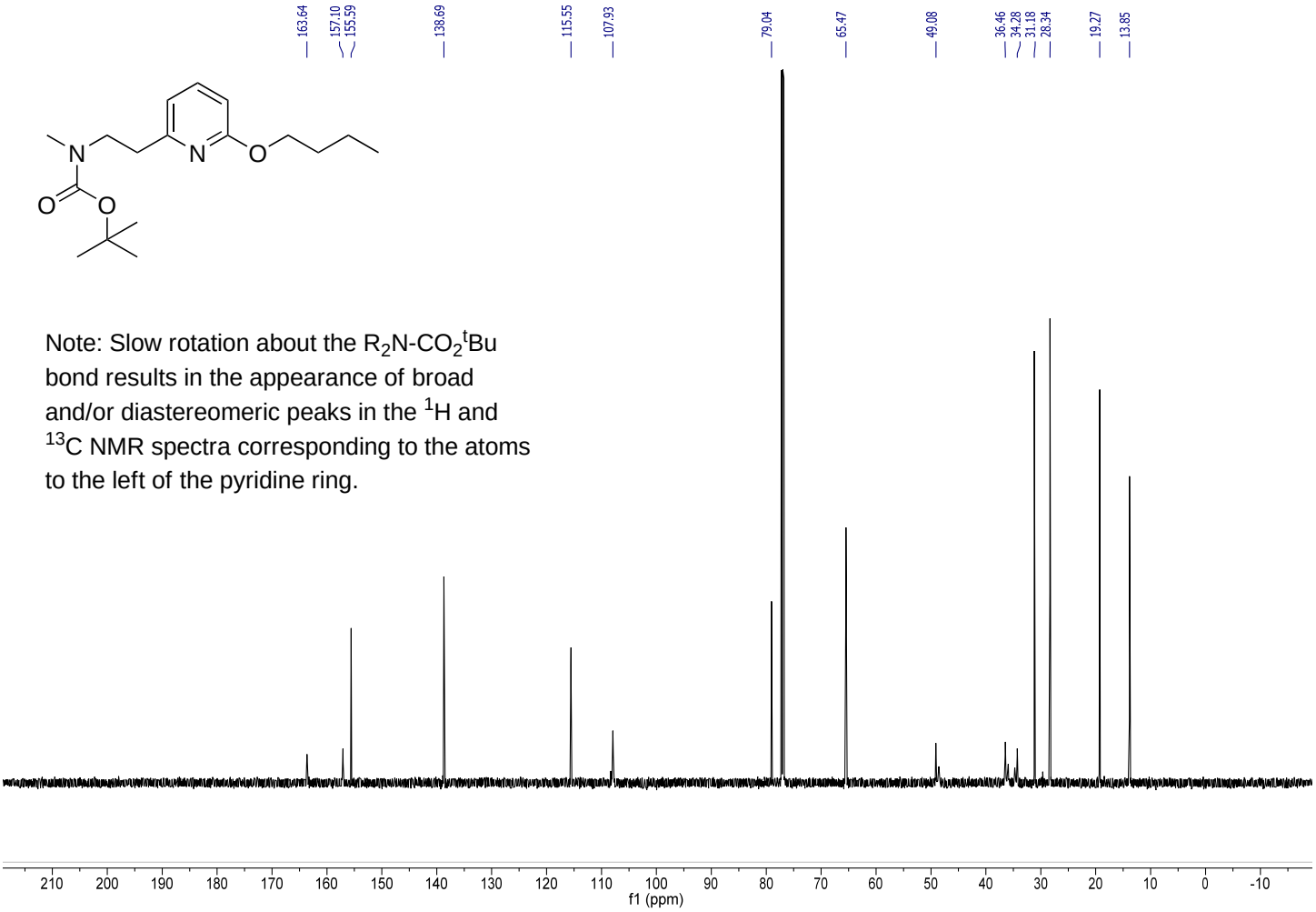
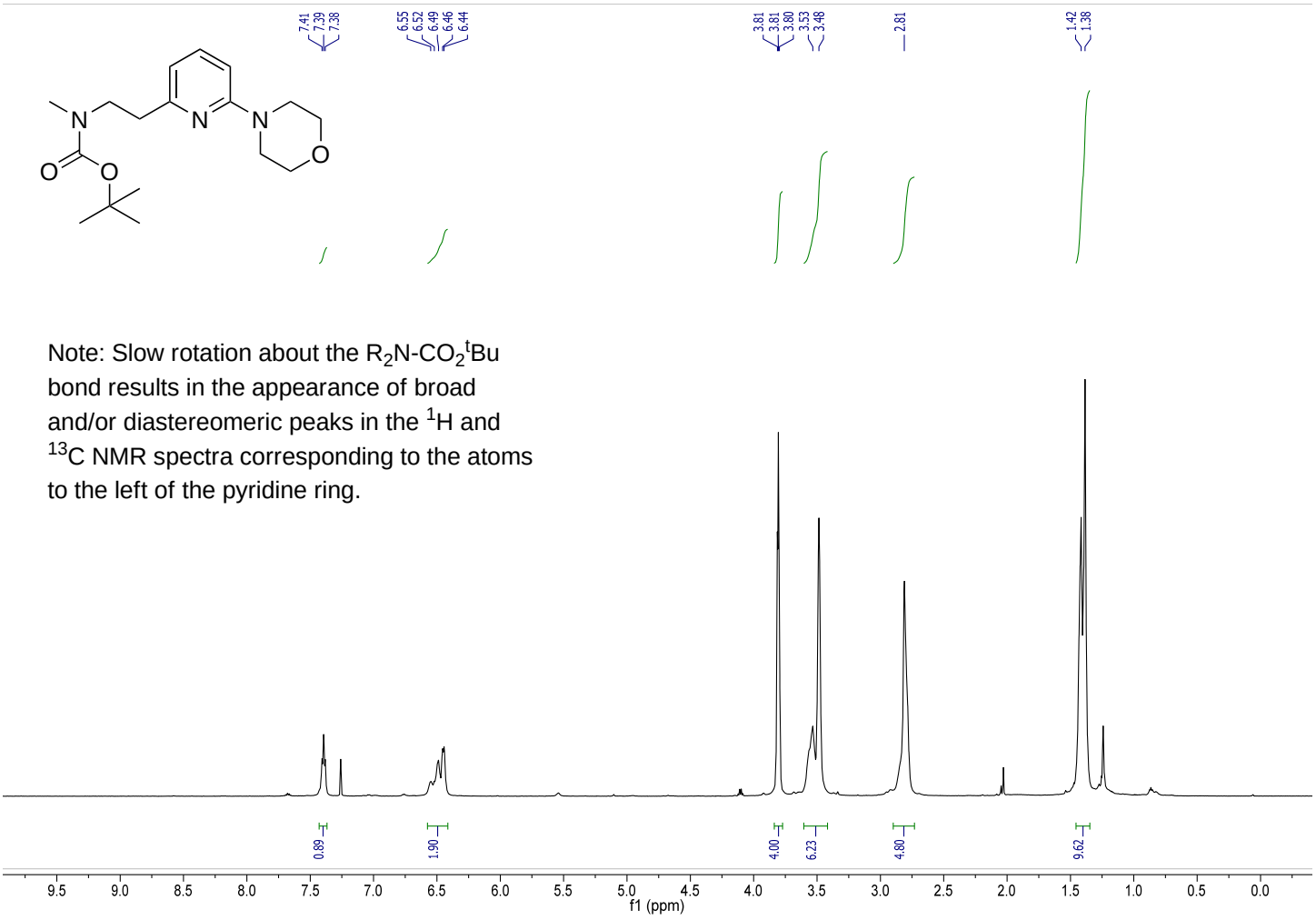
-10
f1 (ppm)



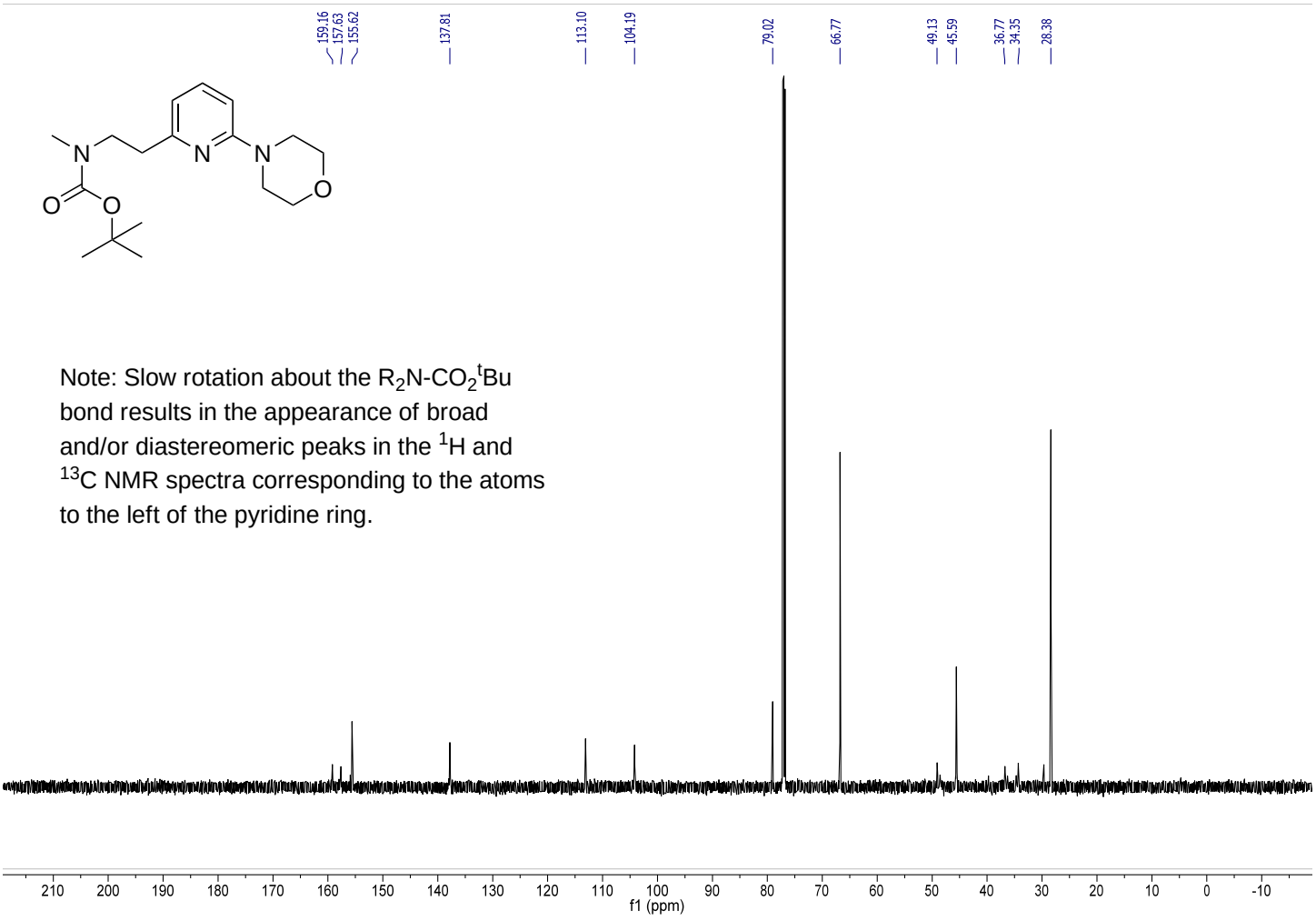
Note: Slow rotation about the $R_2N\text{-}CO_2{}^tBu$ bond results in the appearance of broad and/or diastereomeric peaks in the ^1H and ^{13}C NMR spectra corresponding to the atoms to the left of the pyridine ring.



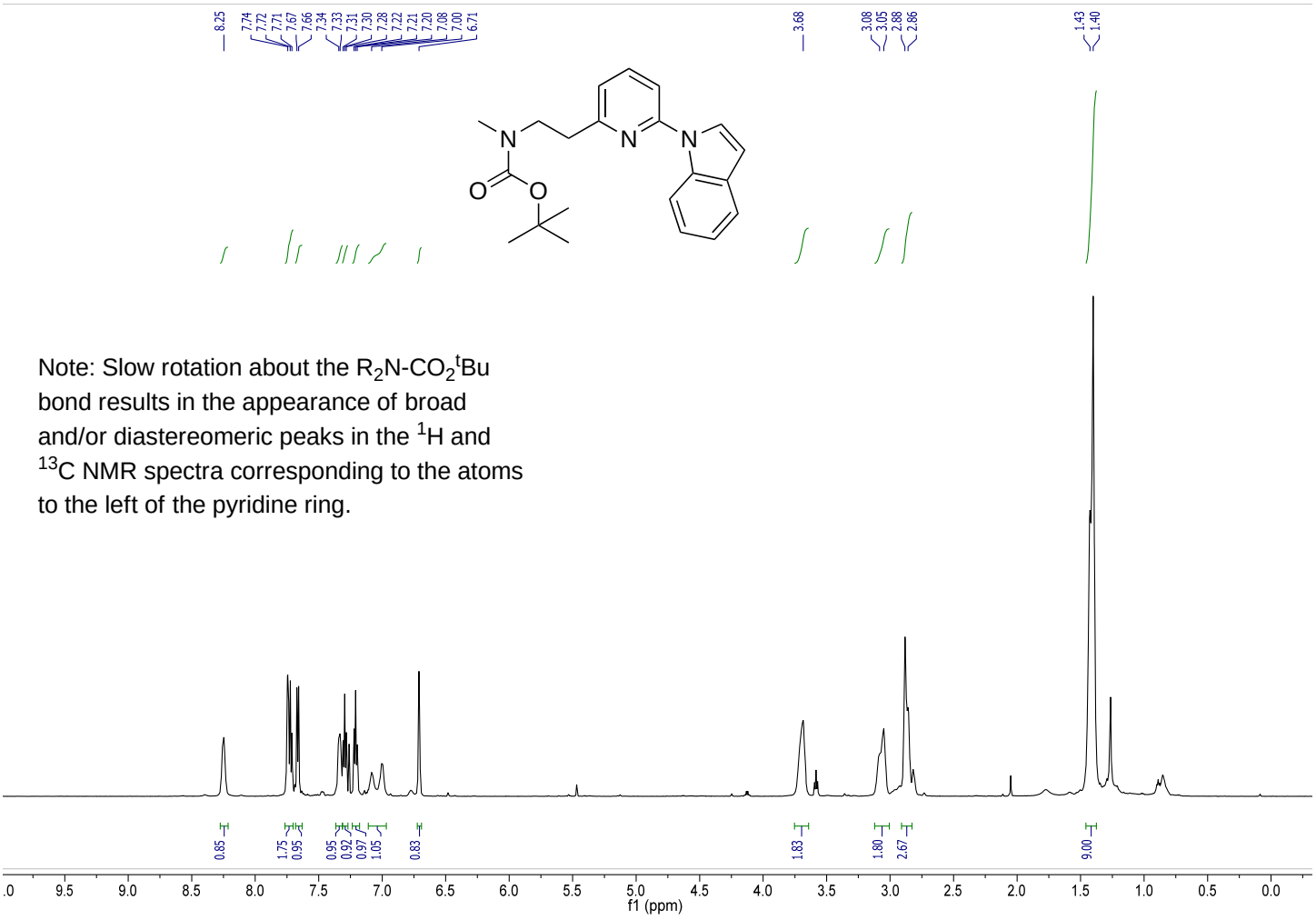
Note: Slow rotation about the $R_2N\text{-}CO_2{}^tBu$ bond results in the appearance of broad and/or diastereomeric peaks in the ^1H and ^{13}C NMR spectra corresponding to the atoms to the left of the pyridine ring.



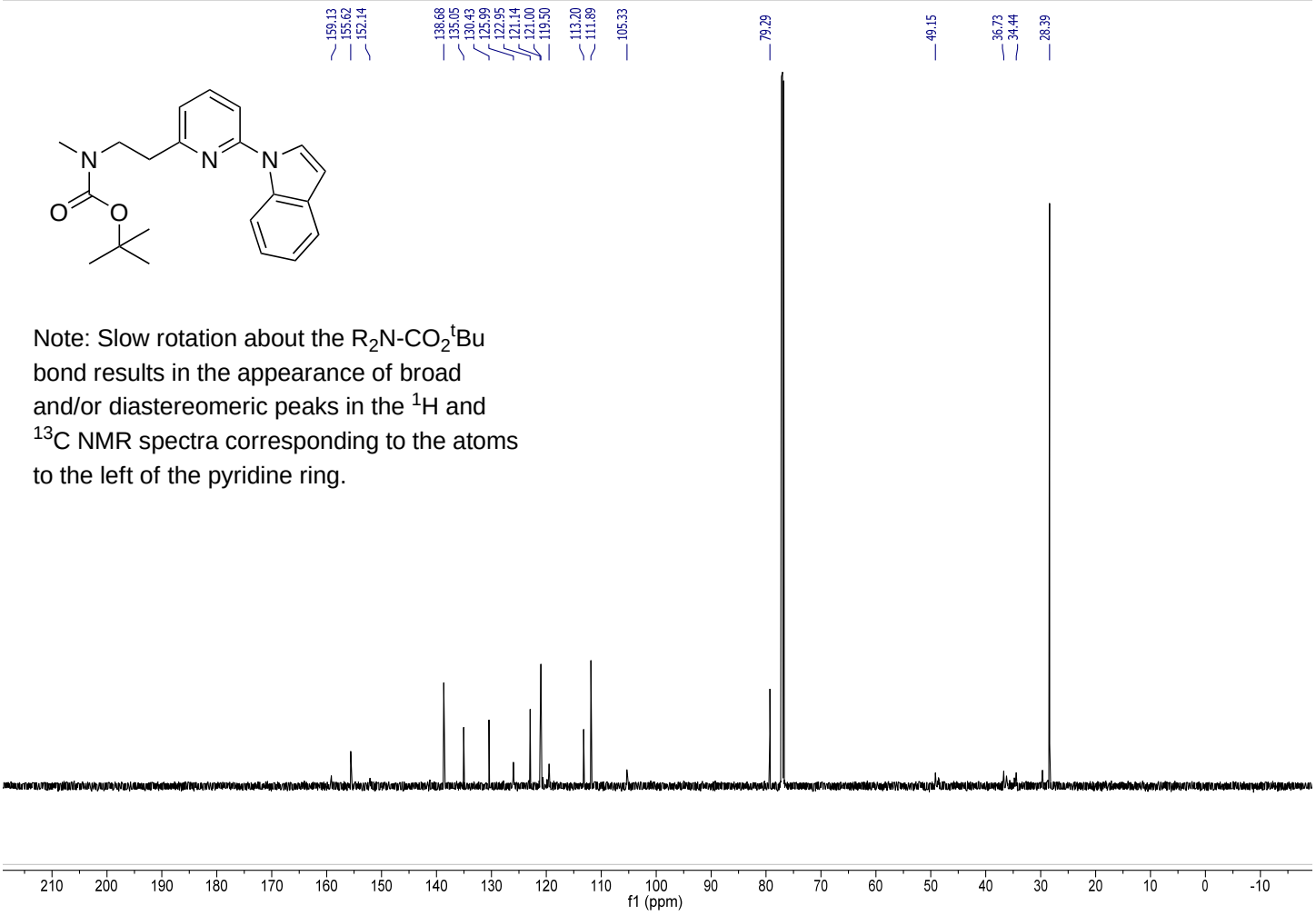
Note: Slow rotation about the R_2N-$CO_2{}^tBu$ bond results in the appearance of broad and/or diastereomeric peaks in the ^1H and ^{13}C NMR spectra corresponding to the atoms to the left of the pyridine ring.



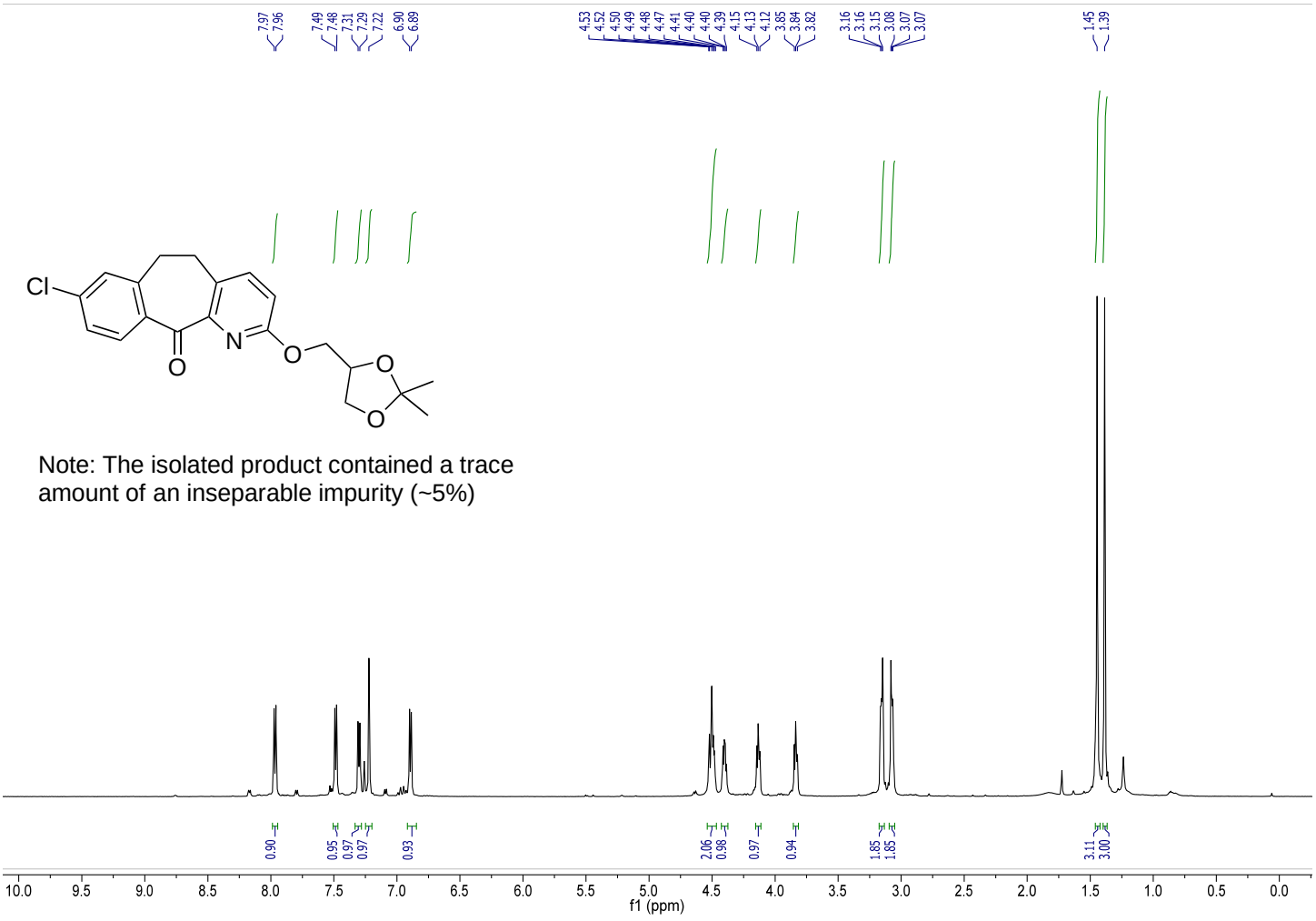
Note: Slow rotation about the $R_2N\text{-}CO_2{}^tBu$ bond results in the appearance of broad and/or diastereomeric peaks in the ^1H and ^{13}C NMR spectra corresponding to the atoms to the left of the pyridine ring.



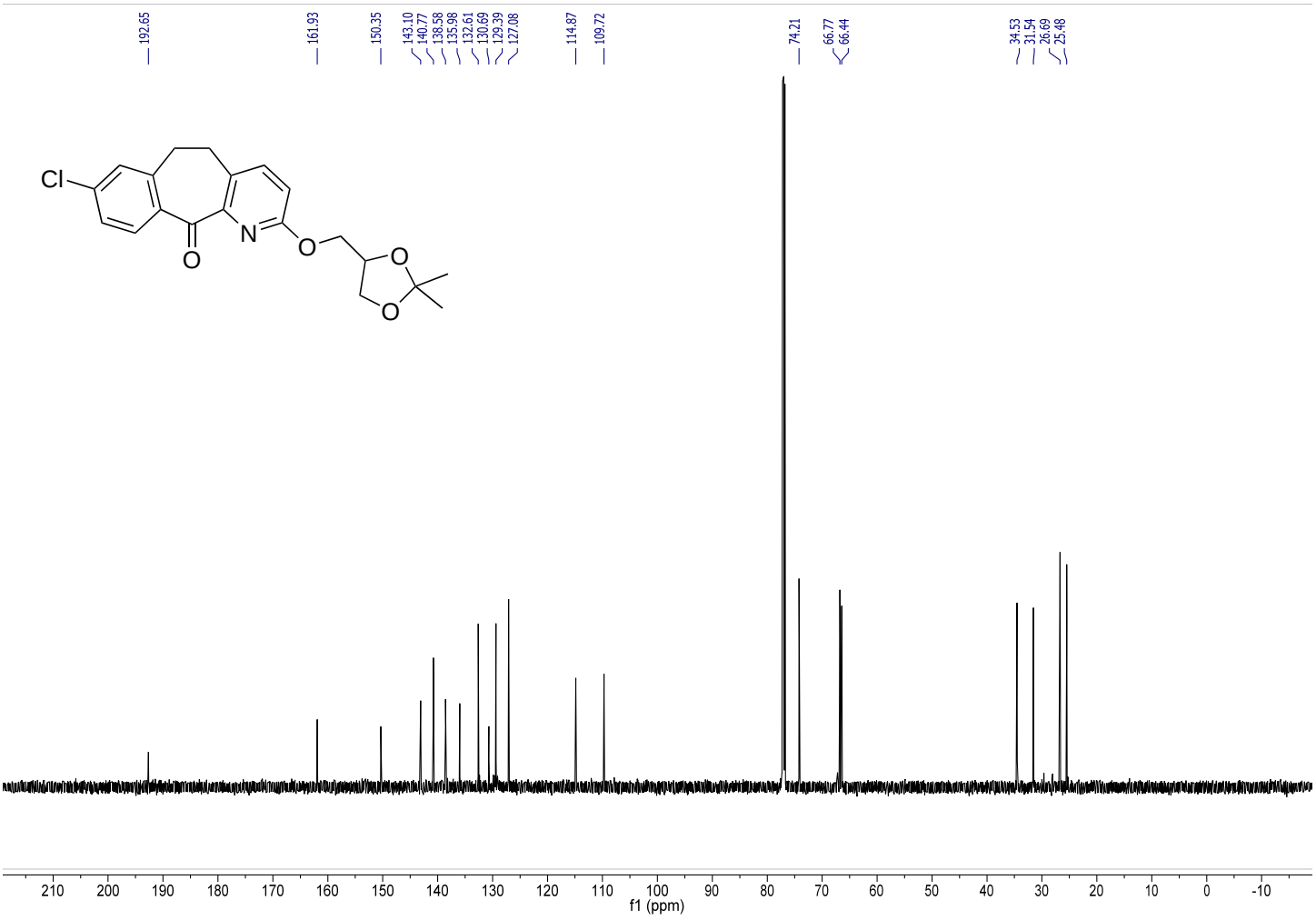
Note: Slow rotation about the $R_2N\text{-}CO_2{}^tBu$ bond results in the appearance of broad and/or diastereomeric peaks in the ^1H and ^{13}C NMR spectra corresponding to the atoms to the left of the pyridine ring.

