Heteroaryl-Heteroaryl, Suzuki-Miyaura, Anhydrous Cross-Coupling Reactions Enabled by Trimethyl Borate

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SUPPORTING INFORMATION

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General Experimental

General Procedures: Reaction solvent 1,2-dimethoxyethane (GFS, HPLC grade) was dried over sodium metal for 1 day upon receiving and then distilled using a solvent still. Solvents for filtration and transfers were purchased from commercial sources and used as received. Potassium trimethylsilanolate was stored in a drybox and removed as needed to prepare fresh 1.00 M stock solutions prior to cross-coupling. Trimethyl borate was stored in a Schlenk bottle. All reactions were conducted under an atmosphere of dry argon. Aqueous ethanolamine (1 M) was employed during workup to sequester boron by-products.

NMR Spectroscopy: ^{1}H, ^{13}C, and ^{11}B NMR spectra for characterization were recorded on a Bruker 500 MHz (500 MHz, ^{1}H; 500.35 MHz, ^{11}B; 160.53 MHz, ^{13}C 125.83 MHz) spectrometer. Quantitative NMR data were obtained on a Varian 400 MHz (400 MHz, ^{1}H NMR; 399.74 MHz, ^{19}F NMR; 376.09 MHz) spectrometer. Quantitative NMR internal standards: ^{1}H NMR; 1,3,5-trimethoxybenzene (Aldrich, 99+%), ^{19}F NMR; 1-flouronaphthalene (Oakwood Chemical, 99%), 1,2-difluorobenzene (Oakwood Chemical, 99%). ^{1}H and ^{13}C NMR spectra are referenced to residual chloroform (δ = 7.26 ppm, ^{1}H; 77.16 ppm, ^{13}C), dichloromethane (δ = 5.32 ppm, ^{1}H; 53.84 ppm, ^{13}C), or dimethyl sulfoxide (δ = 2.50 ppm, ^{1}H; 39.52 ppm, ^{13}C). Chemical shifts are reported in parts per million. Assignments were obtained by reference to COSY, HSQC, and HMBC correlations.

Infrared Spectroscopy: Infrared spectra (IR) were recorded neat on a PerkinElmer FT-IR system and peaks were reported in cm-1 with indicated relative intensities: s (strong, 0-33% T); m (medium, 34-66% T); w (weak, 67-100% T).

Mass Spectrometry: Mass spectrometry (MS) was performed by the University of Illinois Mass Spectrometry Laboratory. Electron Impact (EI) spectra were performed at 70 eV using methane as the carrier gas on a Finnagin-MAT C5 spectrometer. Electrospray Ionization (ESI) spectra were performed on a Micromass Q-ToF Ultima spectrometer. Data are reported in the form of *m/z* (intensity relative to the base peak = 100).

Elemental Analysis: Elemental analysis was performed by the University of Illinois Microanalysis Laboratory. Reported data is the average of at least 2 runs.

Melting Points: Melting points (m.p.) were determined on a SRS DigiMelt MPA 160 melting point apparatus in sealed tubes and are corrected.

Chromatography: Analytical thin-layer chromatography was performed on Merck silica

gel 60 F254 plates or Merck basic aluminum oxide 60 F254 plates. TLC plates were visualized by exposure to ultraviolet light. Retention factor (R_f) values reported were measured using a 10 × 2 cm TLC plate in a developing chamber containing the solvent system described. Flash column chromatography was performed using Silicycle SiliaFlash®P60 (40-63 μm particle size, 230-400 mesh) (SiO_2). Unless otherwise specified, "silica" refers to P60 grade silica gel.