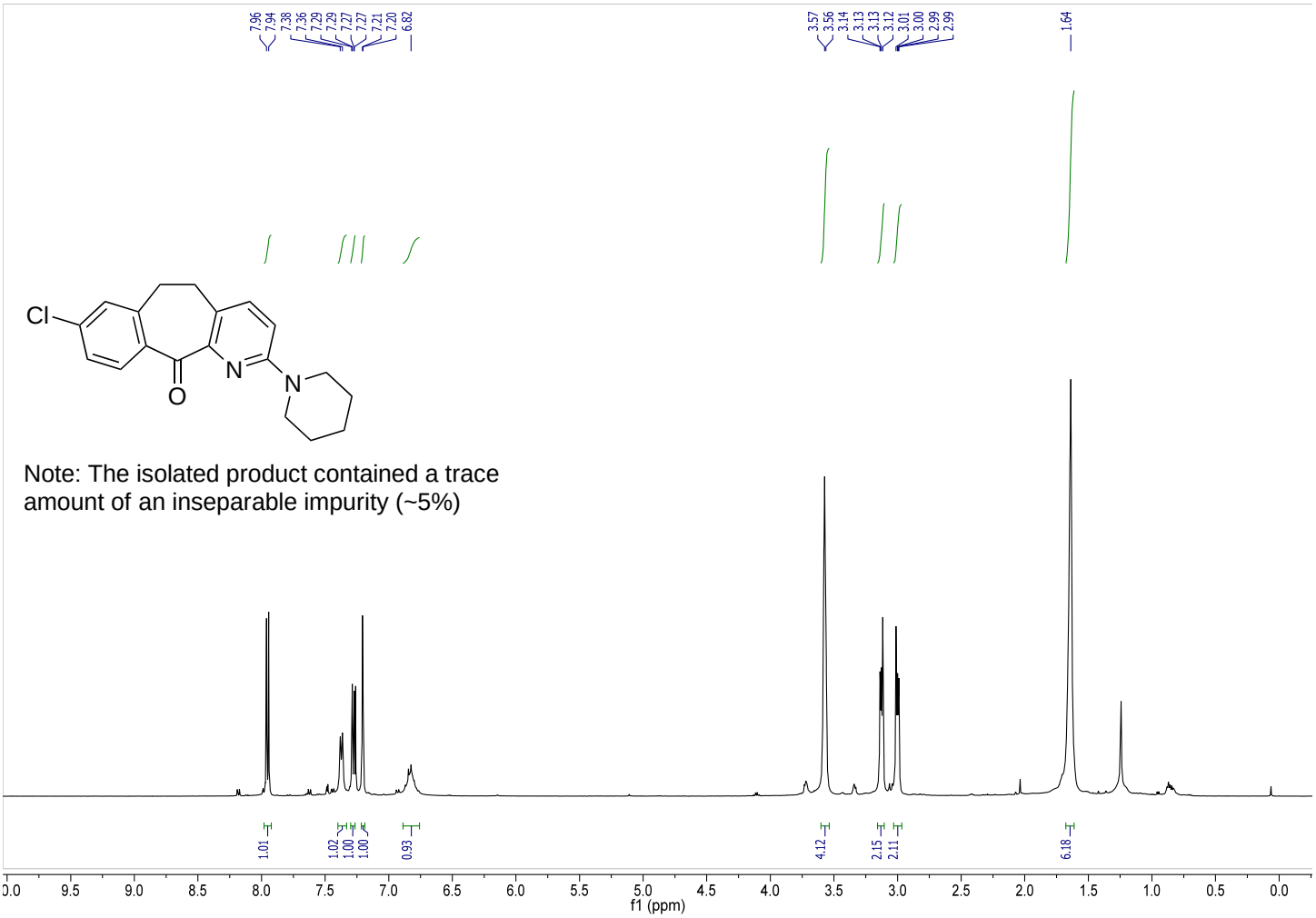


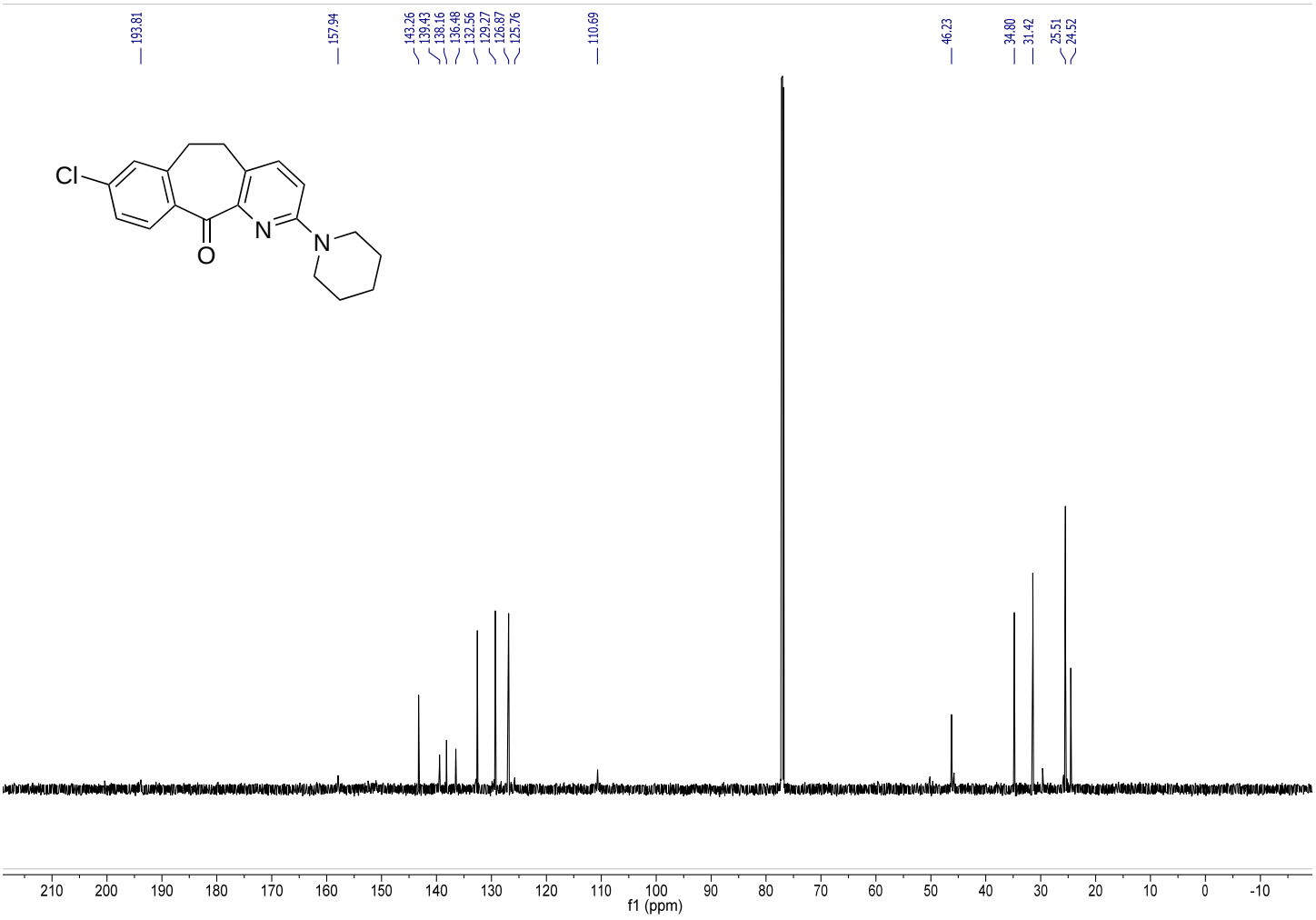
Note: Slow rotation about the $R_2N\text{-}CO_2{}^tBu$ bond results in the appearance of broad and/or diastereomeric peaks in the ^1H and ^{13}C NMR spectra corresponding to the atoms to the left of the pyridine ring.

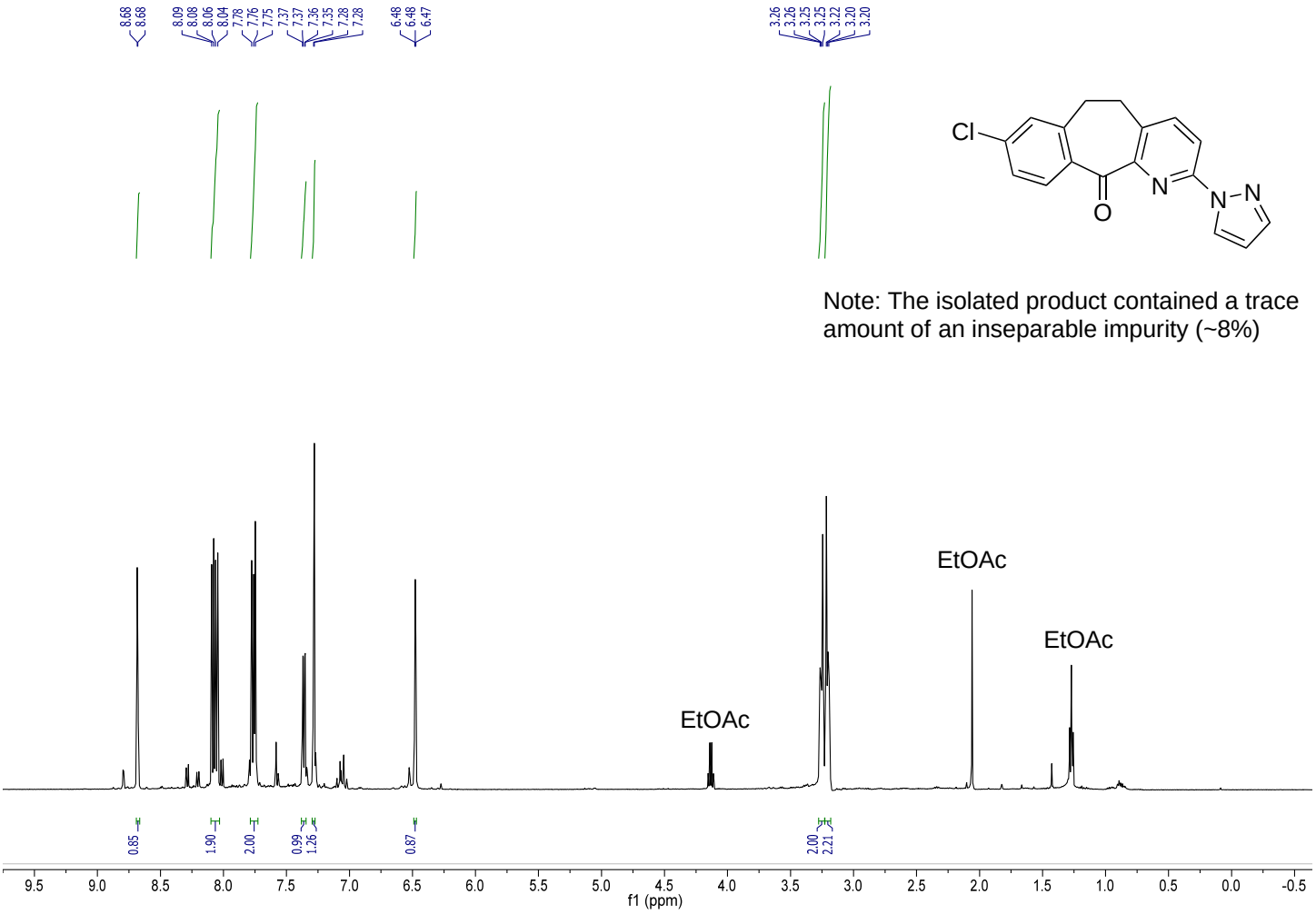


Note: The isolated product contained a trace amount of an inseparable impurity (~5%)

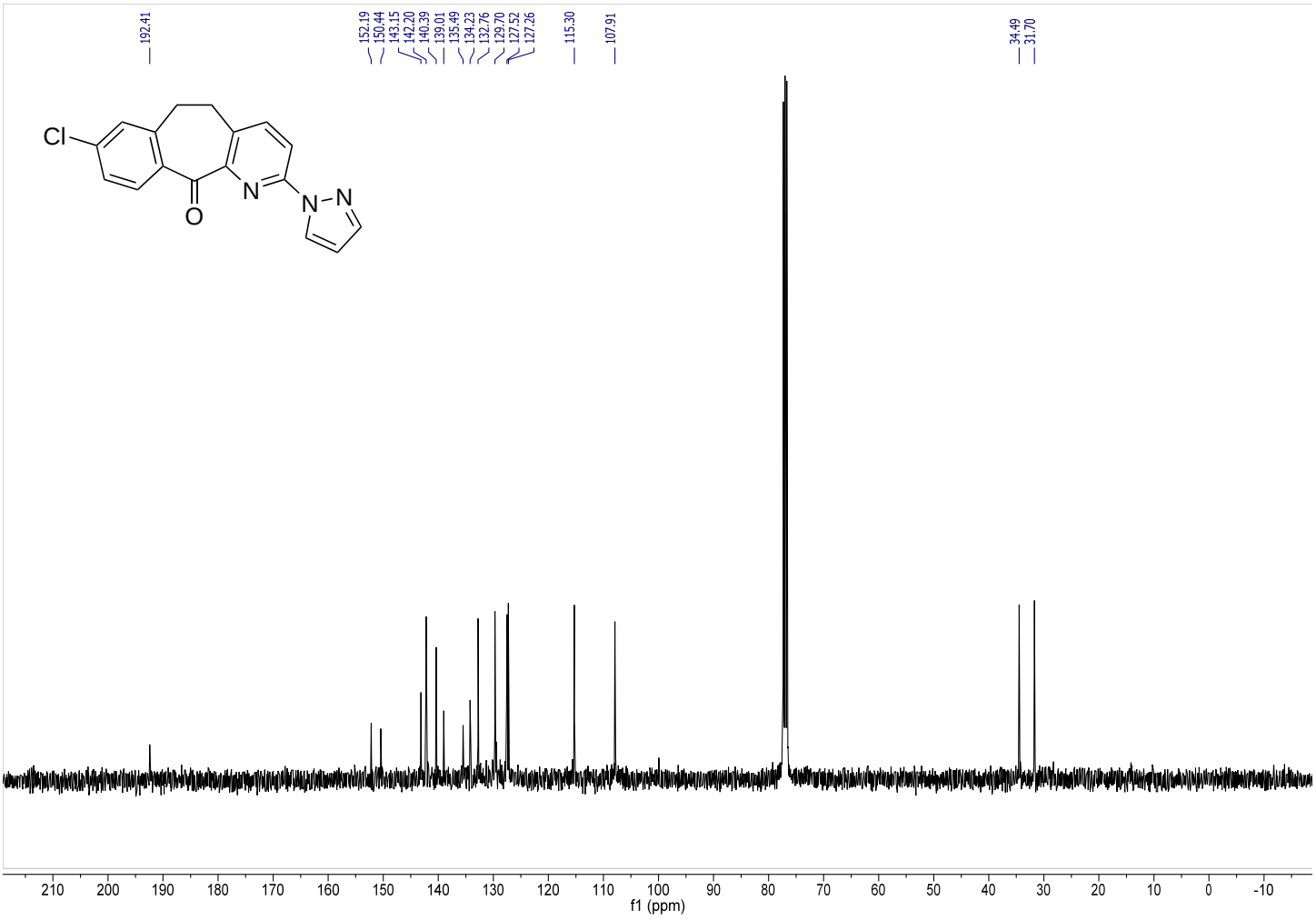

192.65
161.93
150.35
143.10
140.77
138.58
135.98
132.61
130.69
129.39
127.08
114.87
109.72
74.21
66.77
66.44
34.53
31.54
26.69
25.48
Cl
O
N
O
O
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

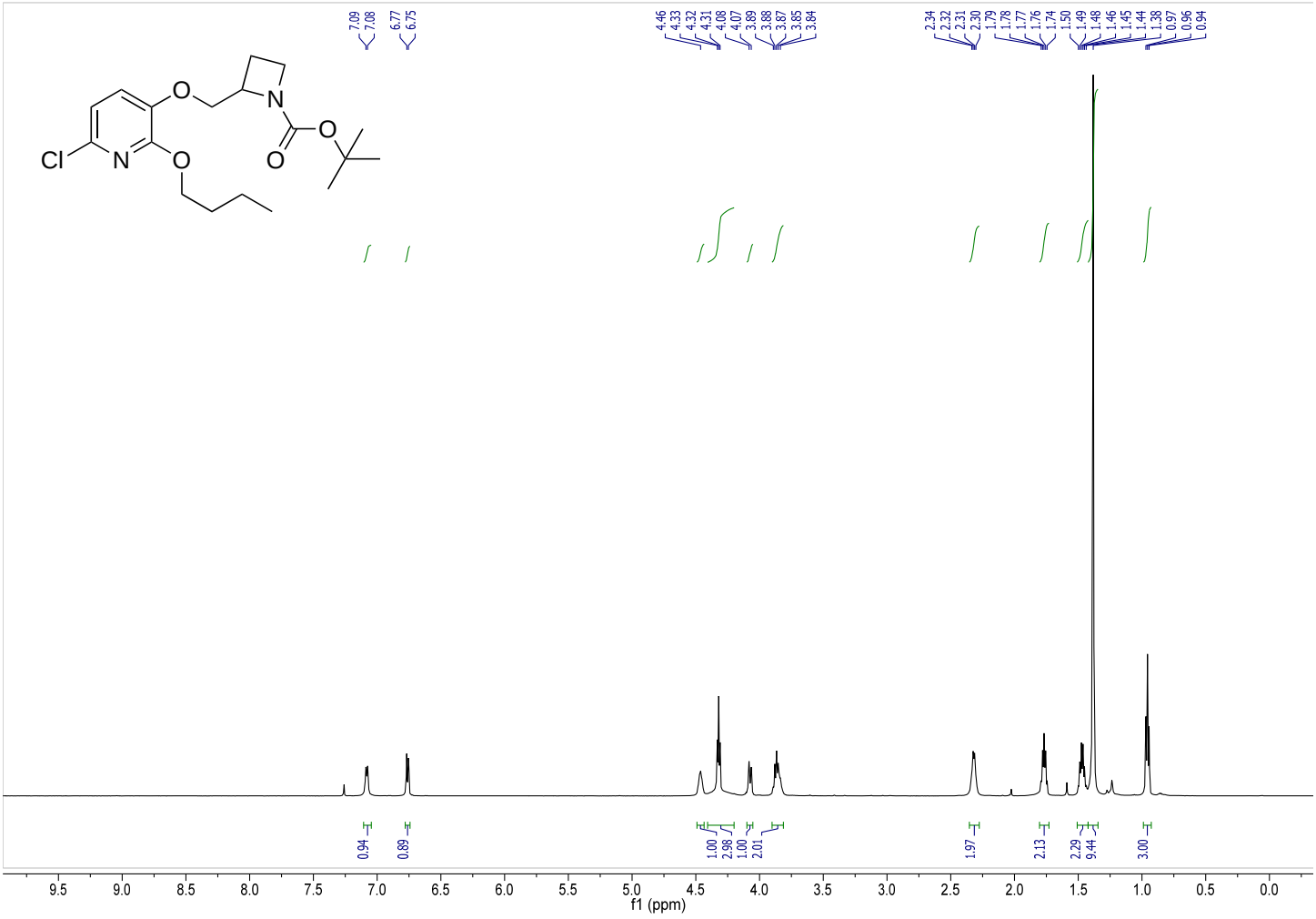

7.96
7.94
7.38
7.36
7.29
7.29
7.27
7.27
7.21
7.20
6.82
3.57
3.56
3.14
3.13
3.13
3.12
3.01
3.00
2.99
2.99
1.64
Cl
N
N
O
Note: The isolated product contained a trace amount of an inseparable impurity (~5%)
1.01
1.02
1.00
1.00
0.93
4.12
2.15
2.11
6.18
f1 (ppm)

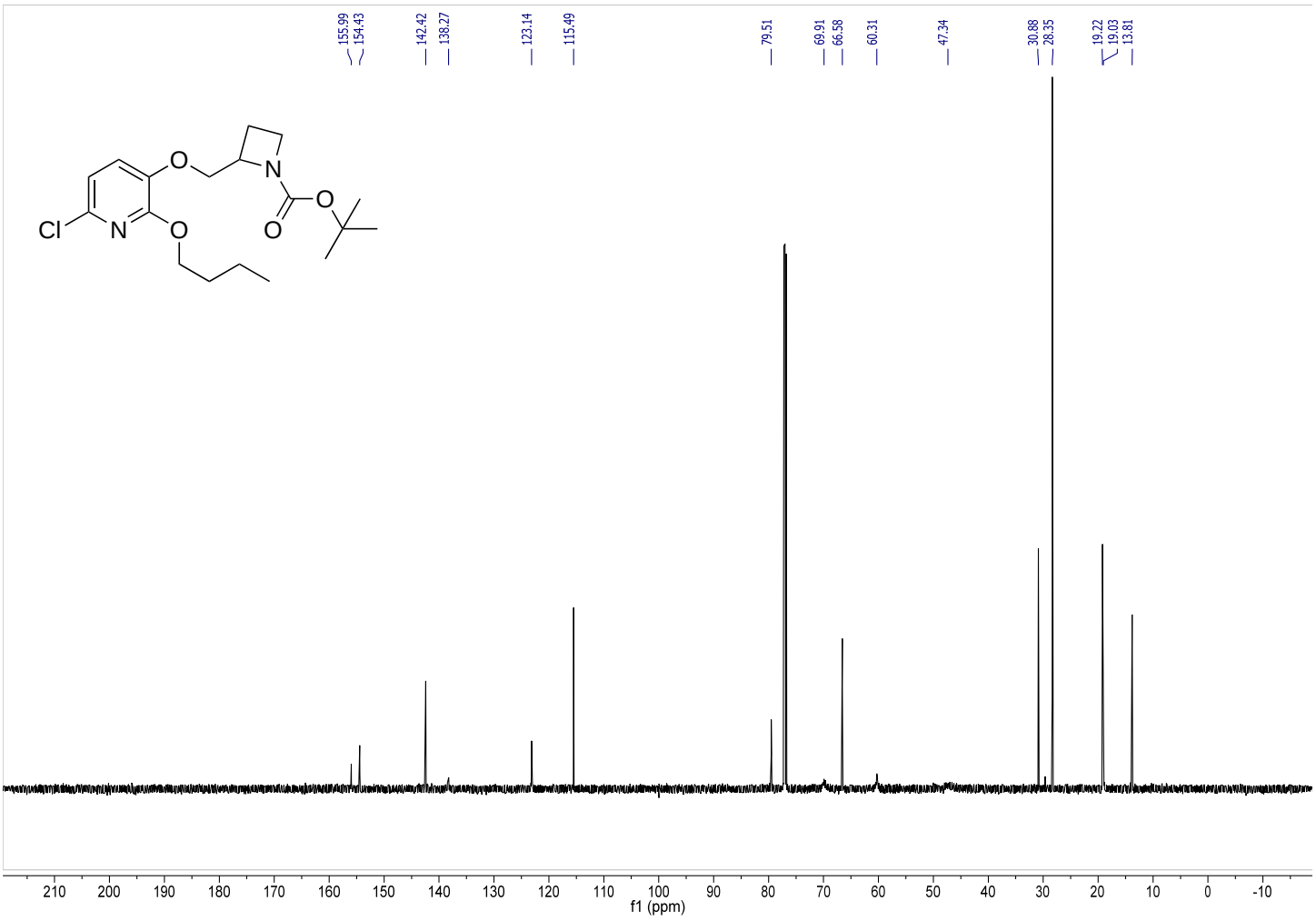

193.81
157.94
143.26
139.43
138.16
136.48
132.56
129.27
126.87
125.76
110.69
46.23
34.80
31.42
25.51
24.52
Cl
O
N
N
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

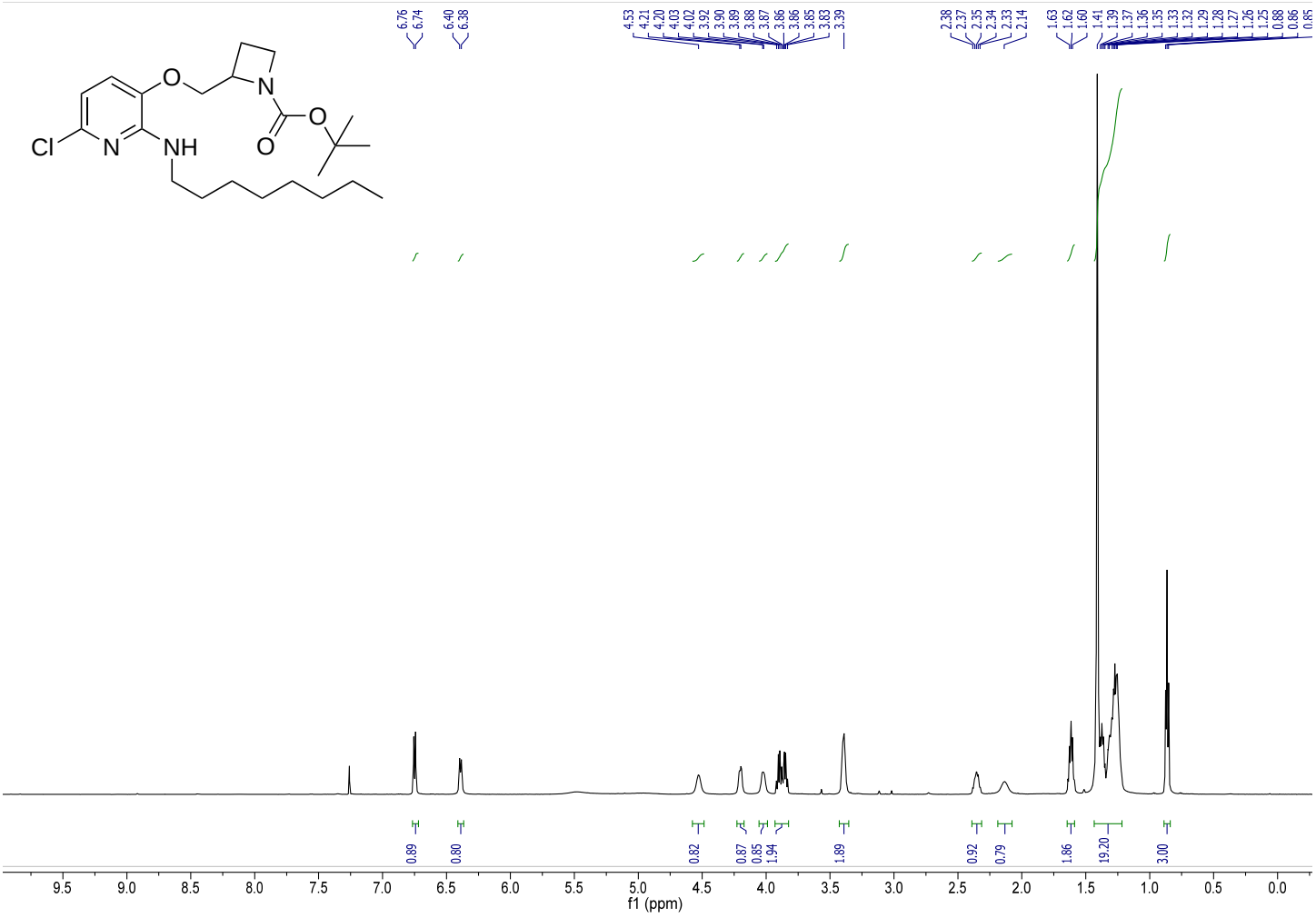


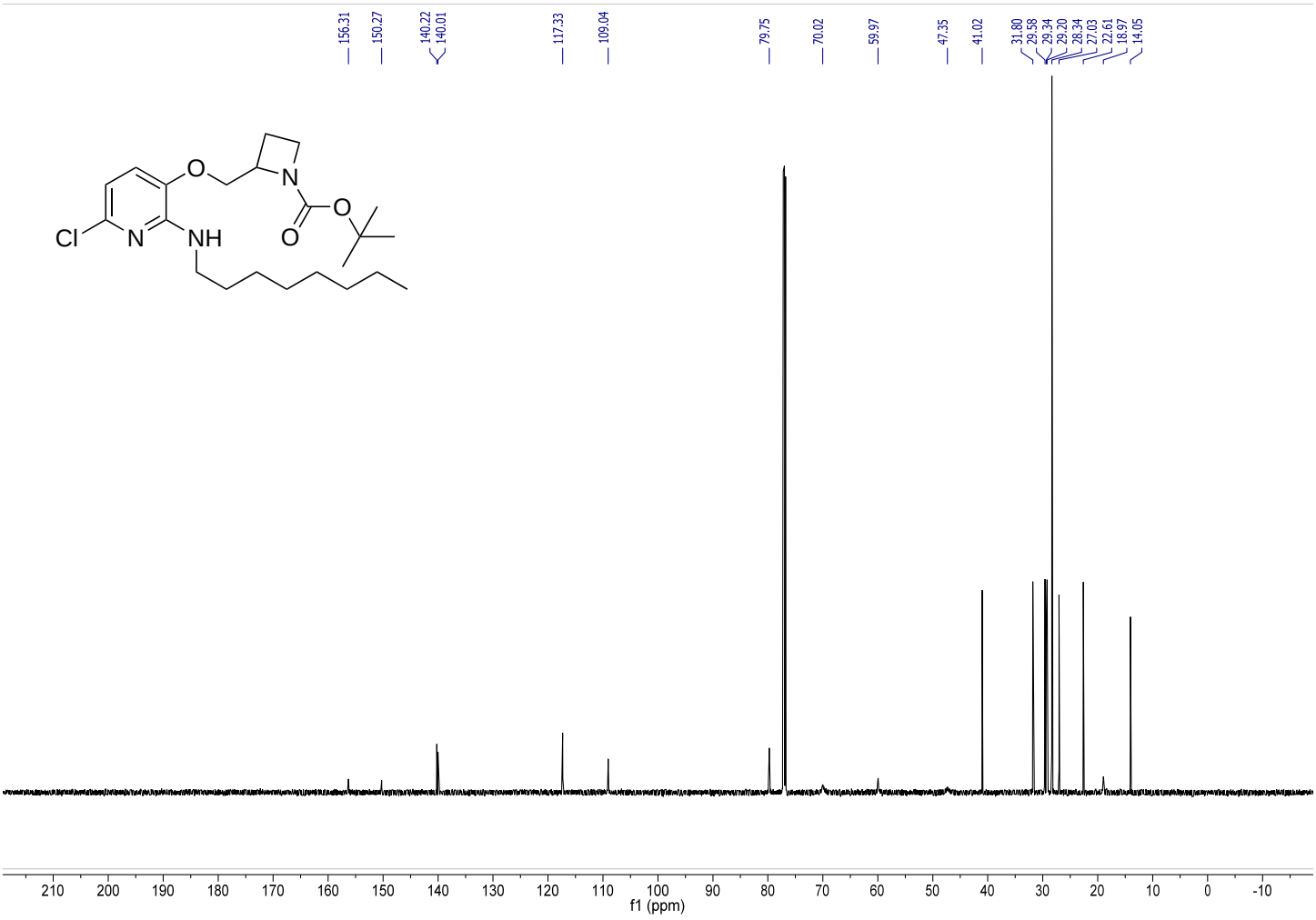
Note: The isolated product contained a trace amount of an inseparable impurity (~8%)


192.41
152.19
150.44
143.15
142.20
140.39
139.01
135.49
134.23
132.76
129.70
127.52
127.26
115.30
107.91
34.49
31.70
Cl
O
N
N-N
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.09
7.08
6.77
6.75
4.46
4.33
4.32
4.31
4.08
4.07
3.89
3.88
3.87
3.85
3.84
2.34
2.32
2.31
2.30
1.79
1.78
1.77
1.76
1.74
1.50
1.49
1.48
1.46
1.45
1.44
1.38
0.97
0.96
0.94
Cl
N
O
O
N
O
O
0.94
0.89
1.00
2.98
1.00
2.01
1.97
2.13
2.29
9.44
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


155.99
154.43
142.42
138.27
123.14
115.49
79.51
69.91
66.58
60.31
47.34
30.88
28.35
19.22
19.03
13.81
Cl
N
O
O
N
O
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


Cl
N
NH
O
N
O
O
6.76
6.74
6.40
6.38
4.53
4.21
4.20
4.03
4.02
3.92
3.90
3.89
3.88
3.87
3.86
3.86
3.85
3.83
3.39
2.38
2.37
2.35
2.34
2.33
2.14
1.63
1.62
1.60
1.41
1.39
1.37
1.36
1.35
1.33
1.32
1.29
1.28
1.27
1.26
1.25
0.88
0.86
0.85
0.89
0.80
0.82
0.87
0.85
1.94
1.89
0.92
0.79
1.86
19.20
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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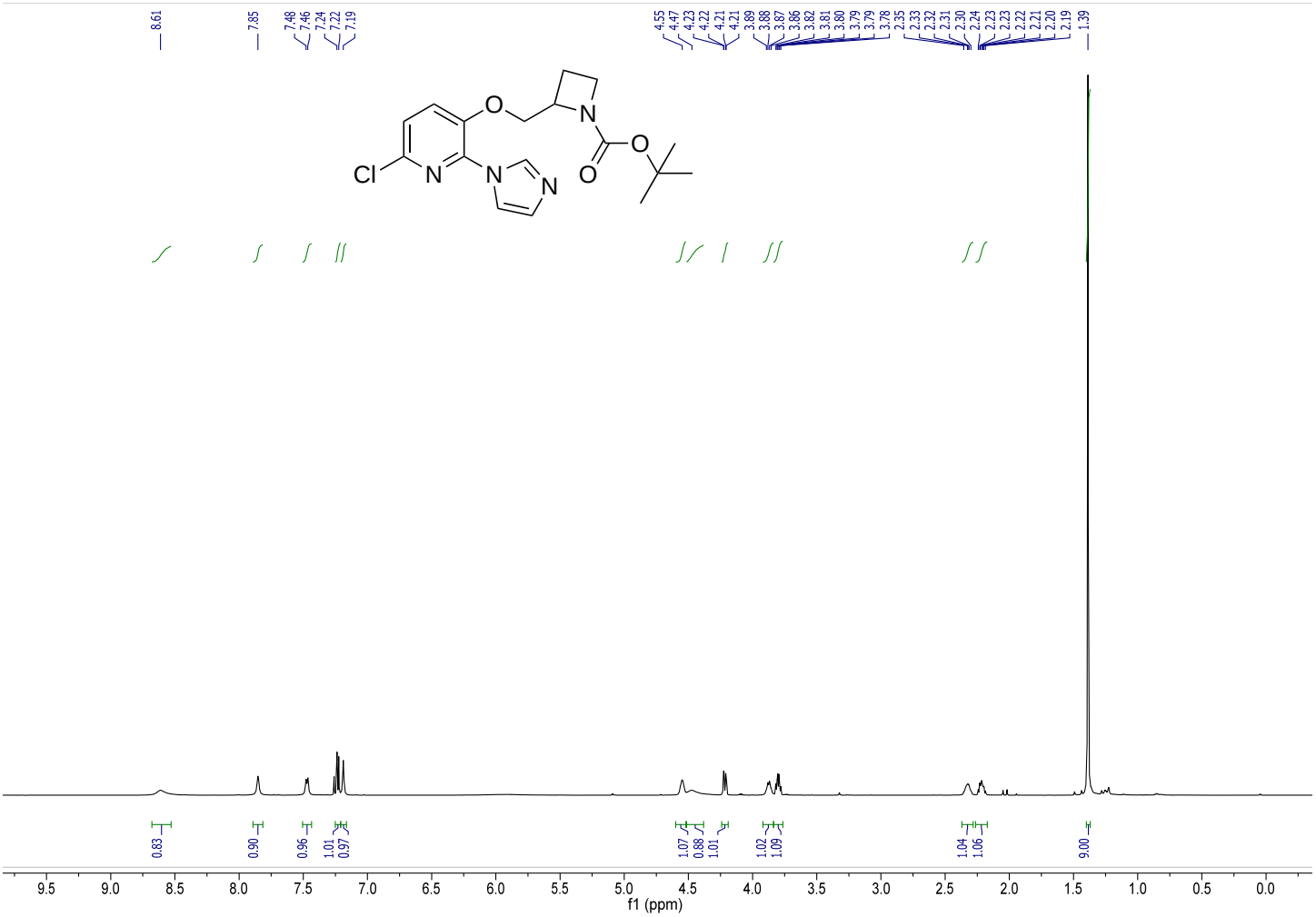
150.27
140.22
140.01
117.33
109.04
79.75
70.02
59.97
47.35
41.02
31.80
29.58
29.34
29.20
28.34
27.03
22.61
18.97
14.05
O
N
O
Cl
N
NH
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.85
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7.24
7.22
7.19
4.55
4.47
4.23
4.22
4.21
4.21
3.89
3.88
3.87
3.86
3.82
3.81
3.80
3.79
3.79
3.78
2.35
2.33
2.32
2.31
2.30
2.24
2.23
2.23
2.22
2.21
2.20
2.19
1.39
Cl
N
N
N
O
N
O
O
0.83
0.90
0.96
1.01
0.97
1.07
0.88
1.01
1.02
1.09
1.04
1.06
9.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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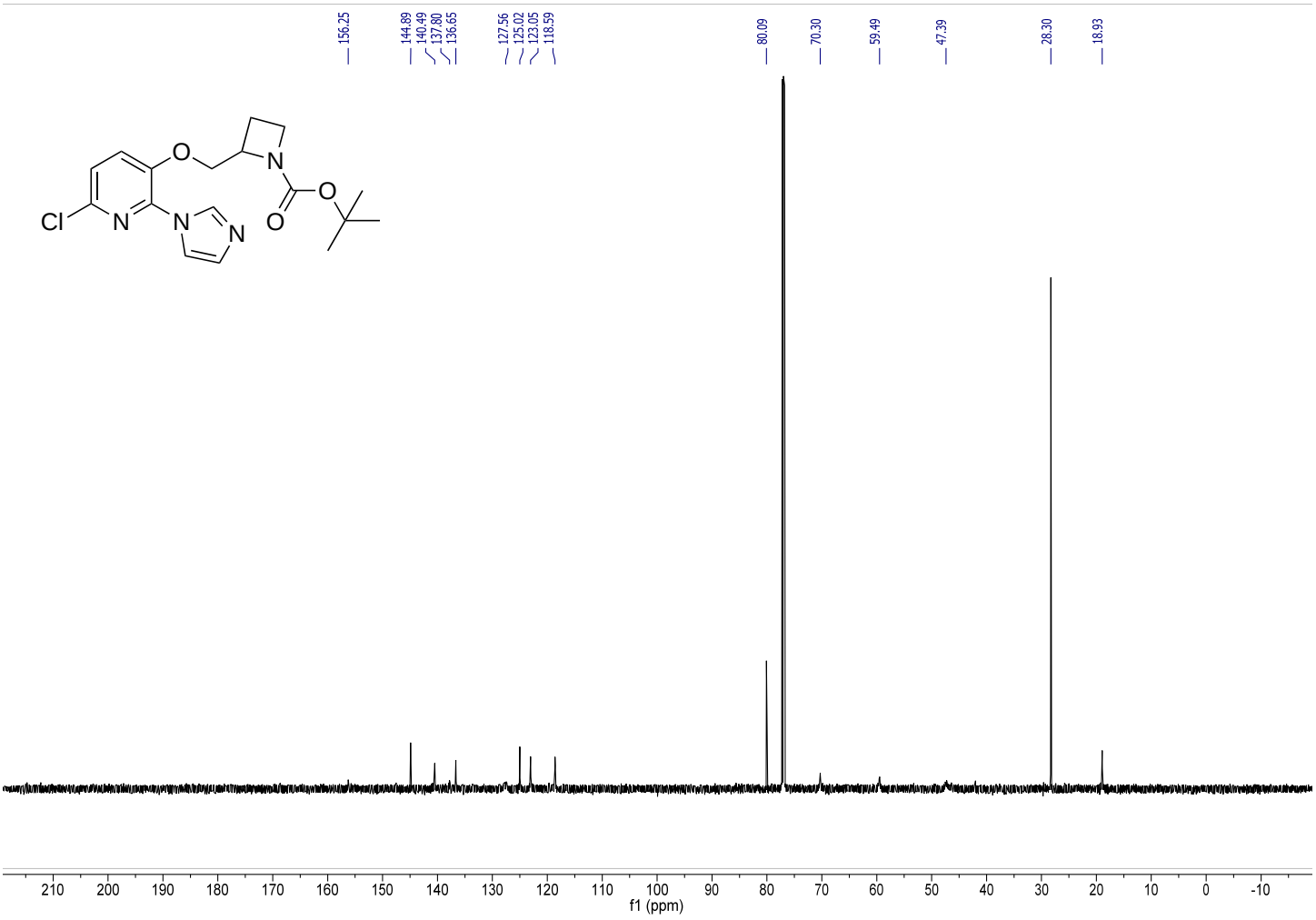
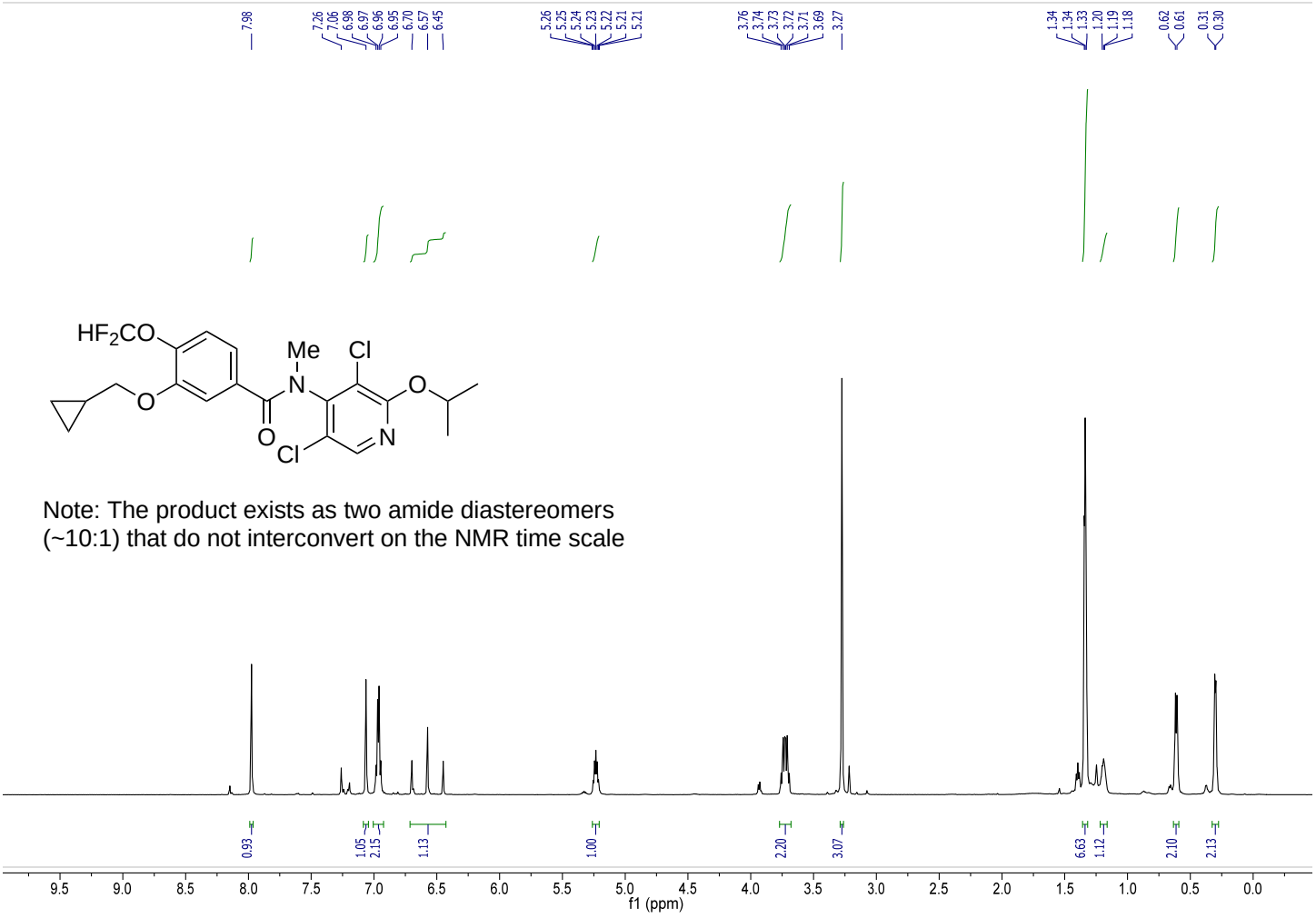
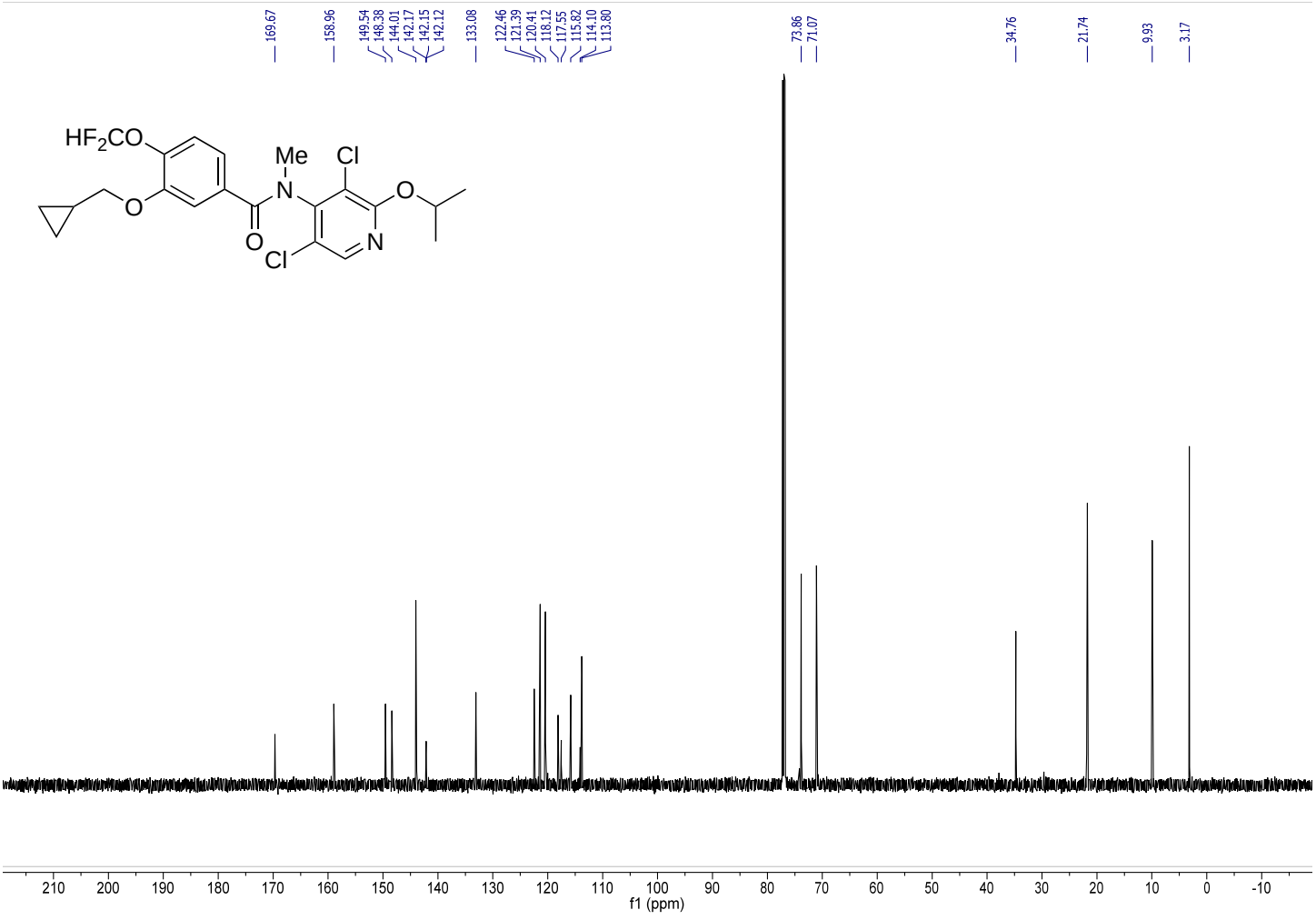
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


156.25
144.89
140.49
137.80
136.65
127.56
125.02
123.05
118.59
80.09
70.30
59.49
47.39
28.30
18.93
Cl
N
N
N
O
O
N
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



Note: The product exists as two amide diastereomers (~10:1) that do not interconvert on the NMR time scale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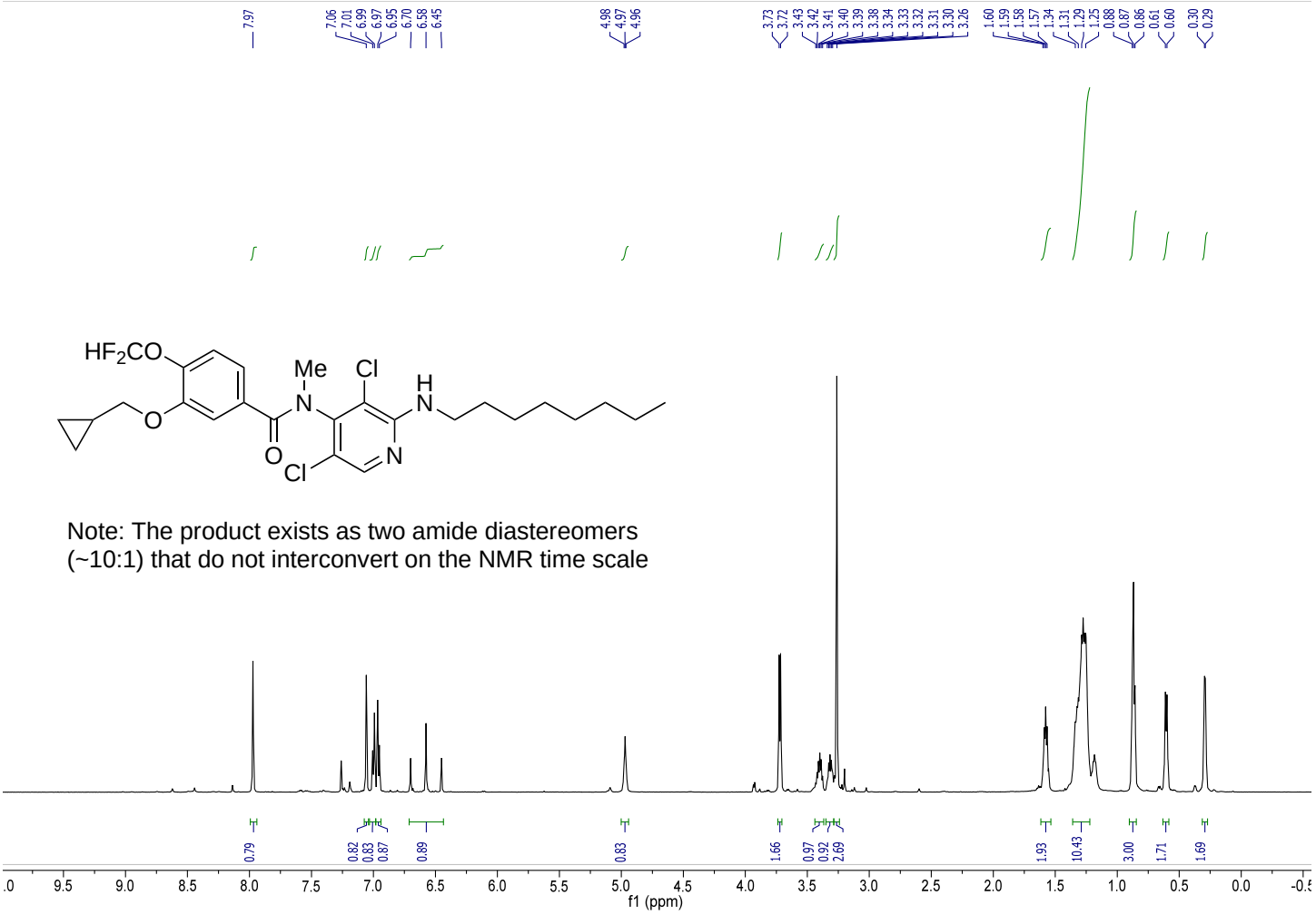
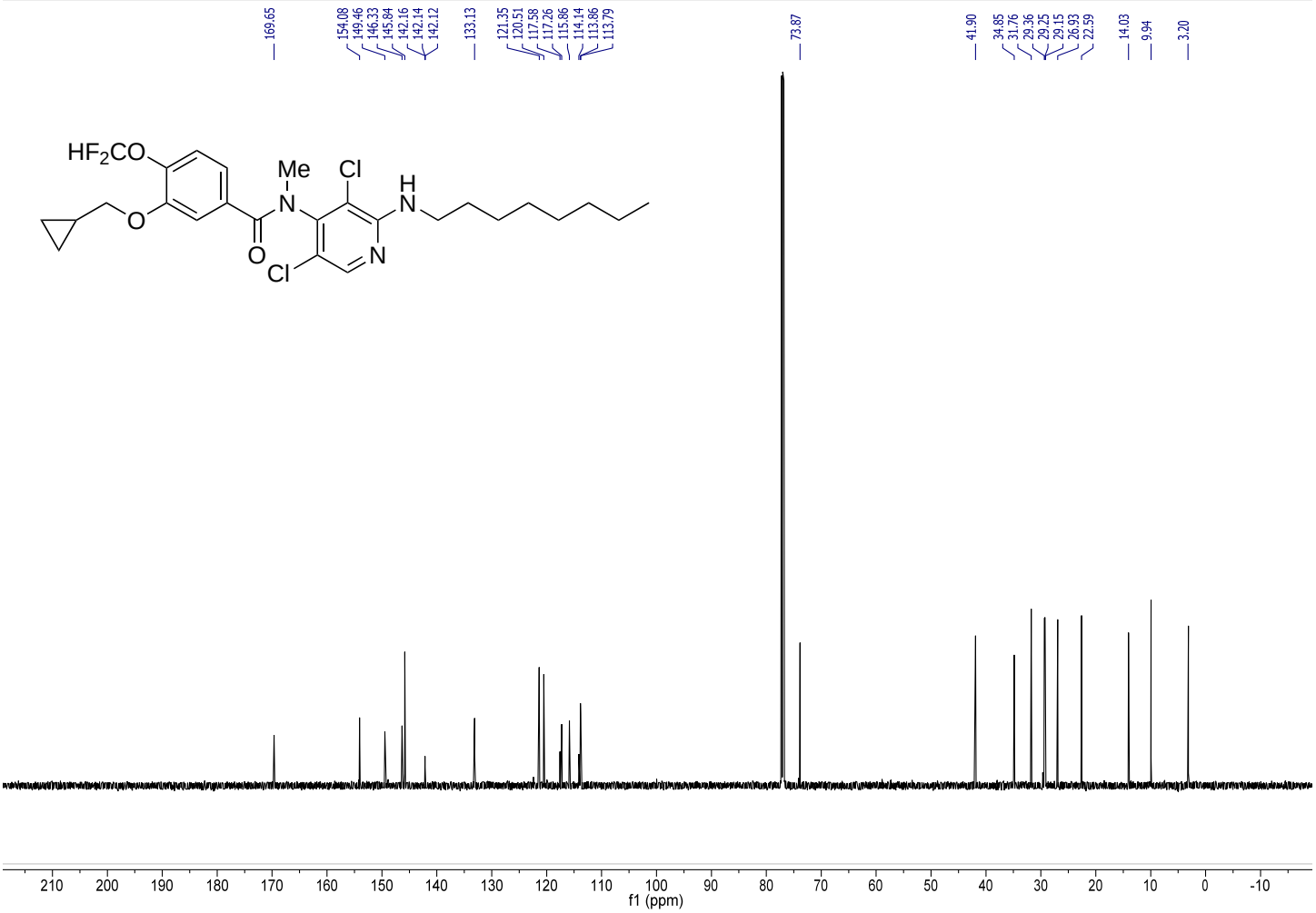
149.54
148.38
144.01
142.17
142.15
142.12
133.08
122.46
121.39
120.41
118.12
117.55
115.82
114.10
113.80
73.86
71.07
34.76
21.74
9.93
3.17
HF2CO
Me
N
Cl
O
O
O
Cl
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