Solvents: Reaction solvent 1,2-dimethoxyethane (GFS, HPLC grade) was dried over sodium metal for 1 day upon receiving and then distilled using a solvent still. Reaction solvent tetrahydrofuran (THF) (Fisher, HPLC grade) was dried by percolation through two columns packed with neutral alumina under a positive pressure of argon. Reaction solvent toluene (ACS grade) was dried by percolation through a column packed with neutral alumina and a column packed with Q5 reactant (supported copper catalyst for scavenging oxygen) under a positive pressure of argon. Reaction solvent acetonitrile (CH_3CN) (Fisher, HPLC grade) was distilled from CaH_2. Reaction solvent 1,4-dioxane (Fisher, ACS grade) was distilled from sodium metal. Reaction solvent 2-methoxyethyl ether (diglyme) (Acros Organics) was purchased commercially and used as received. 1-methyl-2-pyrrolidinone (NMP) (Sigma-Aldrich, anhydrous) was purchased commercially and used as received. Reaction solvent benzene (EMD Millipore Corporation, ACS grade) was purchased commercially and used as received. Reaction solvent toluene (Fischer, ACS grade) was purchased commercially and used as received. Solvents for filtration, transfers, chromatography, and recrystallization were dichloromethane (CH_2Cl_2) (Fischer,amylene stabilized, ACS grade), ethyl acetate (EtOAc) (Fischer, HPLC grade), hexanes (Sigma-Aldrich, HPLC grade), methanol (MeOH) (ACS grade), and petroleum ether (35–60°C, ACS grade).

Commercial Reagents: The following commercial reagents were used as received: potassium trimethylsilanolate (Gelest), trimethyl borate (Sigma-Aldrich), triisopropyl borate (Sigma-Aldrich), tris(trimethylsilyl) borate (Oakwood Chemical), neopentyl glycol (Alfa Aesar), CataCXium A (Strem Chemicals), triphenylphosphine (Oakwood Chemical), 4-fluorophenyl boronic acid (Oakwood Chemical), 3-pyridyl boronic acid (Combi-Blocks), 4-pyridylboronic acid (Combi-Blocks), pyrimidine-5-boronic acid (Oakwood Chemical), 2-chloropyrimidine-5-boronic acid (Combi-Blocks), 3,5-dimethylisoxazole-4-boronic acid (Combi-Blocks), 1-Boc-2-pyrrolylboronic acid (AK Scientific), 1-methyl-1H-pyrazole-5-boronic acid (Combi-Blocks), furan-2-boronic acid (Combi-Blocks), 1-bromo-4-fluorobenzene (Oakwood Chemical), 4-bromo-

benzotrifluoride (Oakwood Chemical), 2-bromo-1,3-benzothiazole (Combi-Blocks), Trazodone hydrochloride (Sigma-Aldrich), 5-bromonicotonic acid (Combi-Blocks), 2-amino-5-bromopyridine (Lancaster Synthesis), 8-bromocaffeine (Sigma-Aldrich), 2-(4-bromophenyl)-1,3,4-oxadiazole (Sigma-Aldrich), 2-bromopyridine (Oakwood Chemical), 2-chloro-pyrimidine (Sigma-Aldrich), 2-bromo-5-methoxypyrimidine (Combi-Blocks), 6-bromo-4-chloroquinoline (Combi-Blocks), 4-bromo-1H-imidazole (AK Scientific), 4-bromoisoquinoline (Oakwood Chemical), 6-bromo-3,4-dihydro-1H-[1,8]naphthyridin-2-one (Combi-Blocks). The following commercial reagents were purified prior to use: 6-bromoquinoline (Combi-Blocks, Kugelrohr distillation), 3-bromoimidazo[1,2-a]pyridine (Combi-Blocks, vacuum sublimation), 4-bromoindole (AK Scientific, Kugelrohr distillation), 2-bromopyrazine (Combi-Blocks, Kugelrohr distillation).

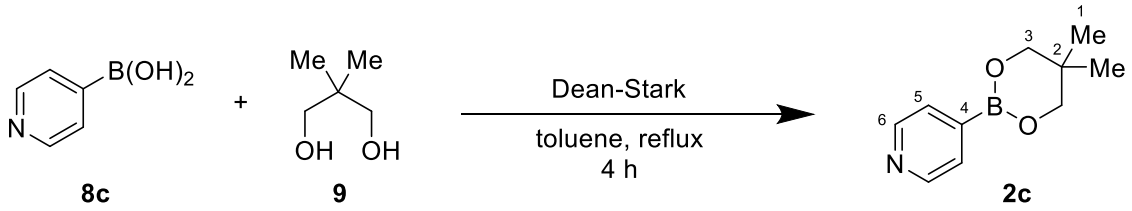
Literature Preparations:

The following compounds were prepared according to reported literature procedures: Pd-CataCXium A-G3,[1] *tert*-butyl-5-bromonicotinate,[2] *tert*-butyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1H-pyrrole-1-carboxylate,[3] 2-(furan-2-yl)-5,5-dimethyl-1,3,2-dioxaborinane,[3] 2-(4-fluorophenyl)-5,5-dimethyl-1,3,2-dioxaborinane,[3] tri-*n*-butyl borate (distilled).[4]

Experimental Procedures

Preparation of Boronic Esters

Preparation of 4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)pyridine (2c)



8c **9** **2c**

A 100-mL, round-bottomed flask containing a 2.0-cm x 1.0-cm football-shaped magnetic stir bar was charged with 4-pyridylboronic acid **8c** (1.33 g, 10.8 mmol), and neopentyl glycol **9** (1.04 g, 9.90 mmol, 1.00 equiv), followed by 50 mL of toluene. The flask was fitted with a Dean-Stark apparatus, and a reflux condenser. The mixture was heated at reflux and stirred for 4 h under nitrogen, at which point it was cooled to room temperature. The toluene was removed by rotary evaporation (30 ºC, 330 mm Hg to 15 mm Hg). The crude material was transferred to a sublimation apparatus which was heated at 120 ºC under high vacuum (0.2 mm Hg). The sublimate was collected, to give 1.63g (85% yield, 8.5 mmol) of analytically pure product as a white solid.

Data for **2c:**

mp: sublimes (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)
8.61 (d, *J*=5.74 2H, HC(6)), 7.65 (d, *J*=5.77 2H, HC(5)), 3.78 (s, 4H, HC(3)), 1.03 (s, 6H, HC(1)

^{13}C NMR: (126 MHz, $CDCl_3$)
148.61 (s, C(6)), 128.37 (s, C(5)), 72.57 (s, C(3)), 32.07 (s, C(2)), 22.00 (s, C(1))

^{11}B NMR: (161 MHz, $CDCl_3$)
26 ppm (br, BC(4))

IR: (neat, ATR)
2943 (w), 2887 (w), 2864 (w), 2821 (w), 1621 (w), 1538 (w), 1467 (w), 1423 (m), 1394 (w), 1360 (w), 1236 (m), 1214 (s), 1144 (w), 1114 (s), 1084 (m), 1064 (s), 1050 (w), 1034 (s), 1007 (m), 964 (w), 908 (w), 767 (s), 735 (s), 673 (s), 624 (s), 563 (m), 492 (m)

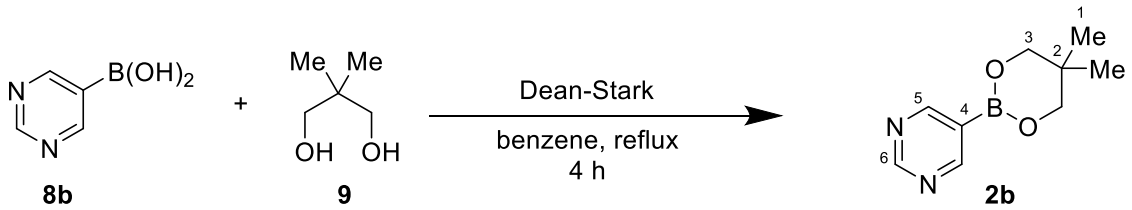
LRMS (ES^+): 200.2 (3), 193.1 (12), 192.1 (100, M+H), 191.1 (25), 124.1 (4)

HRMS (ES$^+$): Calcd for $C_{10}H_{15}BNO_2$ $(M+H)^+$: 192.1196 Found: 192.1194

Analysis: $C_{10}H_{14}BNO_2$ (191.04)

Calcd:	C, 62.87;	H, 7.39;	N, 7.33
Found:	C, 62.82;	H, 7.36;	N, 7.36

Preparation of 5-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)pyrimidine (2b)



8b **9** **2b**

A 100-mL, round-bottomed flask containing a 2.0-cm x 1.0-cm football-shaped magnetic stir bar was charged with pyrimidin-5-ylboronic acid **8b** (1.34 g, 10.8 mmol), and neopentyl glycol **9** (1.04 g, 10.0 mmol, 1.00 equiv), followed by 50 mL of toluene. The flask was fitted with a Dean-Stark apparatus, and a reflux condenser. The mixture was heated at reflux and stirred for 4 h under nitrogen, at which point it was cooled to room temperature. The toluene was removed by rotary evaporation (30 ºC, 330 mm Hg to 15 mm Hg). The crude material was transferred to a sublimation apparatus which was heated at 65 °C under high vacuum (0.2 mm Hg). The sublimate was collected, to give 1.81g (94% yield, 9.4 mmol) of analytically pure product as a white crystalline solid.