Note: The product exists as two amide diastereomers (~10:1) that do not interconvert on the NMR time scale


169.65
154.08
149.46
146.33
145.84
142.16
142.14
142.12
133.13
121.35
120.51
117.58
117.26
115.86
114.14
113.86
113.79
73.87
41.90
34.85
31.76
29.36
29.25
29.15
26.93
22.59
14.03
9.94
3.20
HF2CO
Me
Cl
H
N
O
N
O
Cl
N
210
200
190
180
170
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120
110
100
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80
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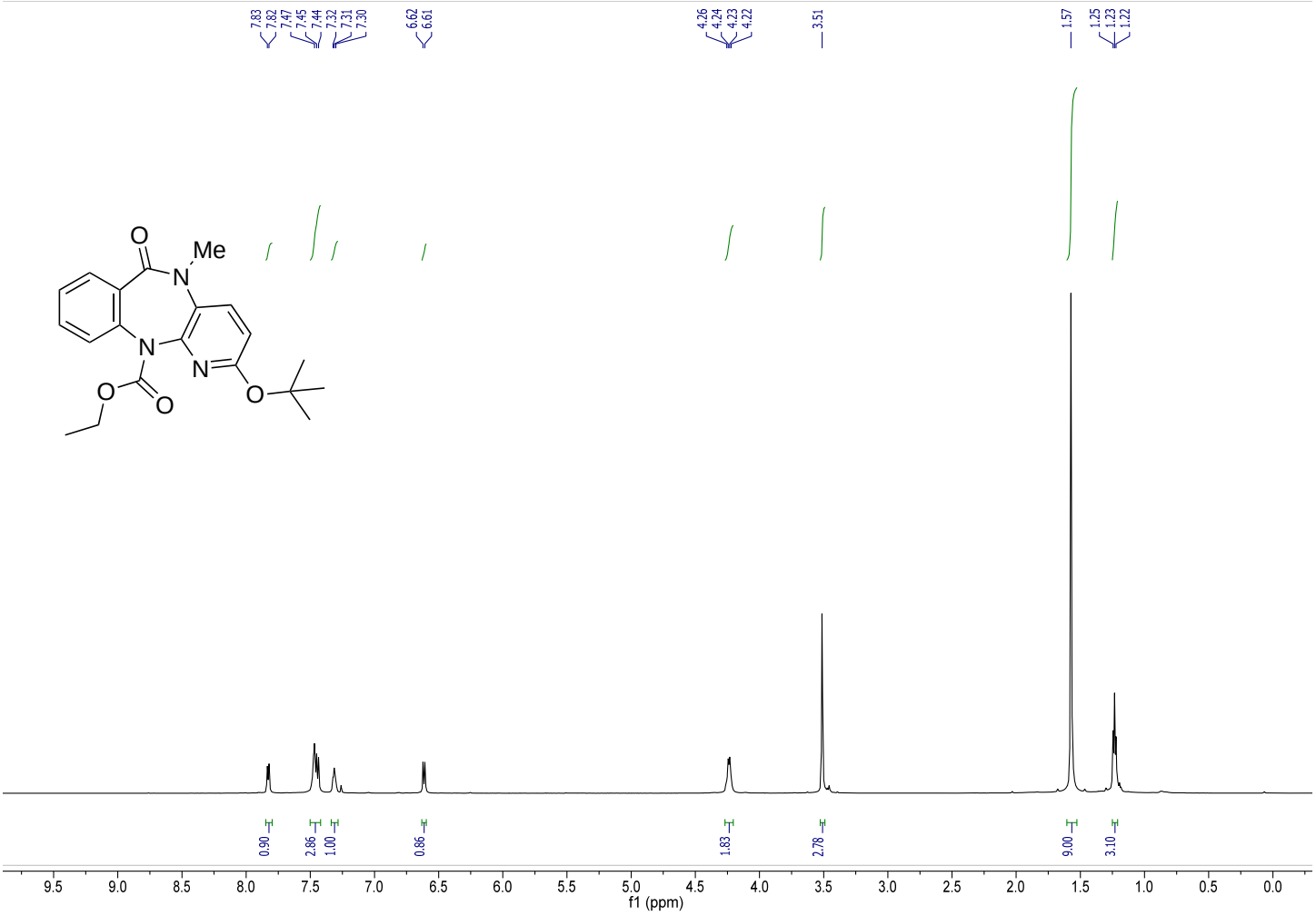
40
30
20
10
0
-10
f1 (ppm)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7.32
7.31
7.30
6.62
6.61
4.26
4.24
4.23
4.22
3.51
1.57
1.25
1.23
1.22
O
Me
N
N
N
O
O
O
0.90
2.86
1.00
0.86
1.83
2.78
9.00
3.10
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.5
3.0
2.5
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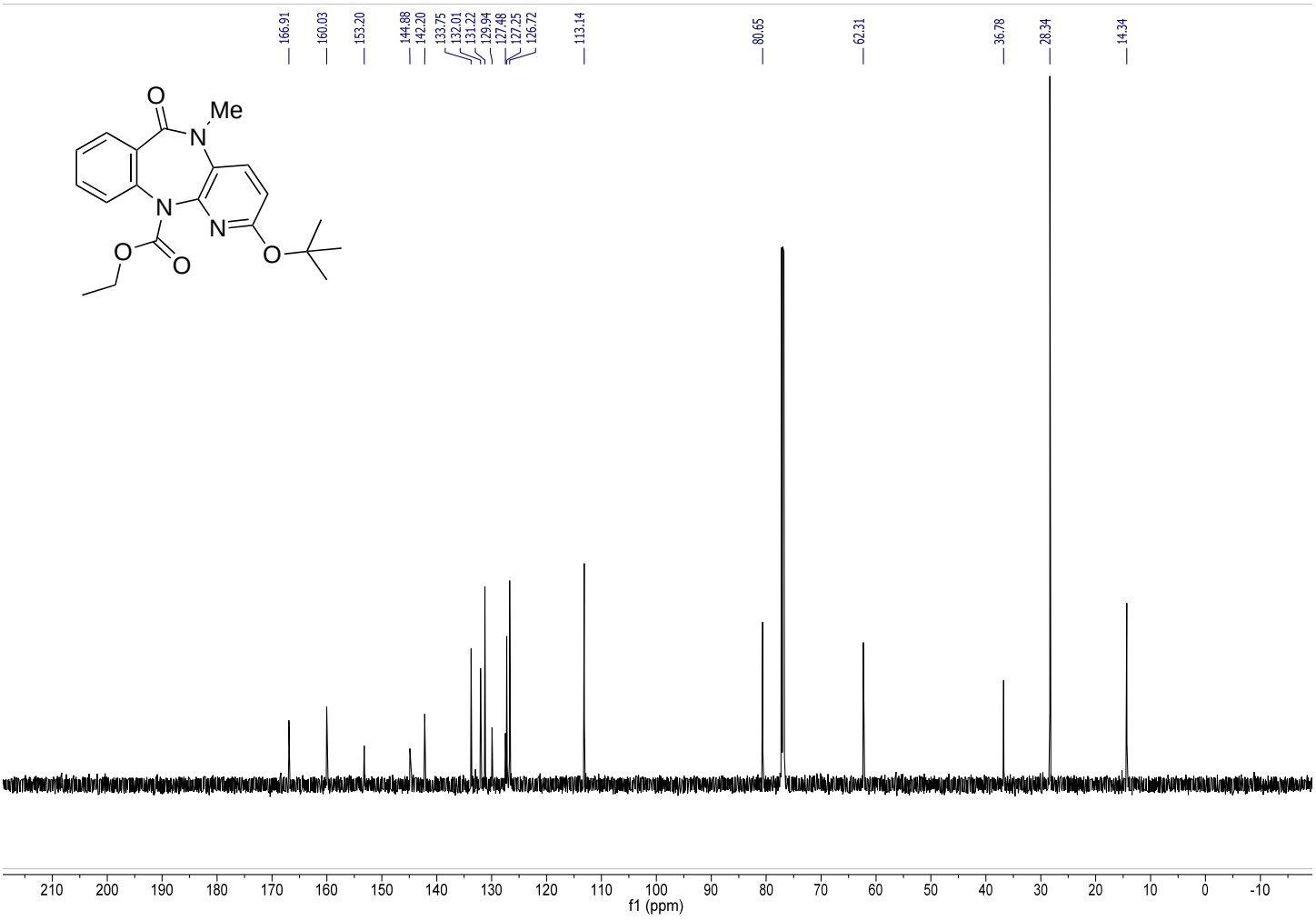
1.0
0.5
0.0
f1 (ppm)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153.20
144.88
142.20
133.75
132.01
131.22
129.94
127.48
127.25
126.72
113.14
80.65
62.31
36.78
28.34
14.34
O
Me
N
N
N
O
O
O
210
200
190
180
170
160
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140
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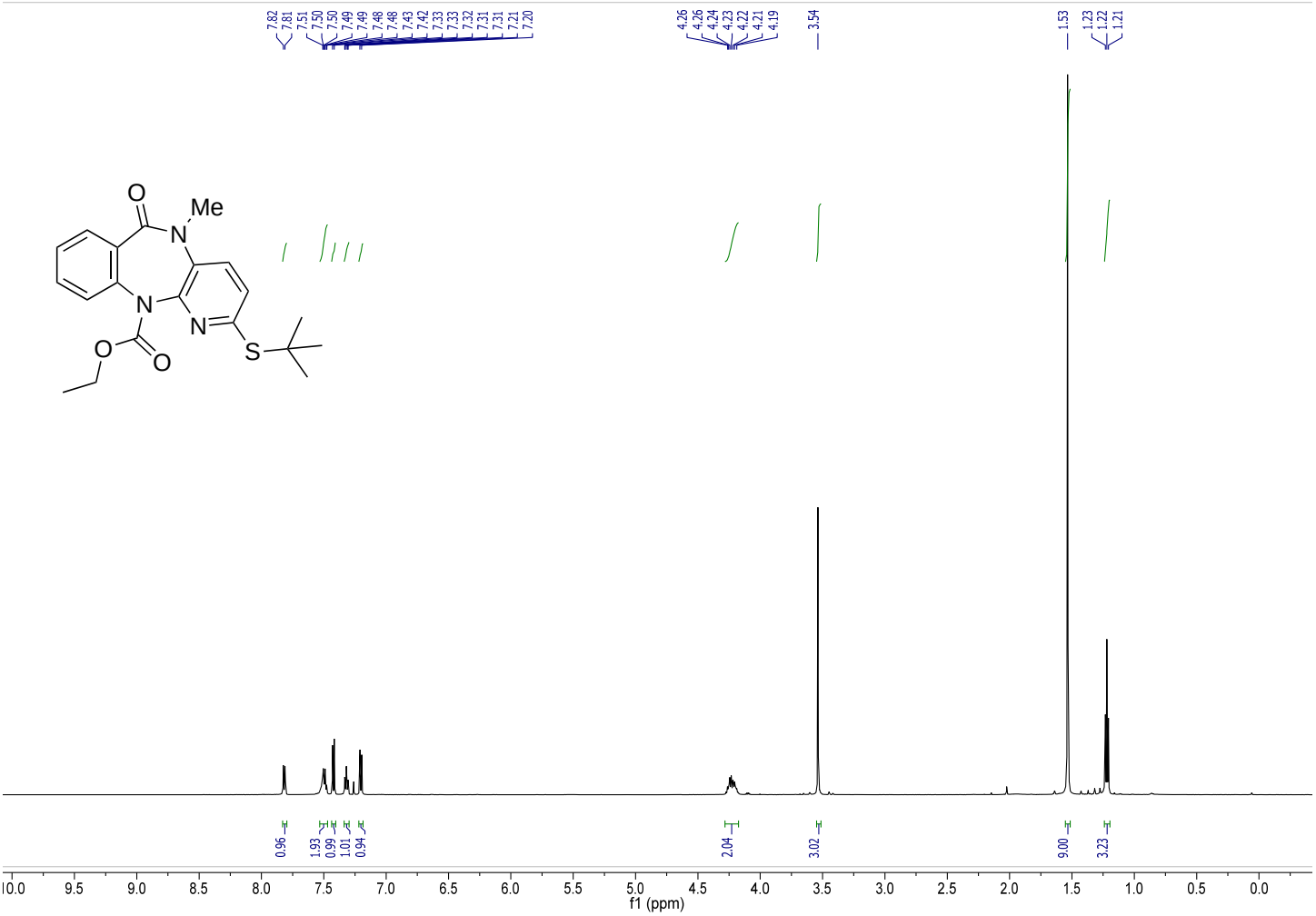
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.42
7.33
7.33
7.32
7.31
7.31
7.21
7.20
4.26
4.26
4.24
4.23
4.22
4.21
4.19
3.54
1.53
1.23
1.22
1.21
O
Me
N
N
N
O
O
S
0.96
1.93
0.99
1.01
0.94
2.04
3.02
9.00
3.23
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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1.0
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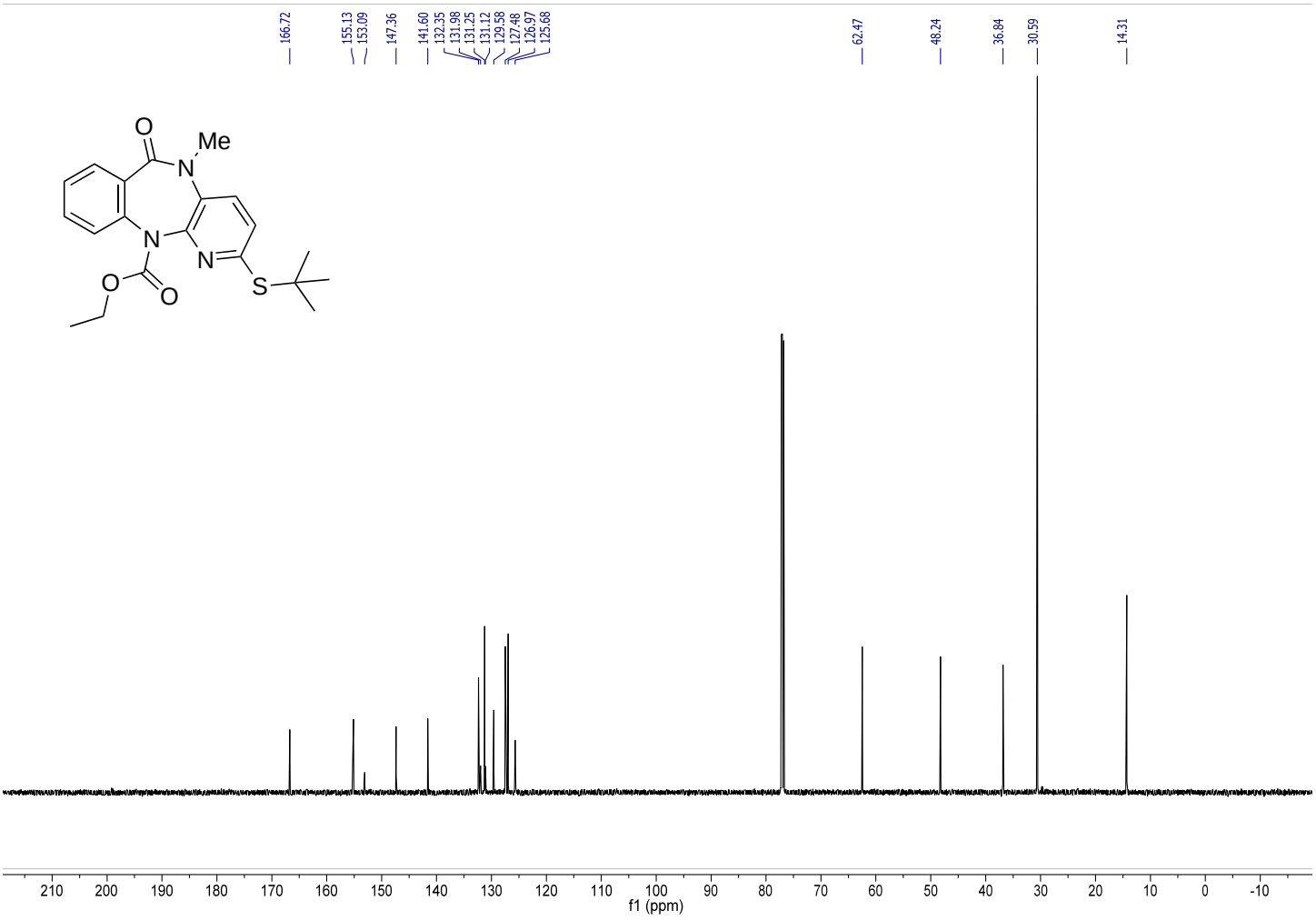
0.0
f1 (ppm)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132.35
131.98
131.25
131.12
129.58
127.48
126.97
125.68
62.47
48.24
36.84
30.59
14.31
O
Me
N
N
N
O
O
S
210
200
190
180
170
160
150
140
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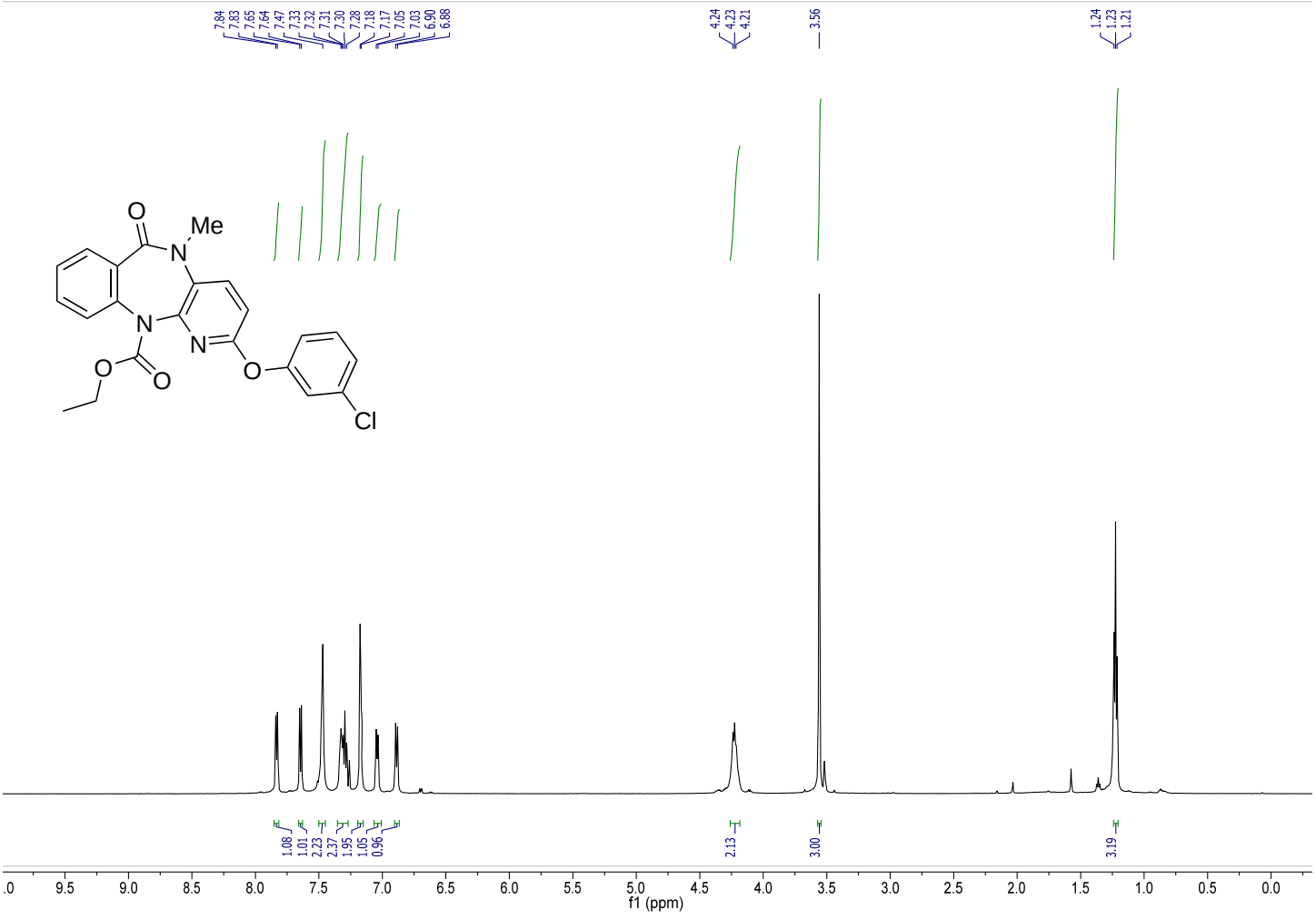
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.32
7.31
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7.28
7.18
7.17
7.05
7.03
6.90
6.88
4.24
4.23
4.21
3.56
1.24
1.23
1.21
O
Me
N
N
N
O
O
O
Cl
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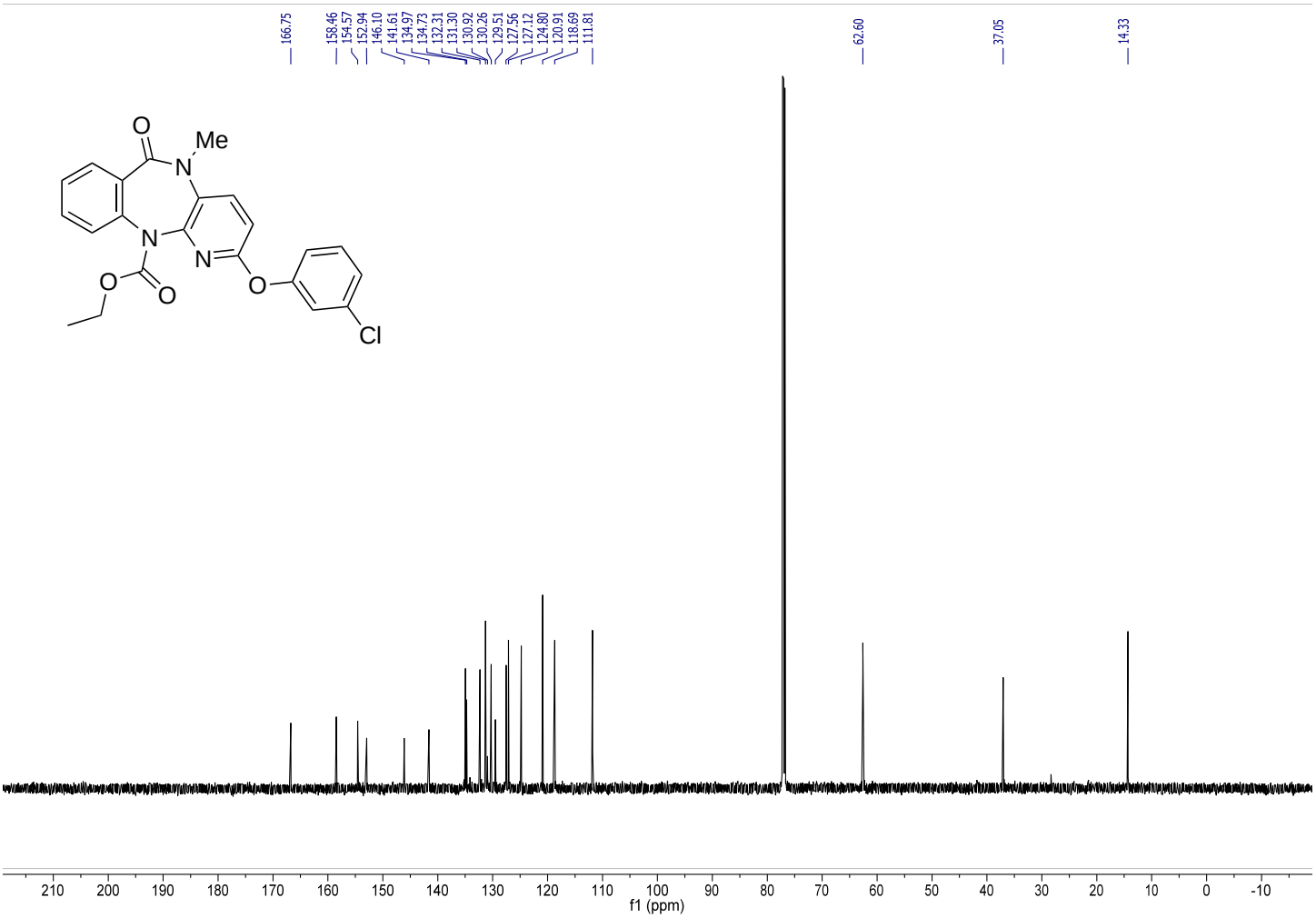
2.23
2.37
1.95
1.05
0.96
2.13
3.00
3.19
f1 (ppm)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131.30
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130.26
129.51
127.56
127.12
124.80
120.91
118.69
111.81
62.60
37.05
14.33
O
Me
N
N
N
O
O
O
Cl
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
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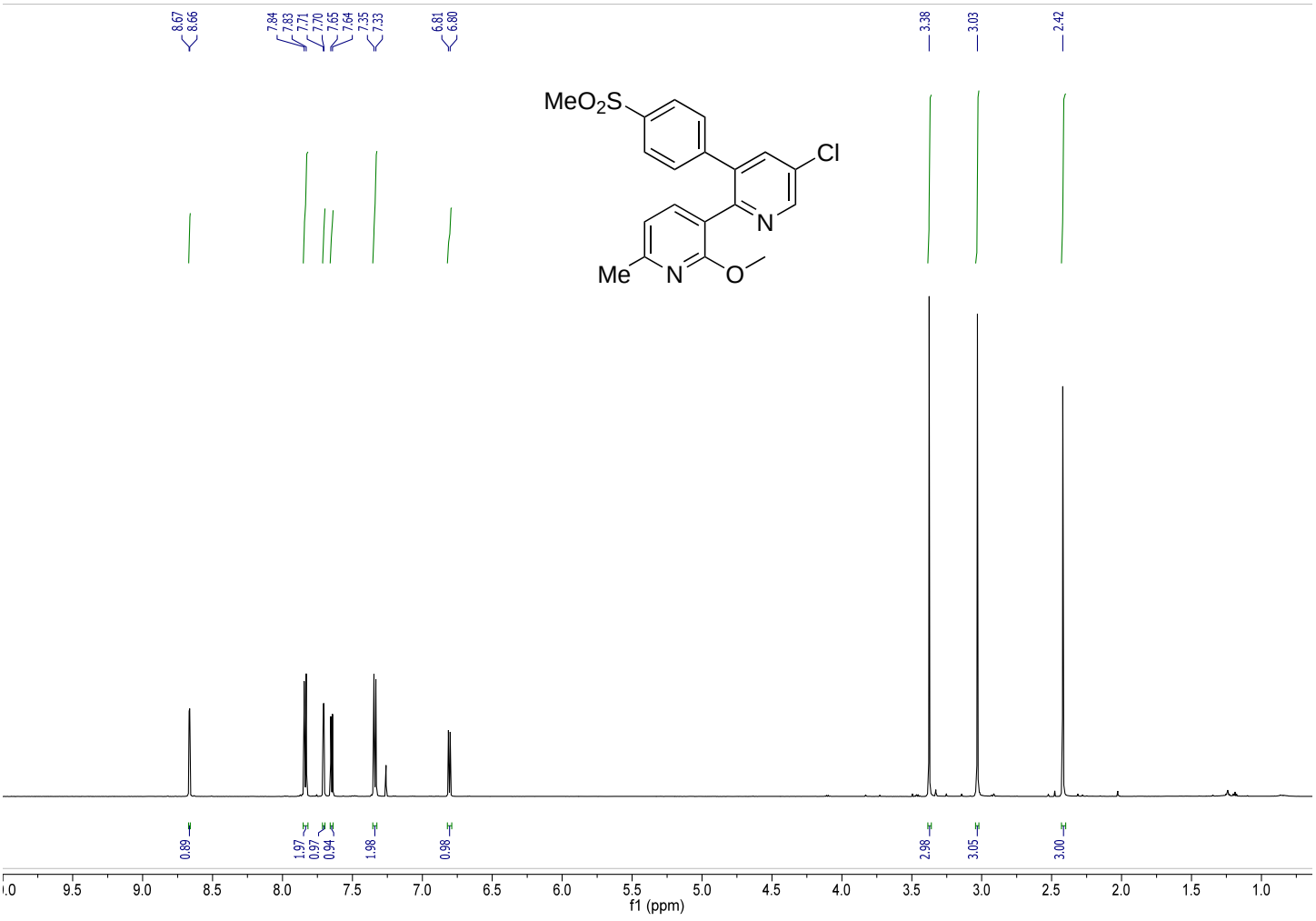
-10
f1 (ppm)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7.64
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7.33
6.81
6.80
3.38
3.03
2.42
MeO2S
Cl
N
Me
N
O
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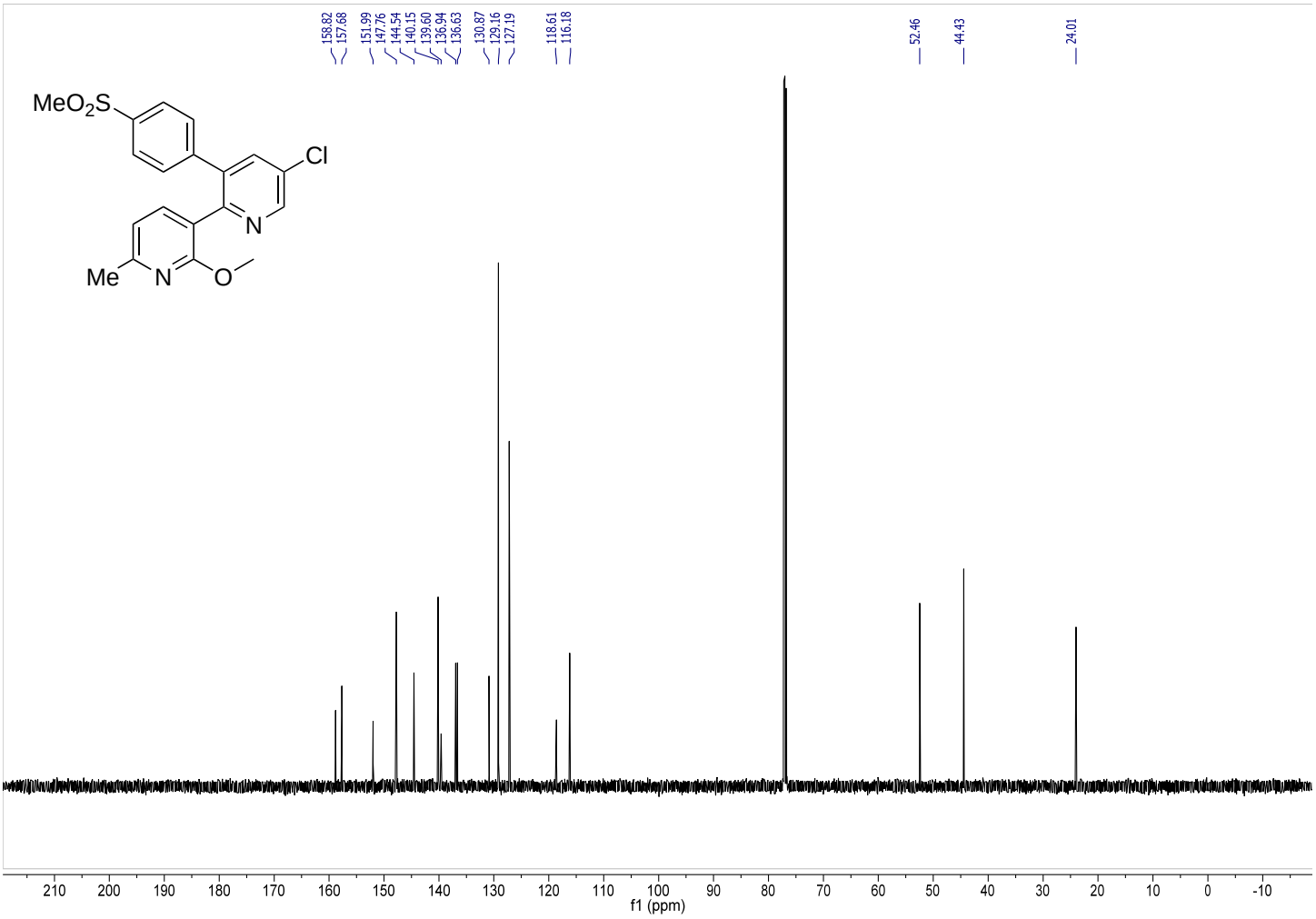
1.97
0.97
0.94
1.98
0.98
2.98
3.05
3.00
f1 (ppm)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130.87
129.16
127.19
118.61
116.18
52.46
44.43
24.01
MeO2S
Cl
N
Me
N
O
210
200
190
180
170
160
150
140
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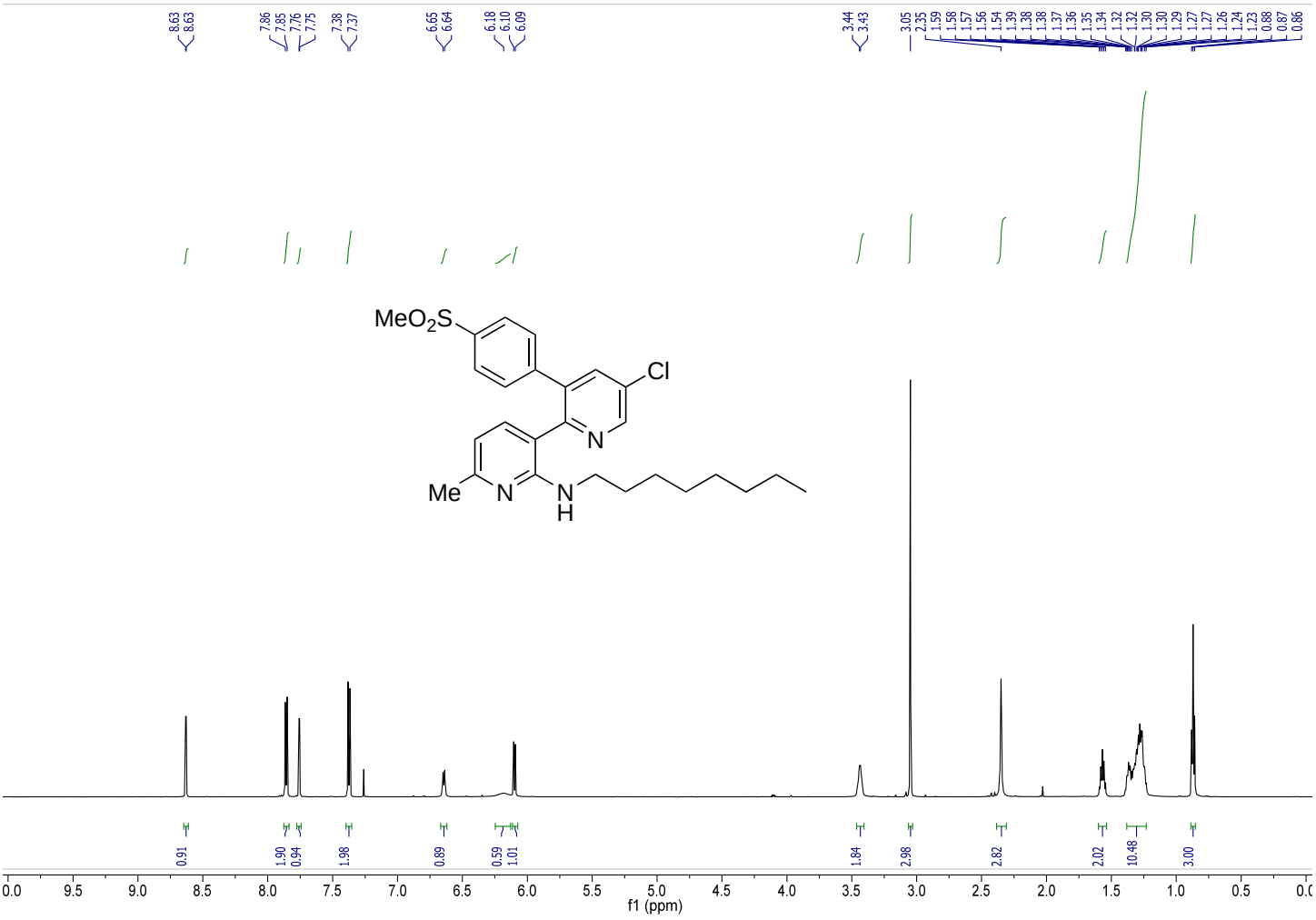
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.37
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6.64
6.18
6.10
6.09
3.44
3.43
3.05
2.35
1.59
1.58
1.57
1.56
1.54
1.39
1.38
1.38
1.37
1.36
1.35
1.34
1.32
1.32
1.30
1.30
1.29
1.27
1.27
1.26
1.24
1.23
0.88
0.87
0.86
MeO2S
Cl
N
Me
N
N
H
0.91
1.90
0.94
1.98
0.89
0.59
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2.98
2.82
2.02
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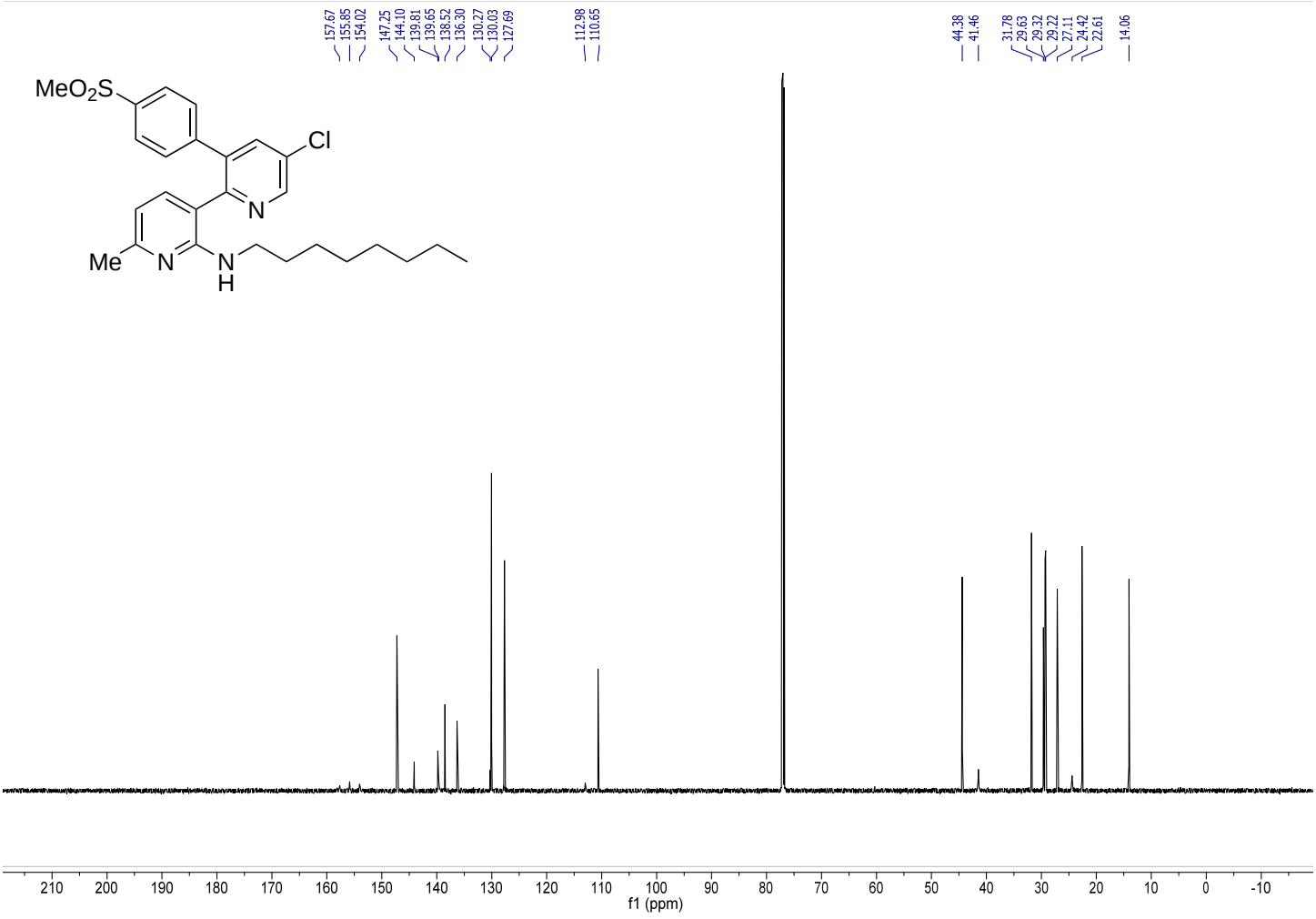
3.00
f1 (ppm)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139.65
138.52
136.30
130.27
130.03
127.69
112.98
110.65
44.38
41.46
31.78
29.63
29.32
29.22
27.11
24.42
22.61
14.06
MeO2S
Cl
N
Me
N
N
H
210
200
190
180
170
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140
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120
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100
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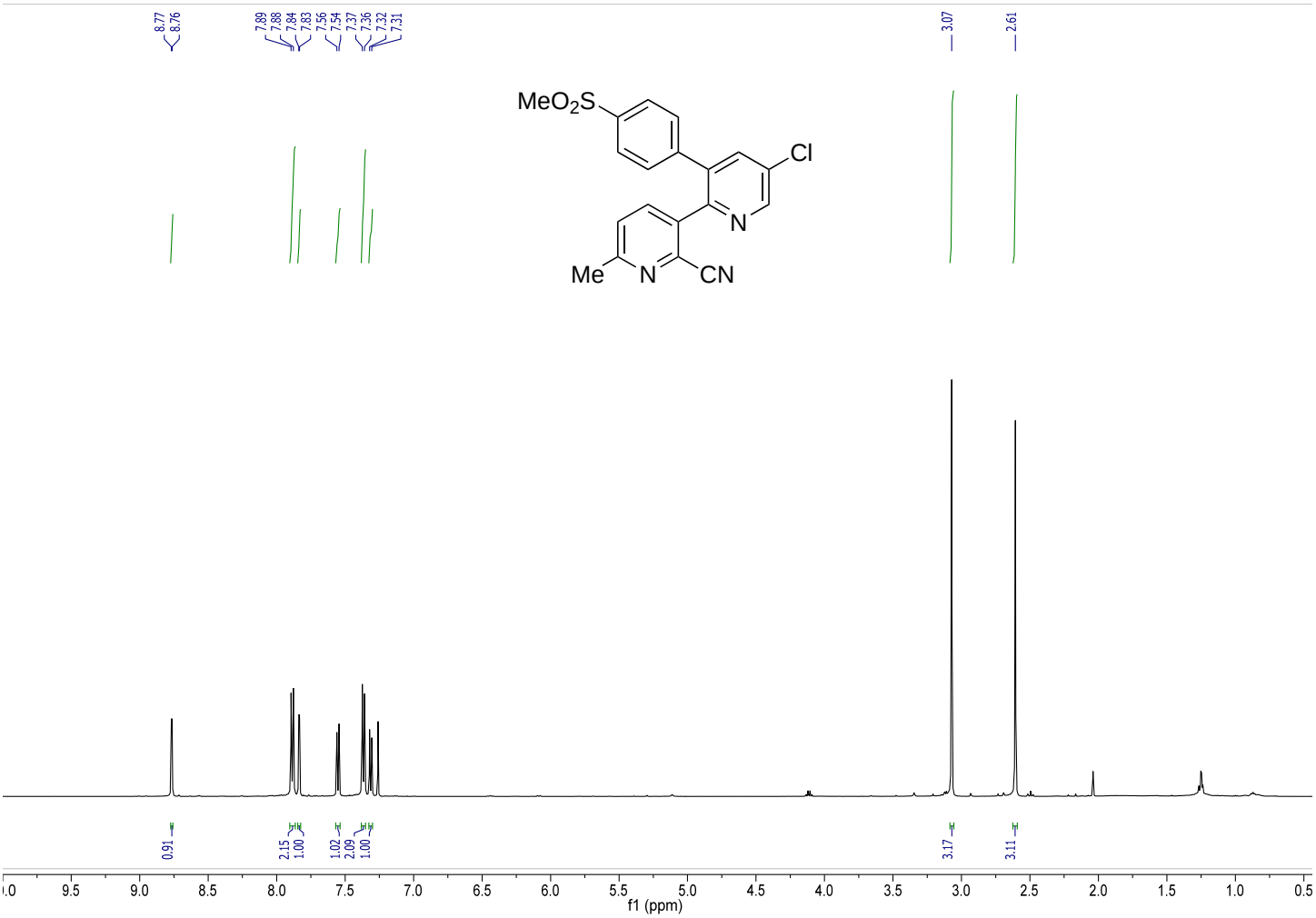
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.88
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7.83
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7.54
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7.36
7.32
7.31
3.07
2.61
MeO2S
Cl
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Me
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CN
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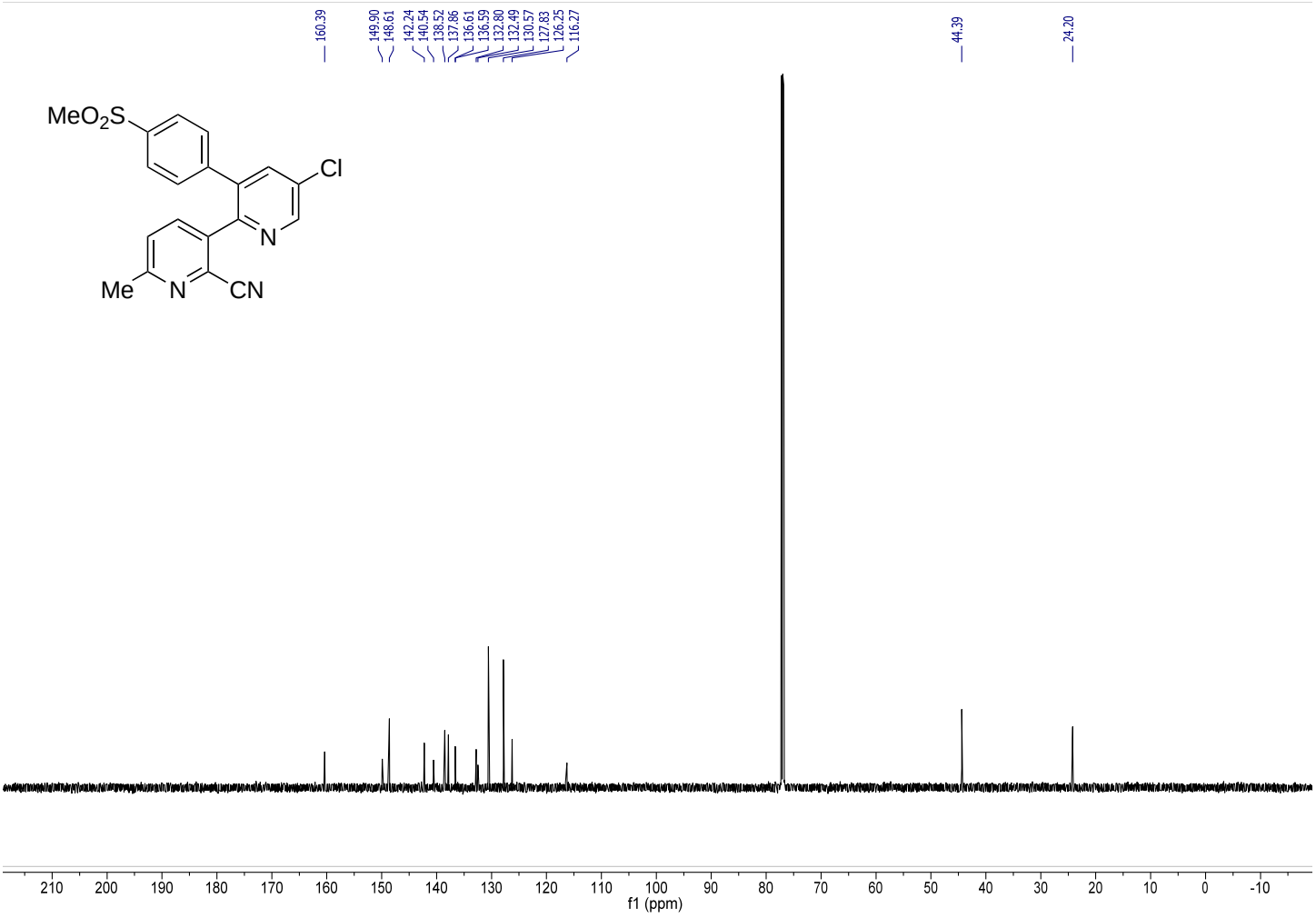
2.15
1.00
1.02
2.09
1.00
3.17
3.11
f1 (ppm)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138.52
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136.61
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132.49
130.57
127.83
126.25
116.27
44.39
24.20
MeO2S
Cl
N
Me
N
CN
210
200
190
180
170
160
150
140
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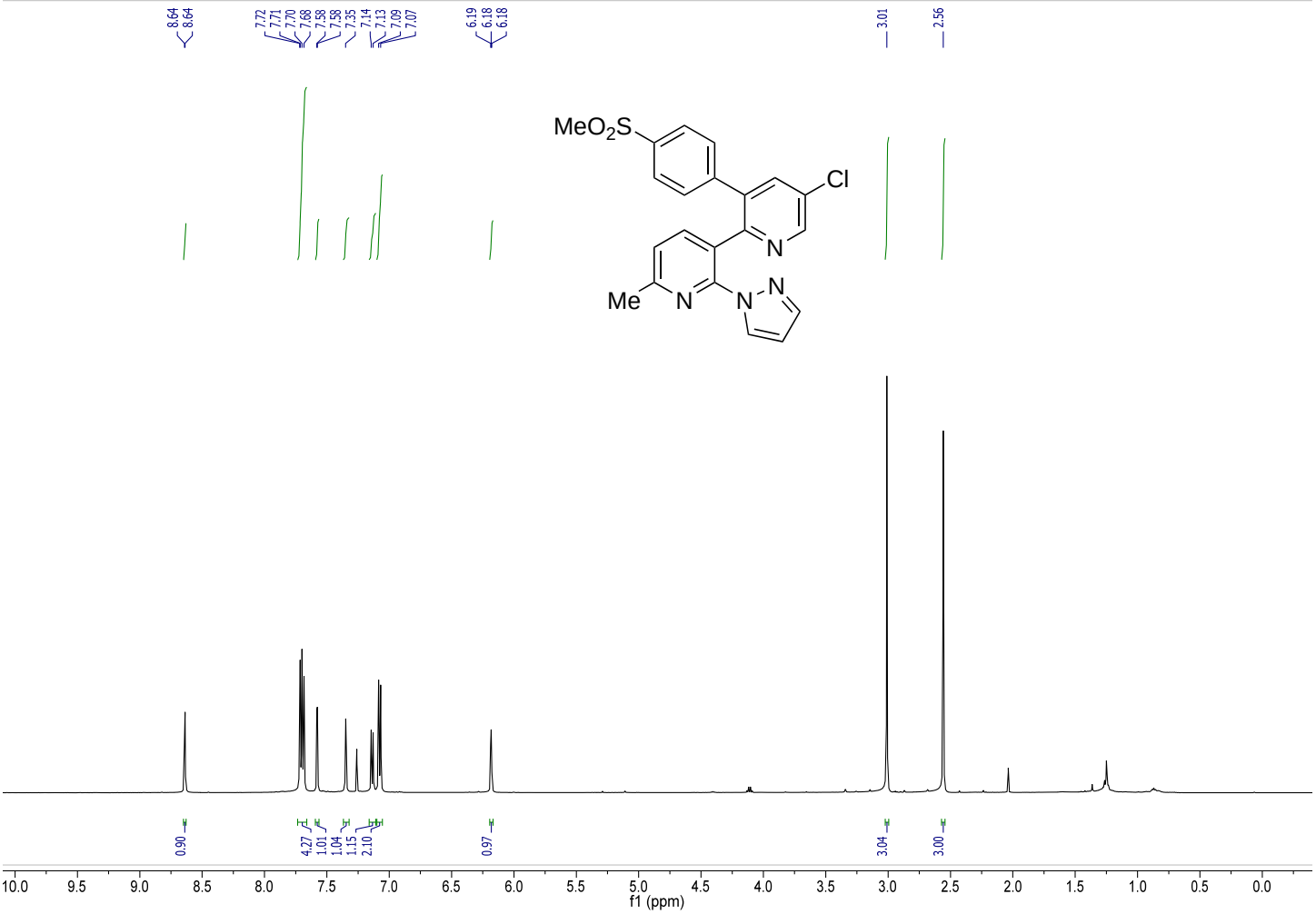
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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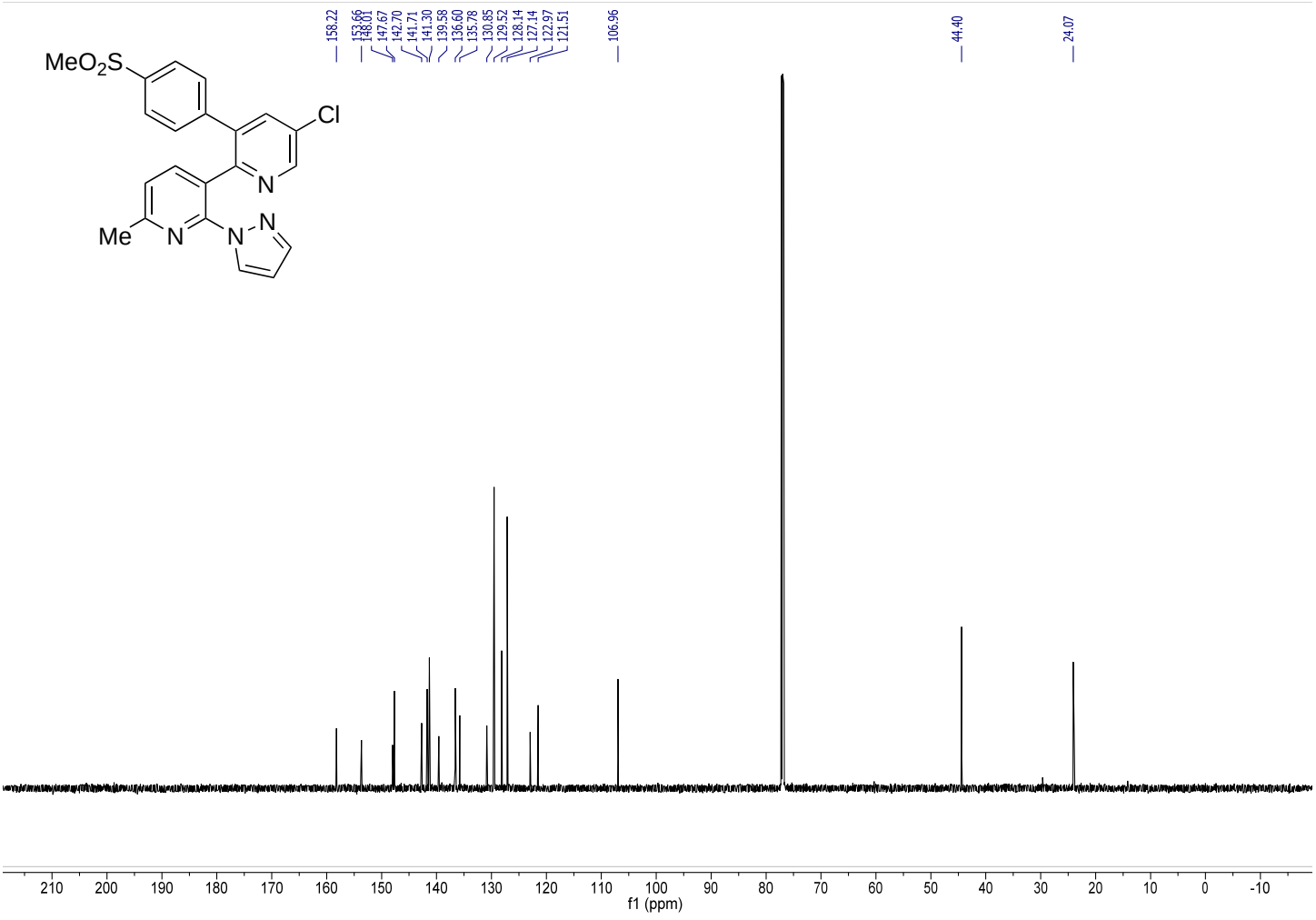
7.58
7.38
7.35
7.14
7.13
7.09
7.07
6.19
6.18
6.18
3.01
2.56
MeO2S
Cl
N
Me
N
N
N
0.90
4.27
1.01
1.04
1.15
2.10
0.97
3.04
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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148.01
147.67
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141.71
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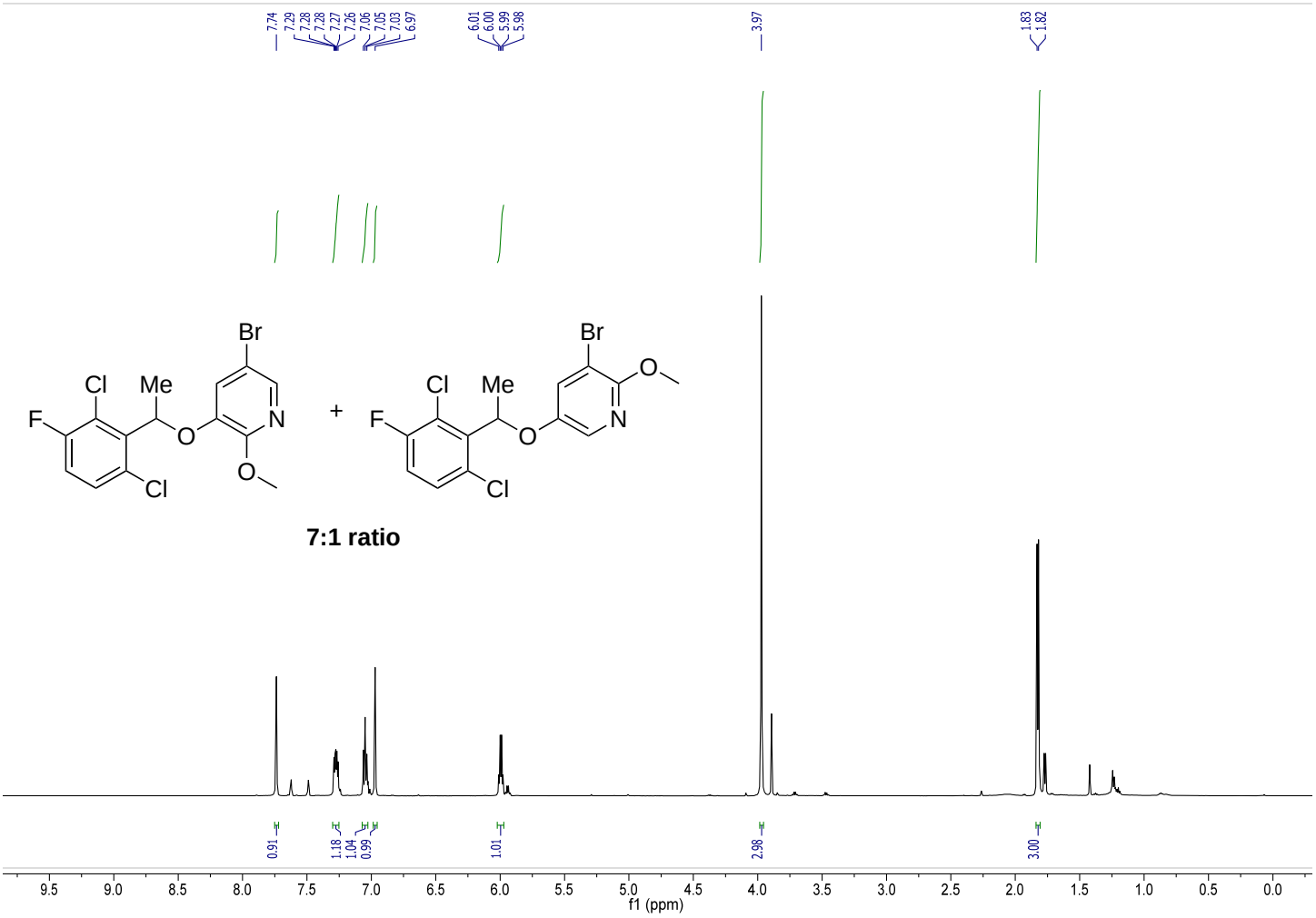
139.58
136.60
135.78
130.85
129.52
128.14
127.14
122.97
121.51
106.96
44.40
24.07
MeO2S
Cl
N
Me
N
N
N
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.29
7.28
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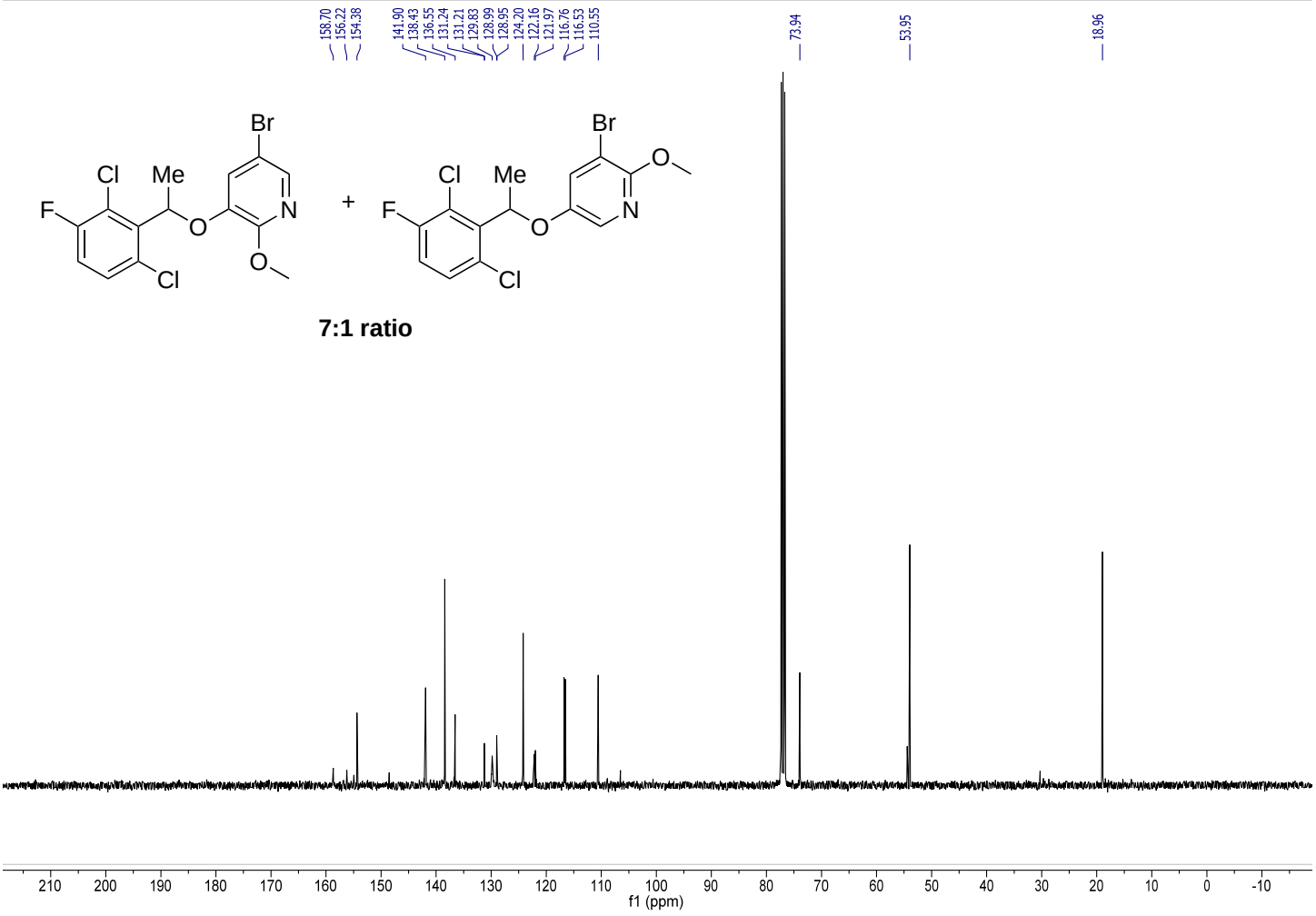
7.27
7.26
7.06
7.05
7.03
6.97
6.01
6.00
5.99
5.98
3.97
1.83
1.82
Br
Cl
Me
F
O
N
Cl
O
+
Br
Cl
Me
O
F
O
N
Cl
7:1 ratio
0.91
1.18
1.04
0.99
1.01
2.98
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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154.38
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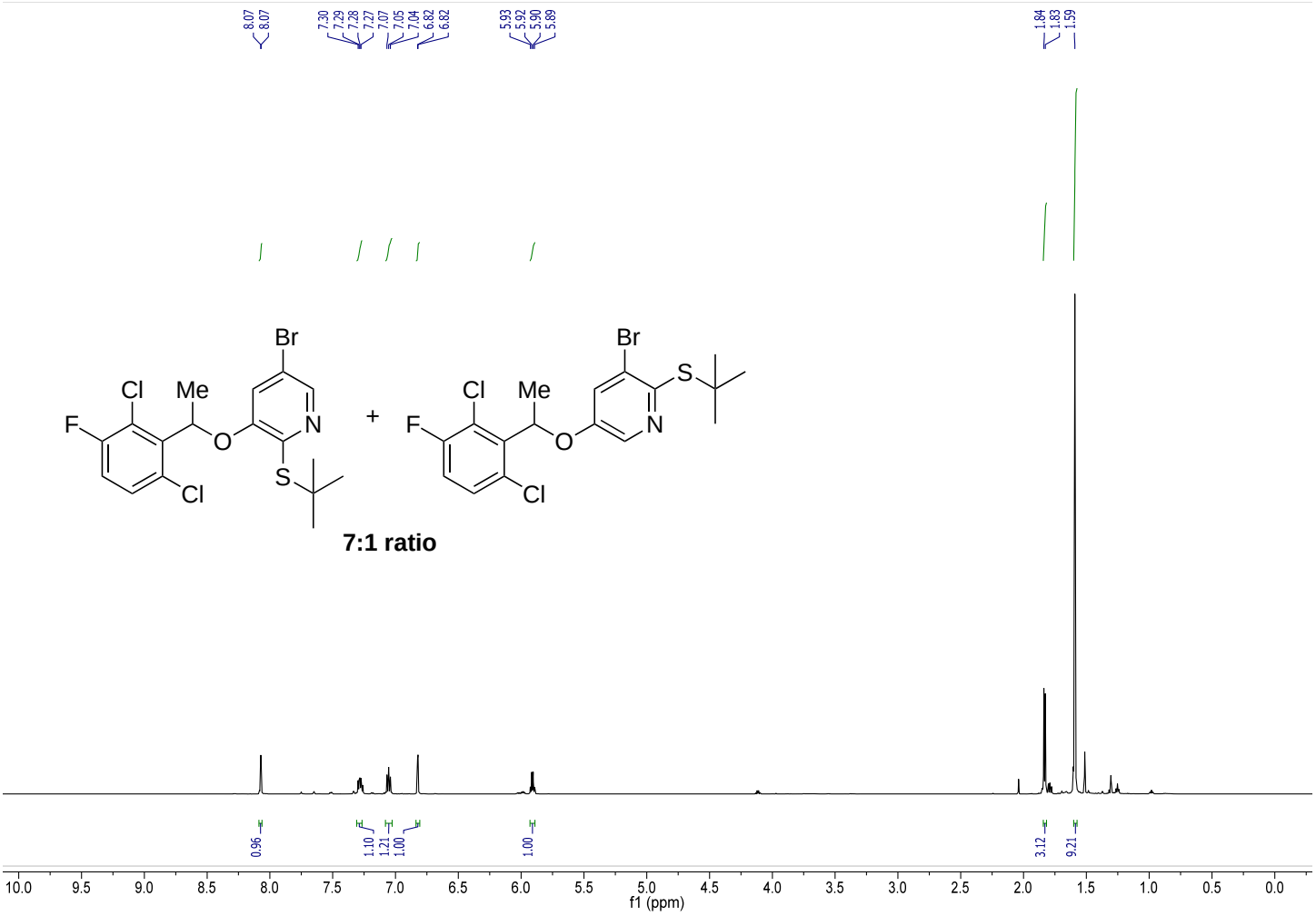
136.55
131.24
131.21
129.83
128.99
128.95
124.20
122.16
121.97
116.76
116.53
110.55
73.94
53.95
18.96
Br
Cl
Me
F
O
N
Cl
O
+
Br
O
Cl
Me
F
O
N
Cl
7:1 ratio
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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8.07
7.30
7.29
7.28
7.27
7.07
7.05
7.04
6.82
6.82
5.93
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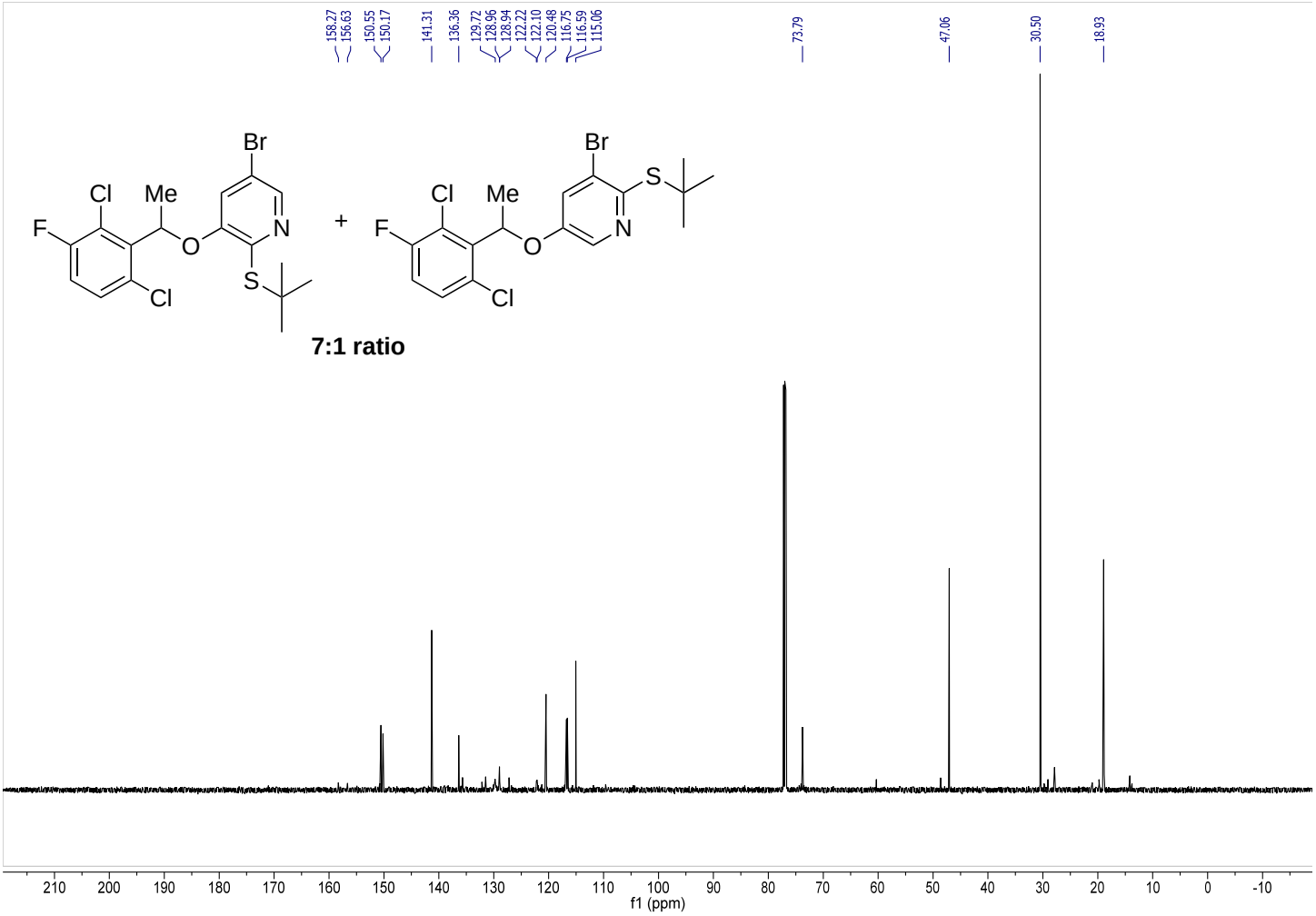
5.90
5.89
1.84
1.83
1.59
Br
Cl
Me
F
O
N
S
Cl
+
Br
Cl
Me
S
F
O
N
Cl
7:1 ratio
0.96
1.10
1.21
1.00
1.00
3.12
9.21
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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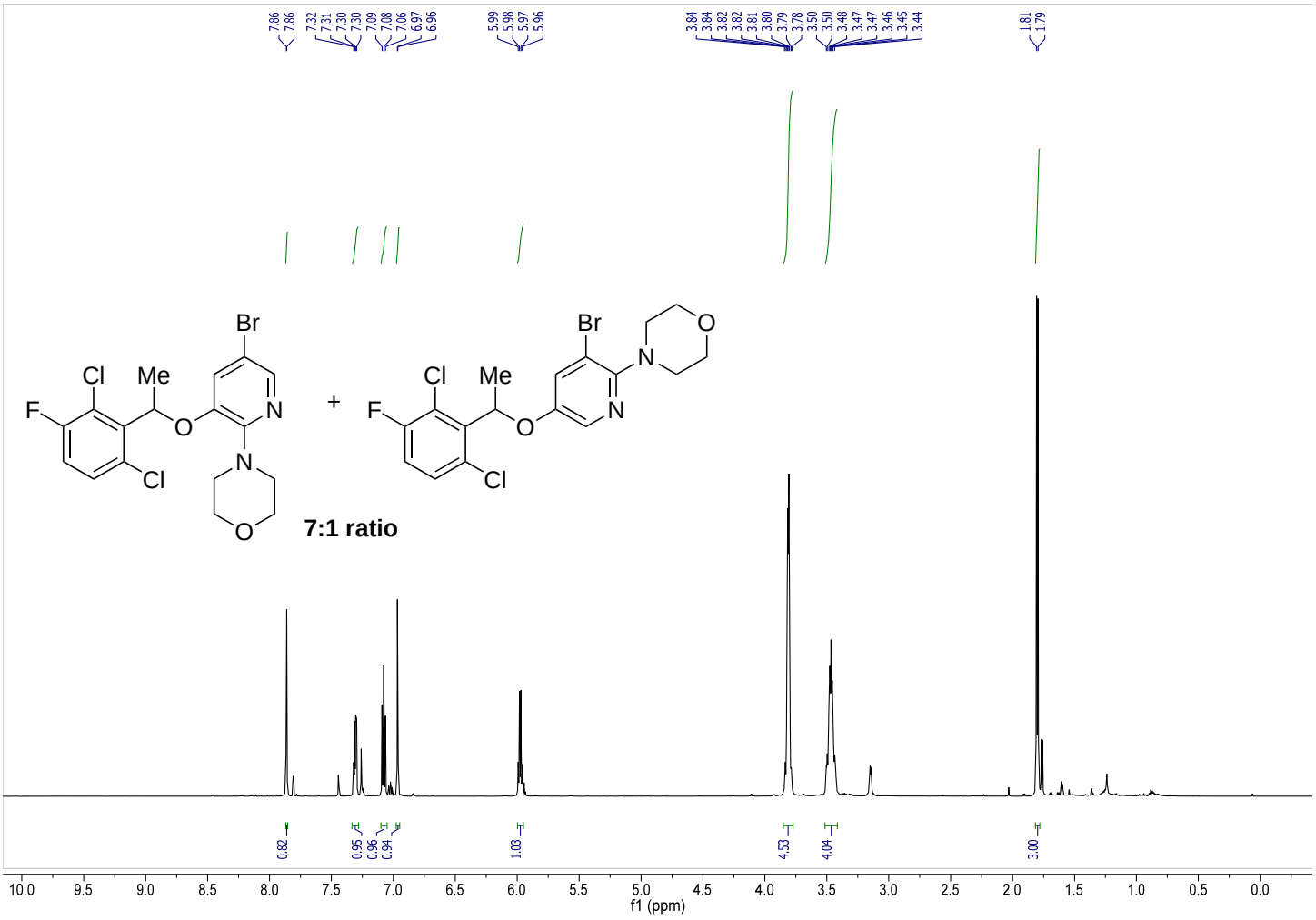
136.36
129.72
128.96
128.94
122.22
122.10
120.48
116.75
116.59
115.06
73.79
47.06
30.50
18.93
Br
Cl
Me
F
O
N
S
Cl
+
Br
S
Cl
Me
F
O
N
Cl
7:1 ratio
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.30
7.09
7.08
7.06
6.97
6.96
5.99
5.98
5.97
5.96
3.84
3.84
3.82
3.82
3.81
3.80
3.79
3.78
3.50
3.50
3.48
3.47
3.47
3.46
3.45
3.44
1.81
1.79
Br
Cl
Me
F
O
N
Cl
N
O
+
Br
O
N
Cl
Me
F
O
N
Cl
7:1 ratio
0.82
0.95
0.96
0.94
1.03
4.53
4.04
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.5
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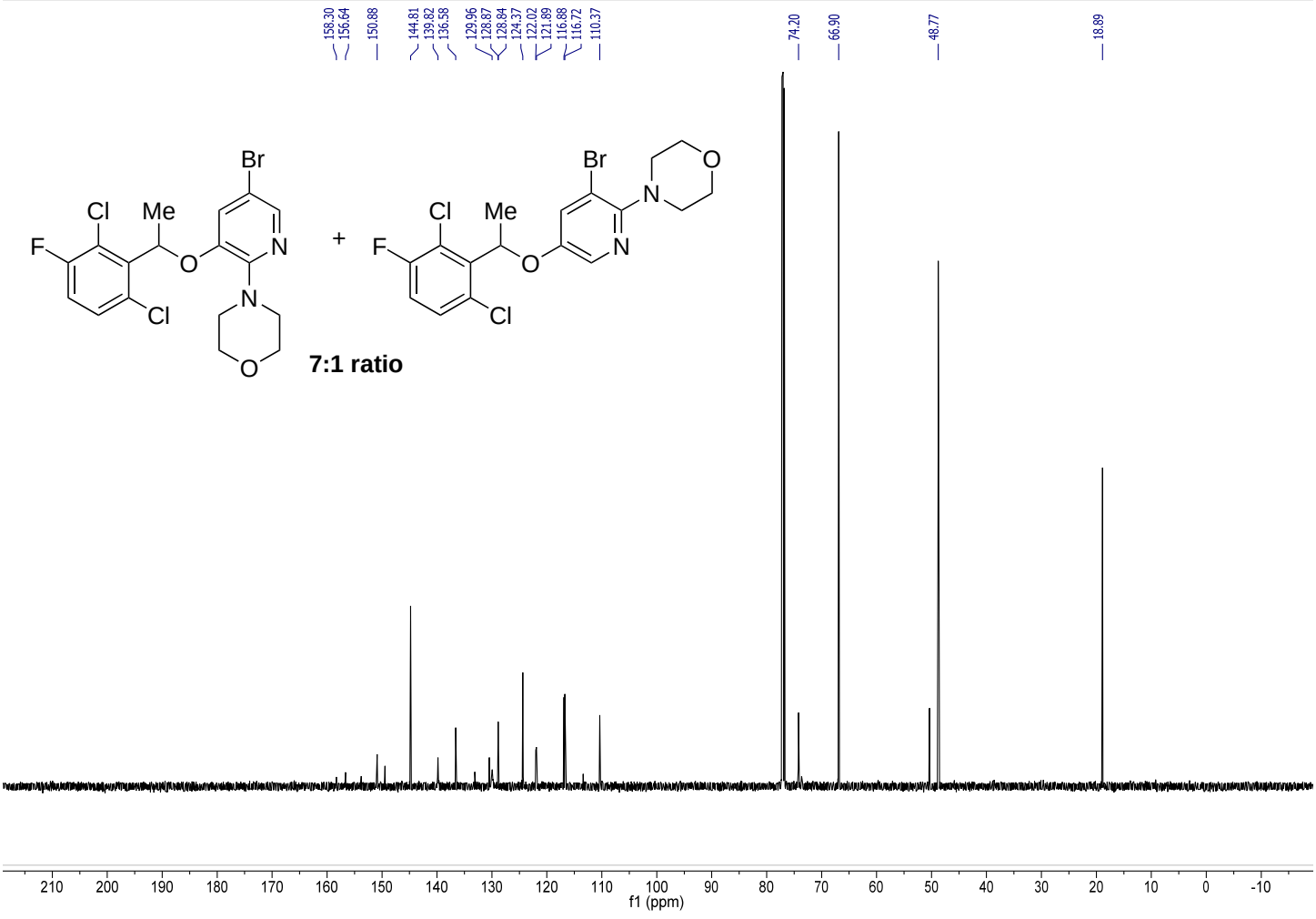
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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128.87
128.84
124.37
122.02
121.89
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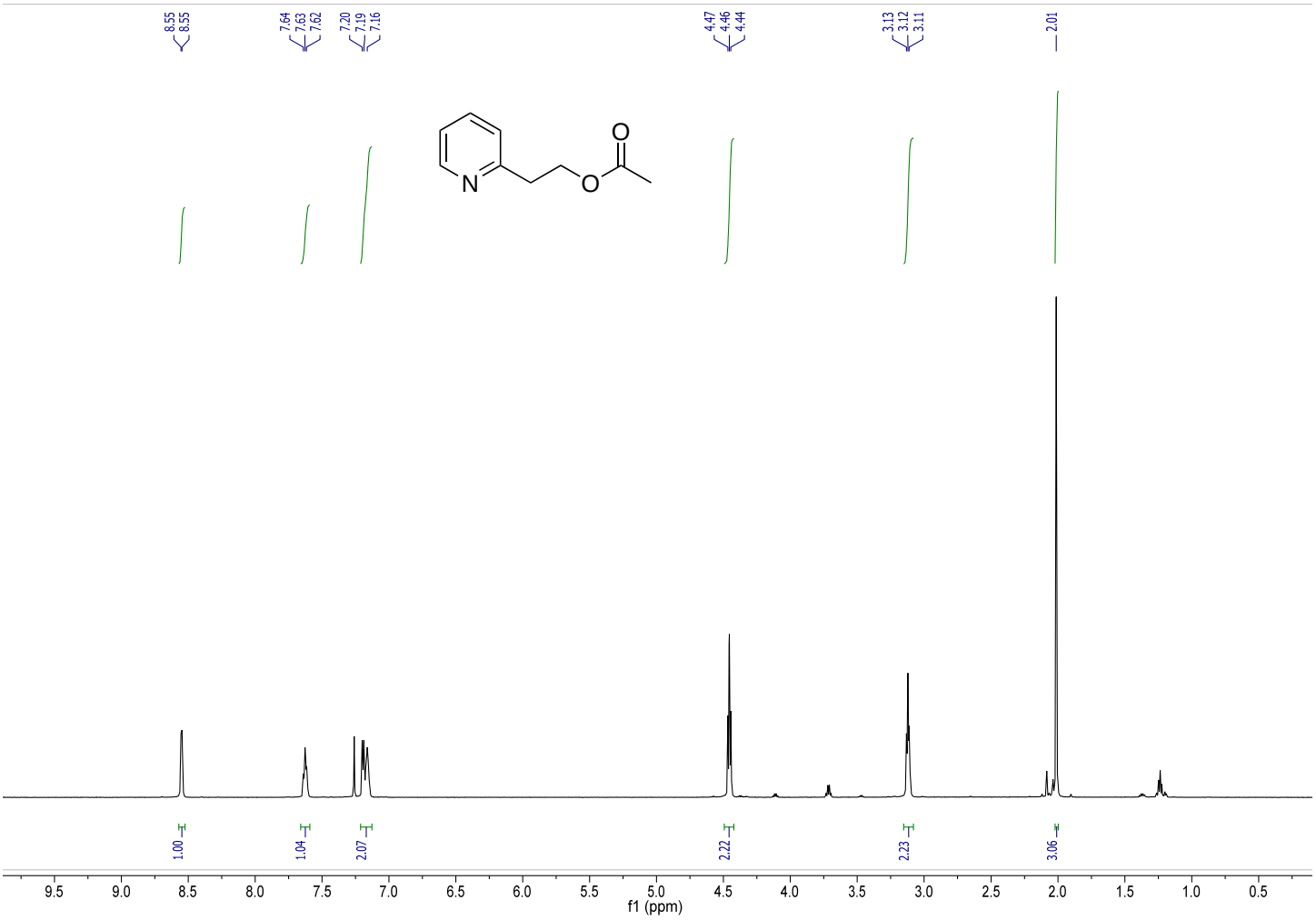
116.72
110.37
74.20
66.90
48.77
18.89
Br
Cl
Me
F
O
N
Cl
N
O
+
Br
O
N
Cl
Me
F
O
N
Cl
7:1 ratio
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.16
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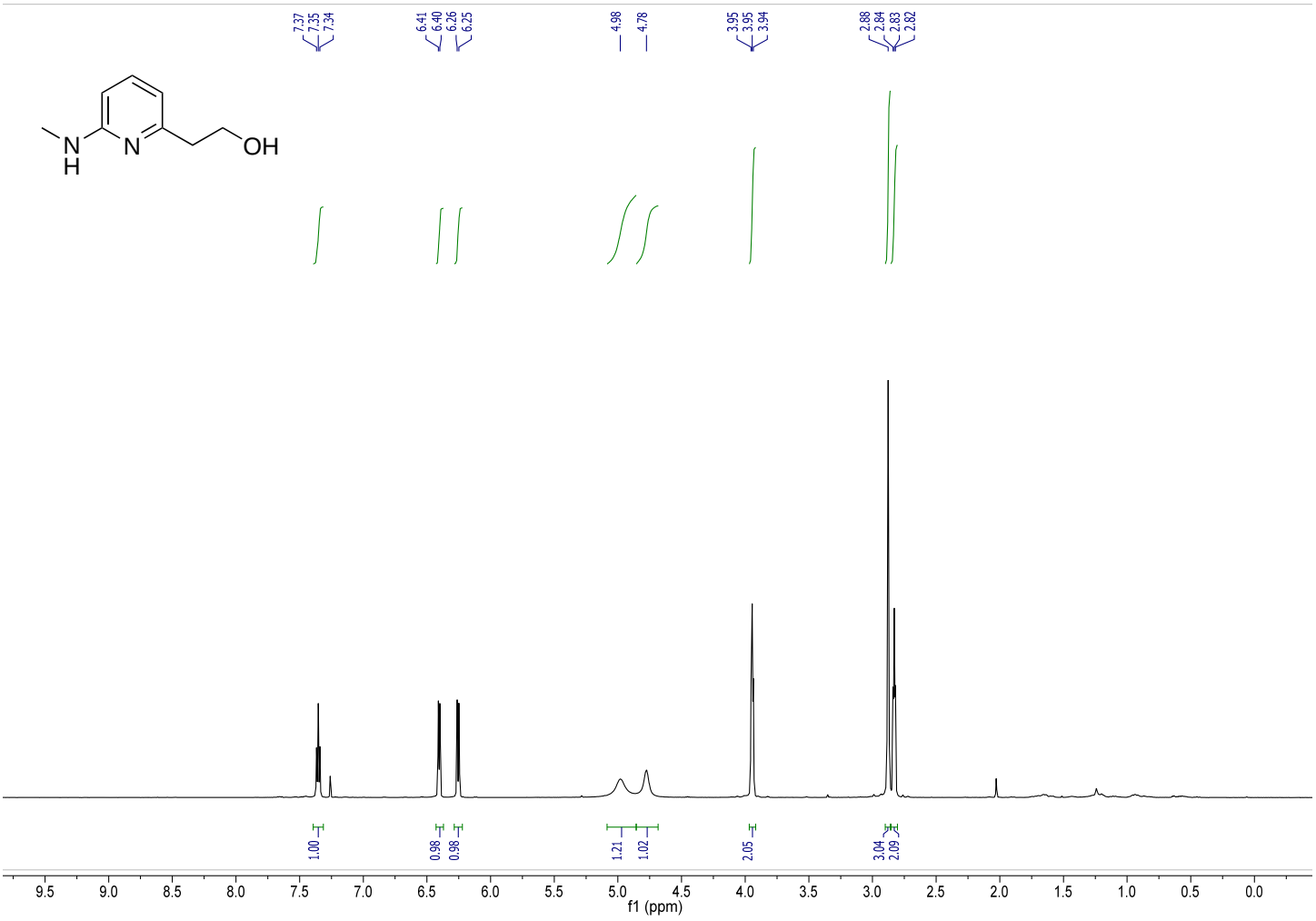
4.46
4.44
3.13
3.12
3.11
2.01
O
N
O
1.00
1.04
2.07
2.22
2.23
3.06
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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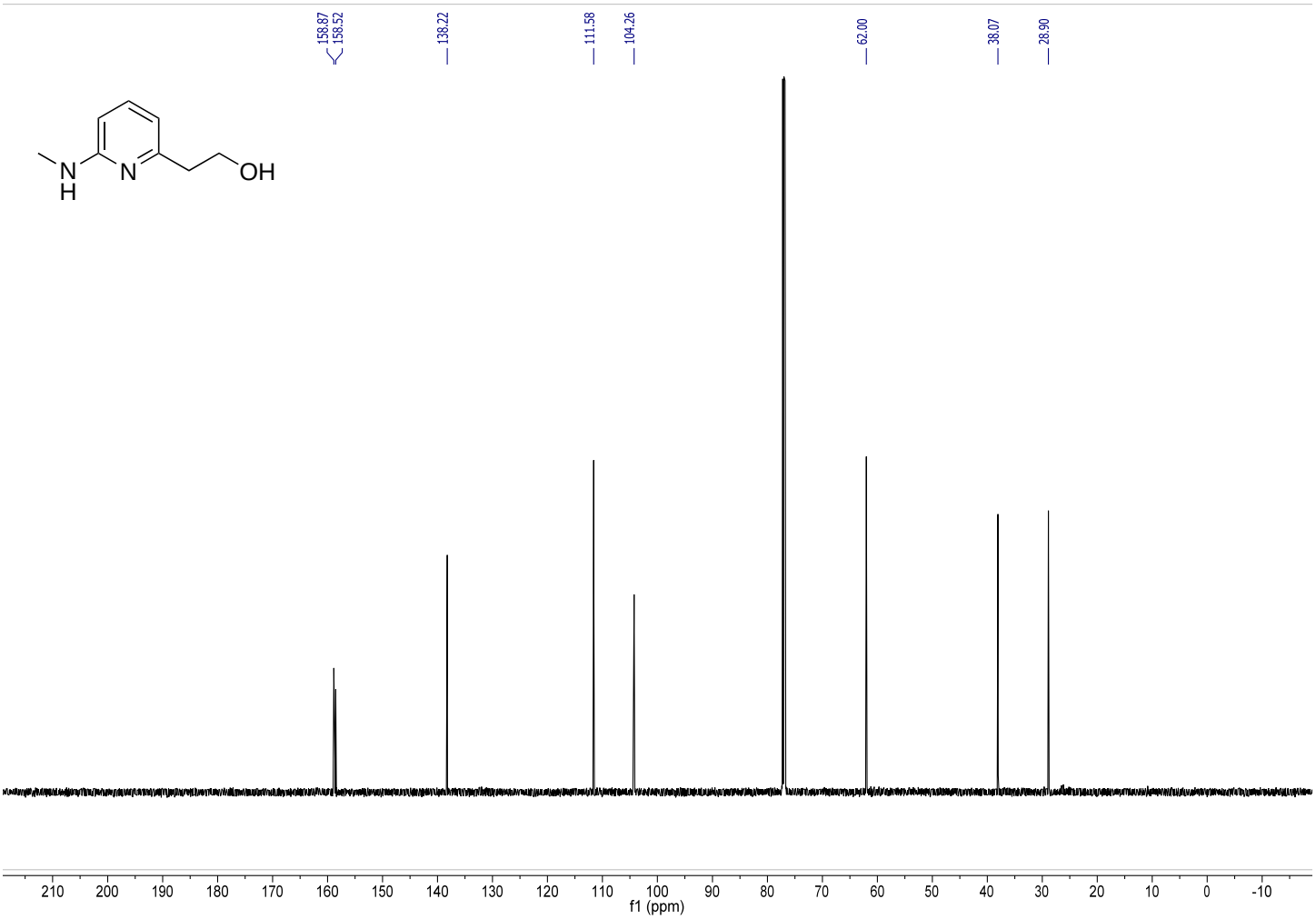
7.35
7.34
6.41
6.40
6.26
6.25
4.98
4.78
3.95
3.95
3.94
2.88
2.84
2.83
2.82
N
H
N
OH
1.00
0.98
0.98
1.21
1.02
2.05
3.04
2.09
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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158.52
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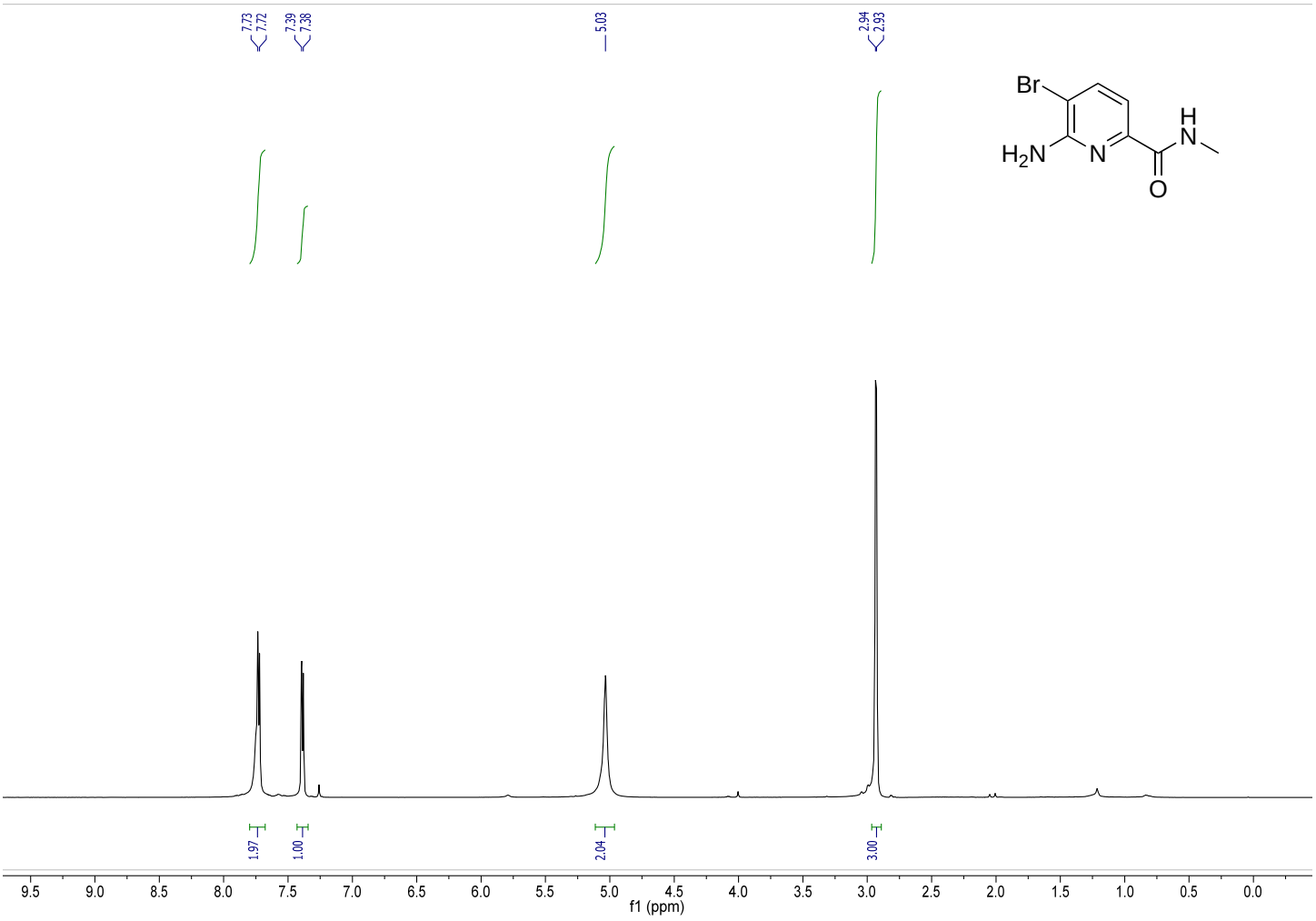
111.58
104.26
62.00
38.07
28.90
N
H
N
OH
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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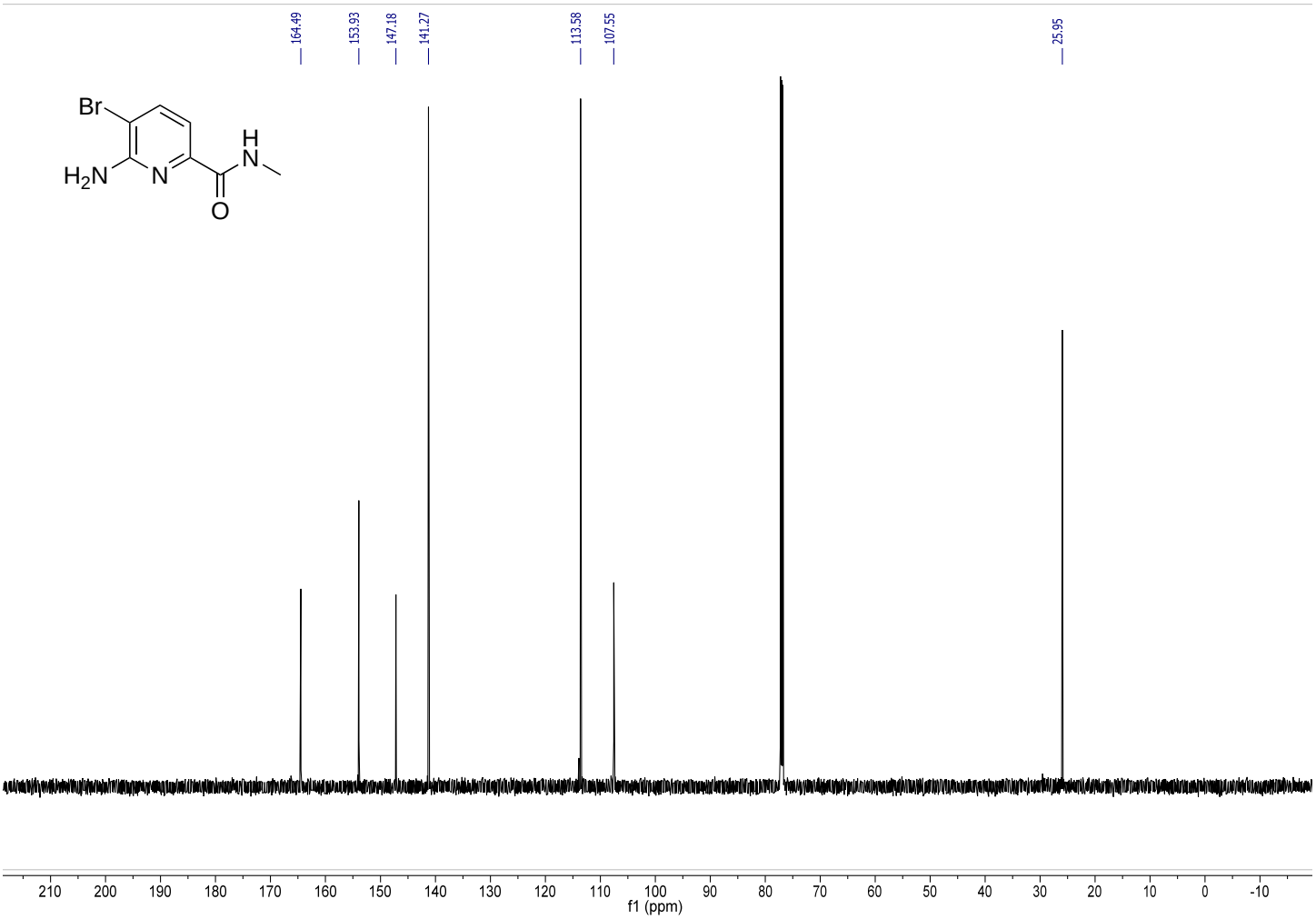
7.72
7.39
7.38
5.03
2.94
2.93
Br
H2N
N
H
N
O
1.97
1.00
2.04
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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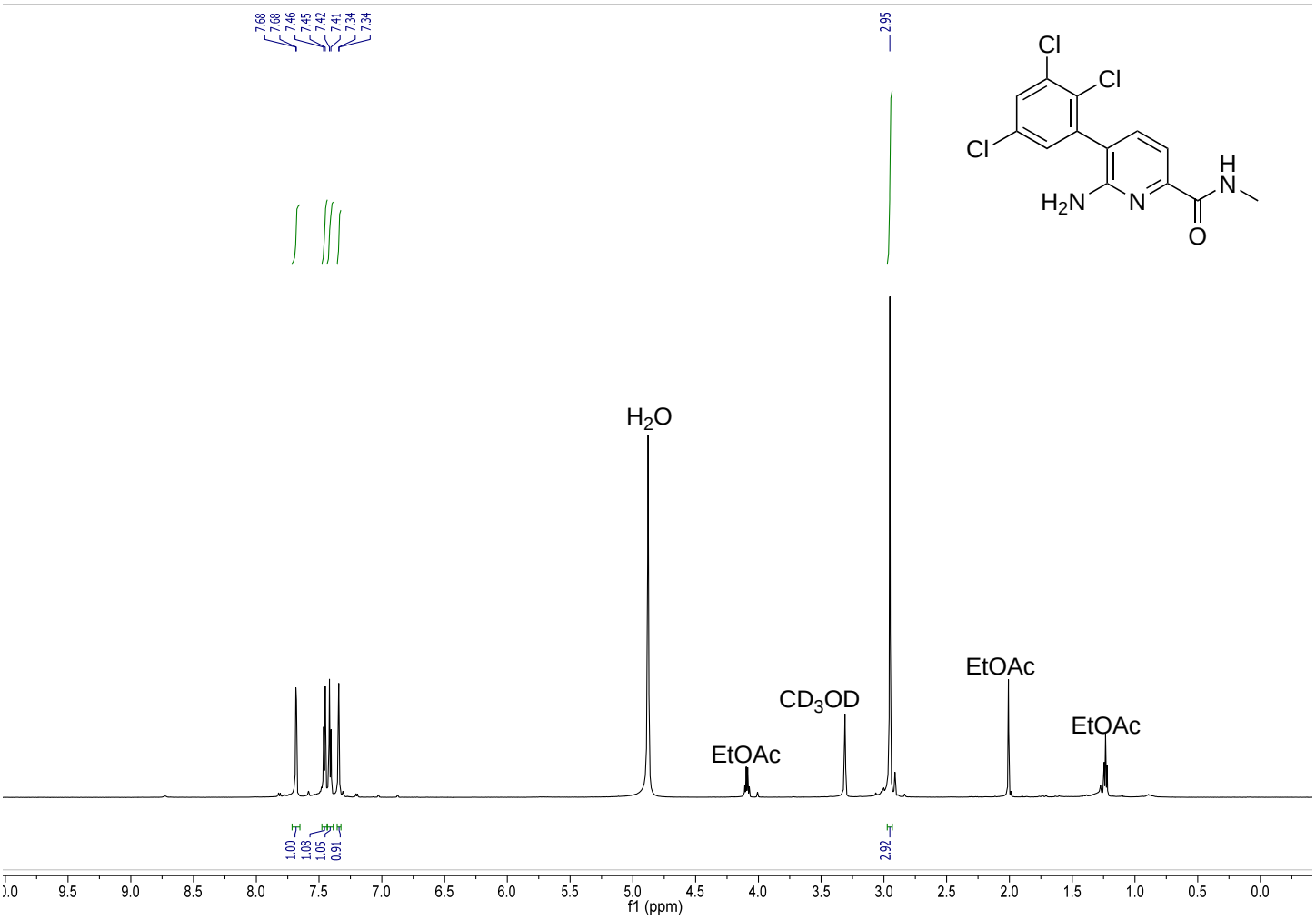
141.27
113.58
107.55
25.95
Br
H2N
N
H
N
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.68
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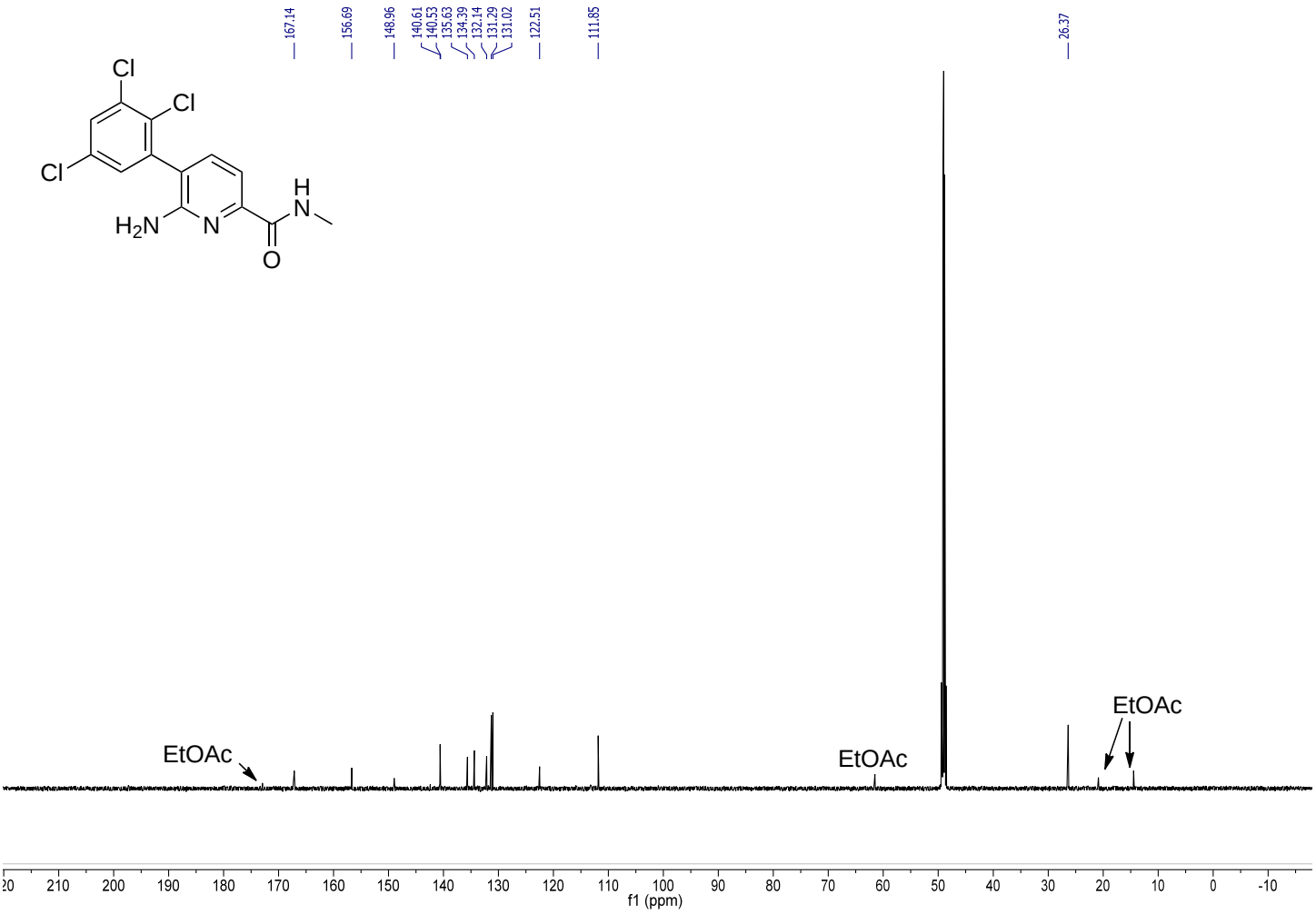
7.45
7.42
7.41
7.34
7.34
2.95
Cl
Cl
Cl
H
N
H_2N
N
O
H_2O
EtOAc
CD_3OD
EtOAc
EtOAc
1.00
1.08
1.05
0.91
2.92
f1 (ppm)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156.69
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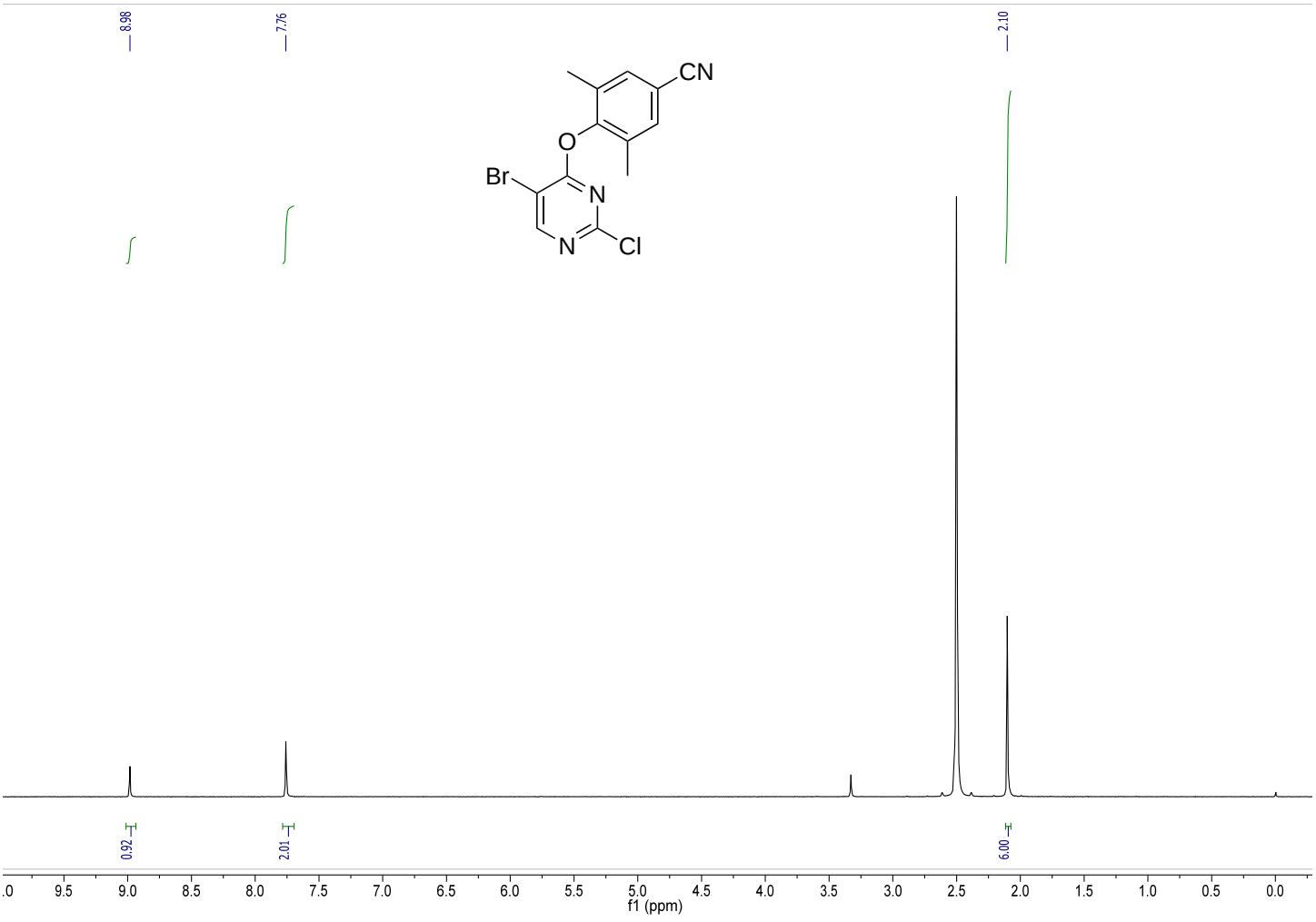
140.61
140.53
135.63
134.39
132.14
131.29
131.02
122.51
111.85
26.37
Cl
Cl
Cl
H
N
H_2N
N
O
EtOAc
EtOAc
EtOAc
f1 (ppm)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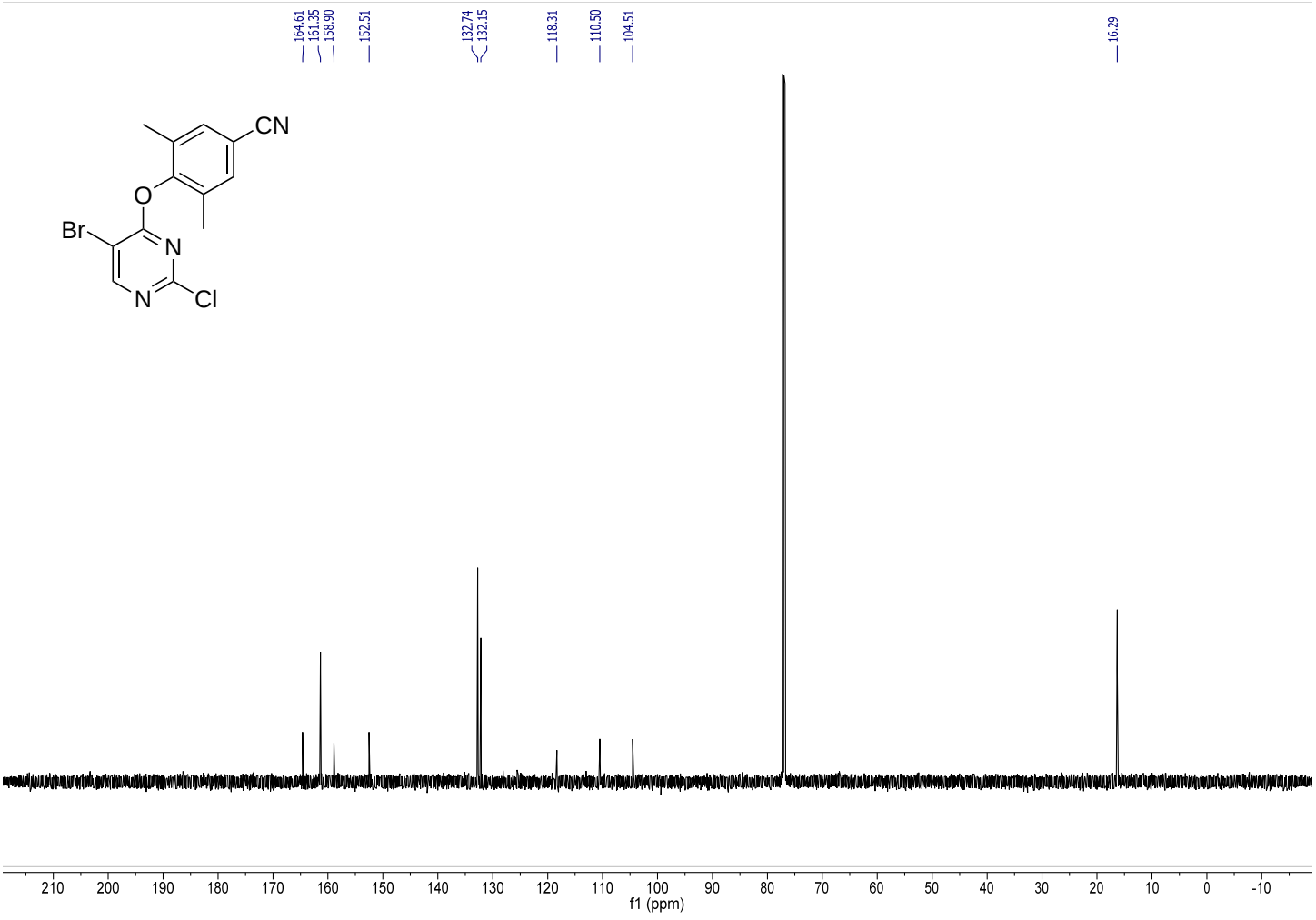
CN
O
Br
N
N
Cl
0.92
2.01
6.00
f1 (ppm)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161.35
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152.51
132.74
132.15
118.31
110.50
104.51
16.29
CN
O
Br
N
N
Cl
210
200
190
180
170
160
150
140
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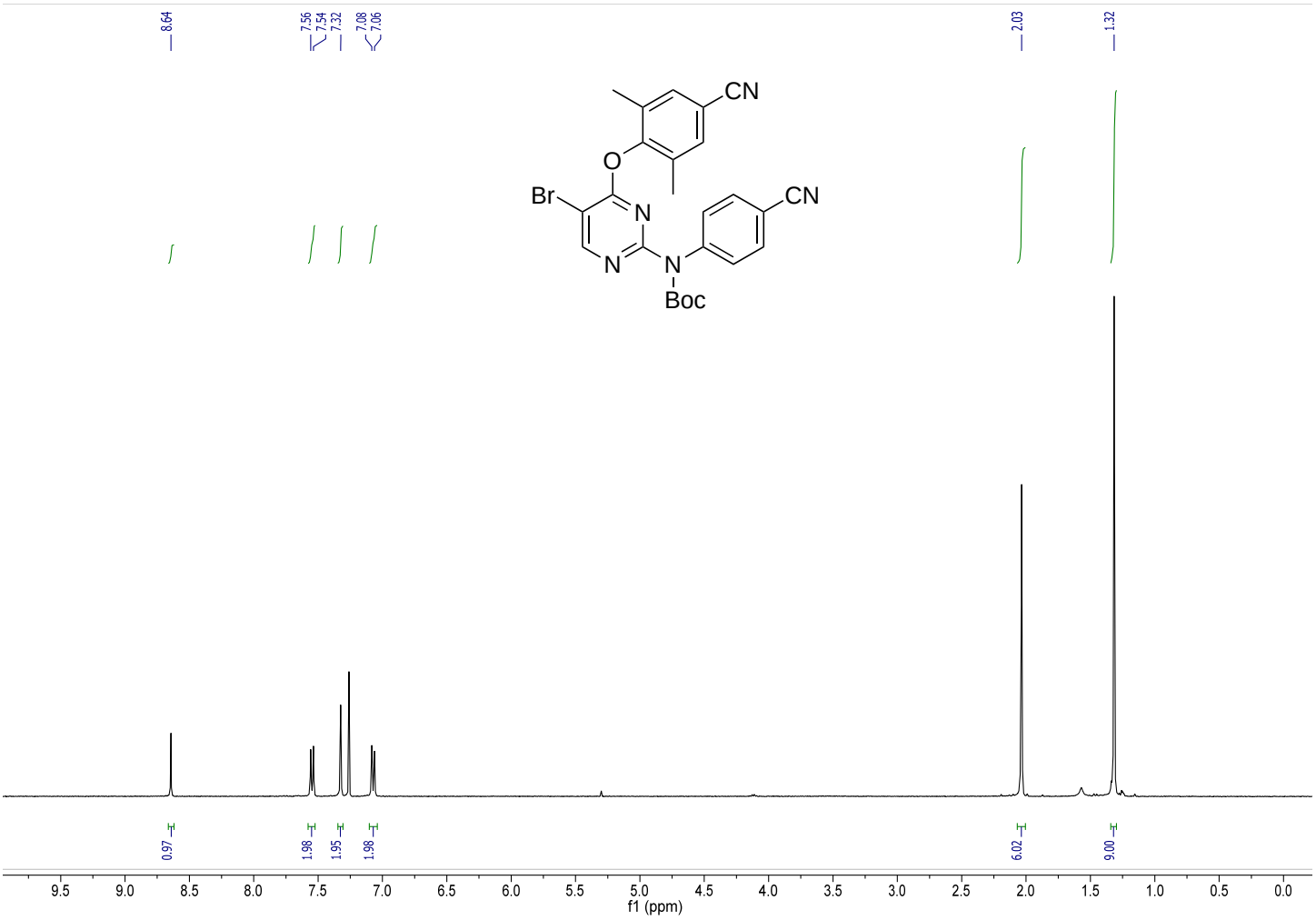
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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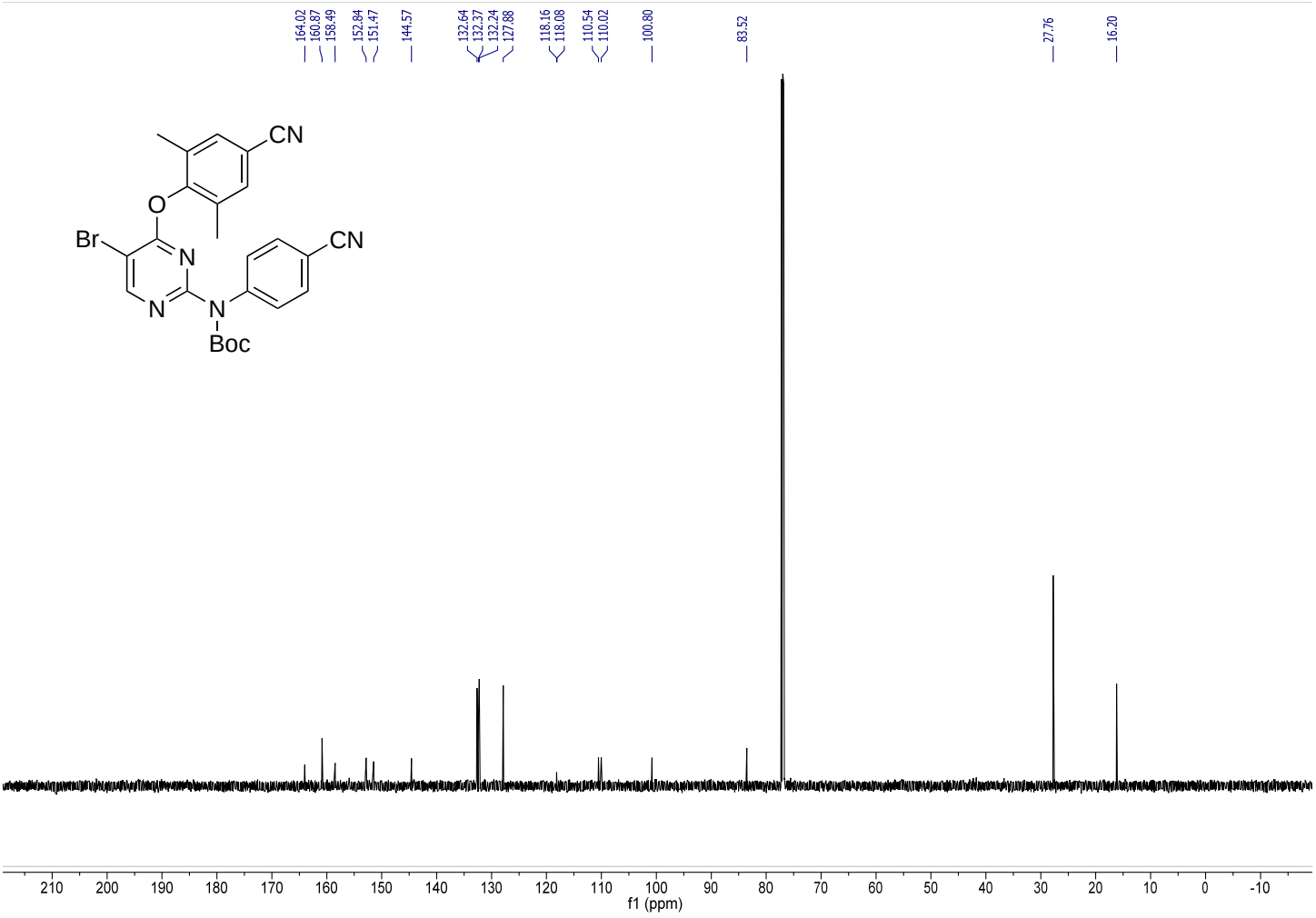
7.56
7.54
7.32
7.08
7.06
2.03
1.32
CN
O
Br
N
CN
N
N
Boc
0.97
1.98
1.95
1.98
6.02
9.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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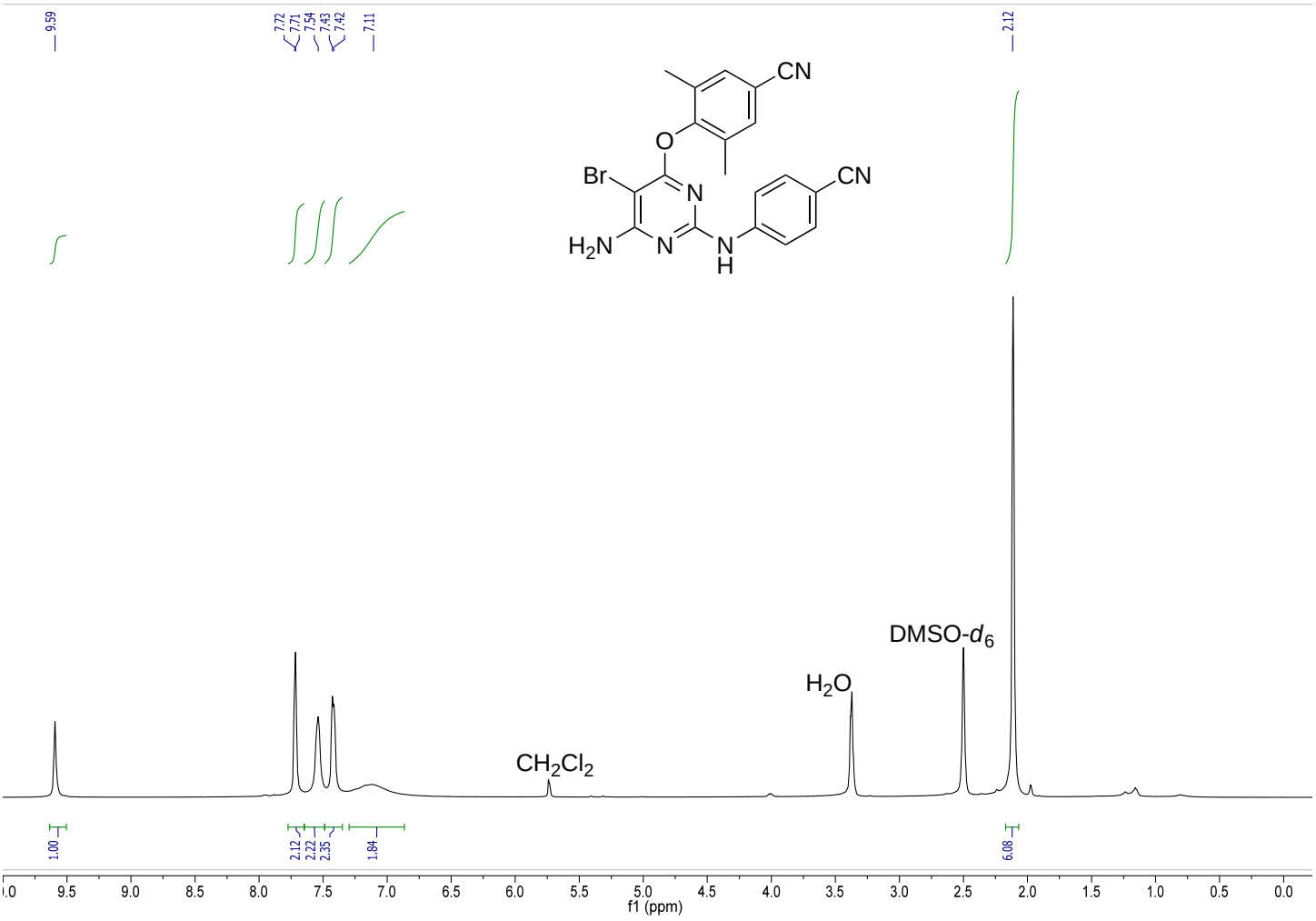
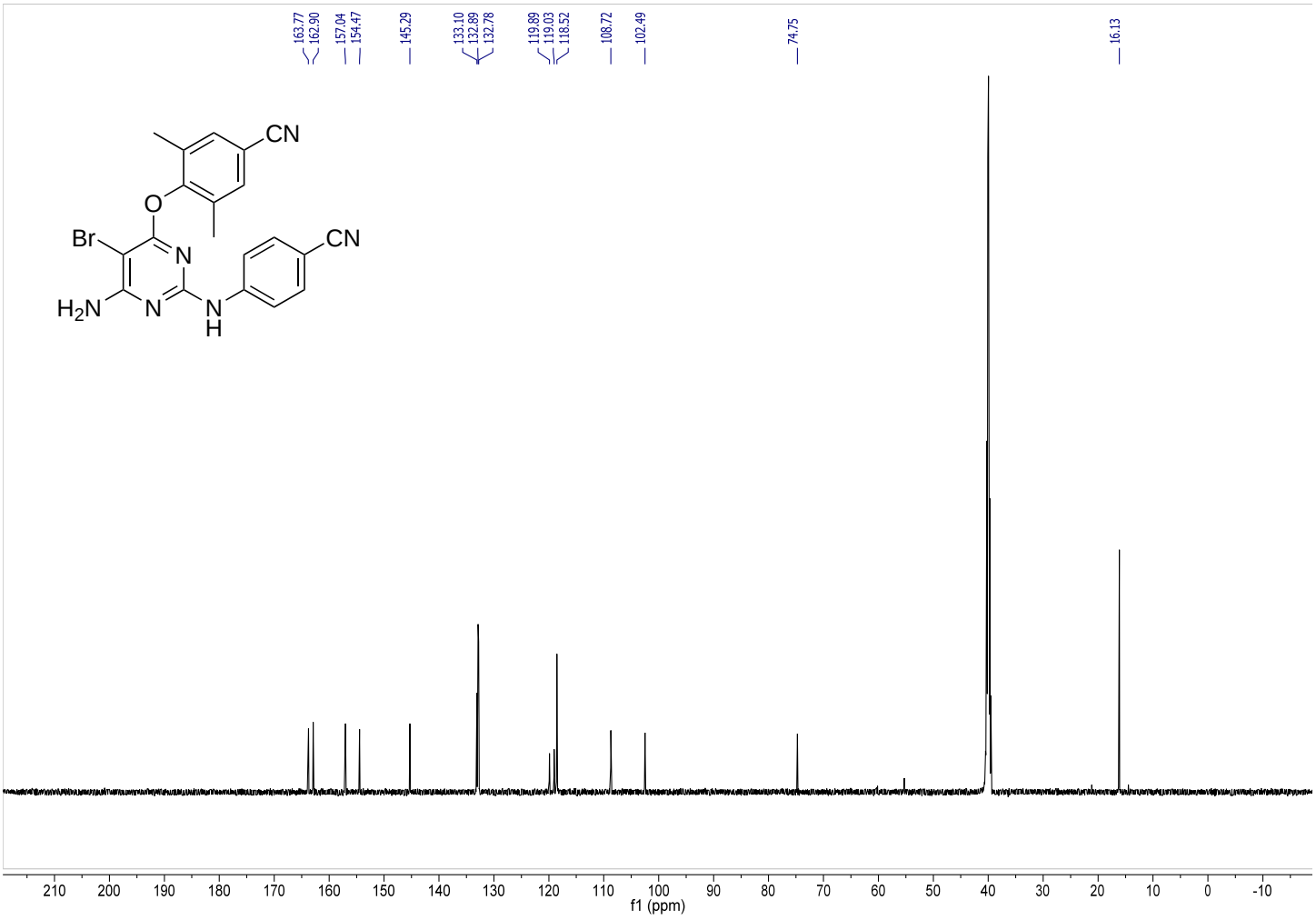
160.87
158.49
152.84
151.47
144.57
132.64
132.37
132.24
127.88
118.16
118.08
110.54
110.02
100.80
83.52
27.76
16.20
CN
O
Br
N
CN
N
N
Boc
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


9.59
7.72
7.71
7.54
7.43
7.42
7.11
2.12
CN
O
Br
N
CN
H_2N
N
N
H
DMSO-d_6
H_2O
CH_2Cl_2
1.00
2.12
2.22
2.35
1.84
6.08
f1 (ppm)


163.77
162.90
157.04
154.47
145.29
133.10
132.89
132.78
119.89
119.03
118.52
108.72
102.49
74.75
16.13
CN
O
Br
N
CN
H_2N
N
N
H
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)