Data for **2b:**

mp: 93.5-94.2°C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

9.24 (s, 1H, HC(6)), 9.00 (s, 2H, HC(5)), 3.79 (s, 4H, HC(3)), 1.04 (s, 6H, HC(1))

^{13}C NMR: (126 MHz, $CDCl_3$)

162.16 (s, C(6)), 160.17 (s, C(5)), 77.55 (s, C(3)), 32.18 (s, C(2)), 21.99 (s, C(1))

^{11}B NMR: (161 MHz, $CDCl_3$)

26 ppm (br, BC(4))

IR: (neat, ATR)

2964 (w), 2936 (w), 1577 (m), 1555 (m), 1479 (m), 1429 (m), 1407 (w), 1379 (m), 1342 (m), 1318 (s), 1307 (s), 1270 (w), 1255 (s), 1217 (w), 1185 (m), 1157 (s), 1117 (m), 1094 (m), 1051 (m), 1028 (m), 930 (w), 813 (m), 747 (m), 732 (s), 686

(m), 663 (s), 638 (m), 500 (m)

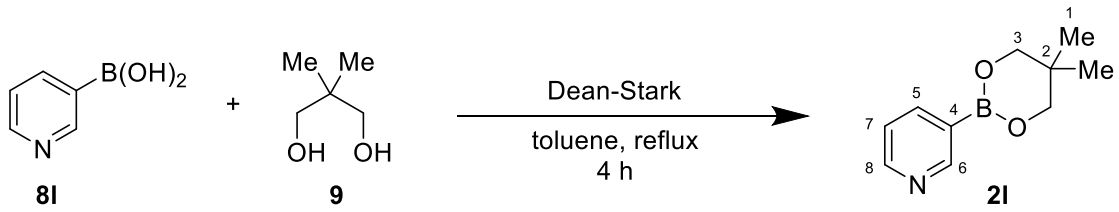
LRMS (ES^+): 233.1 (7), 194.1 (13), 193.1 (100, M+H), 192.1 (31), 125.1 (10)

HRMS (ES^+): Calcd for $C_9H_{14}BN_2O_2$ $(M+H)^+$: 193.1148 Found: 193.1144

Analysis: $C_9H_{13}BN_2O_2$ (192.03)

Calcd:	C, 56.29;	H, 6.82;	N, 14.59
Found:	C, 56.34;	H, 6.67;	N, 14.39

Preparation of 3-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)pyridine (2l)



A 100-mL, round-bottomed flask containing a 2.0-cm x 1.0-cm football-shaped magnetic stir bar was charged with 3-pyridylboronic acid **8l** (1.77 g, 14.4 mmol), and neopentyl glycol **9** (1.04 g, 10.0 mmol, 1.00 equiv), followed by 50 mL of toluene. The flask was fitted with a Dean-Stark apparatus, and a reflux condenser. The mixture was heated at reflux and stirred for 4 h under nitrogen, at which point it was cooled to room temperature. The toluene was removed by rotary evaporation (30 ºC, 330 mm Hg to 15 mm Hg). The crude material was transferred to a sublimation apparatus which was heated at 65 °C under high vacuum (0.2 mm Hg). The sublimate was collected, to give 1.57g (82% yield, 8.2 mmol) of analytically pure product as a white solid.

Data for **2l:**

mp: 90.9-91.6°C (sealed tube)

^{1}H NMR: (500 MHz, CD_2Cl_2)

8.87 (s, 1H, HC(6)), 8.59 (dd, *J*= 4.89, 1.97 Hz, 1H, HC(8)), 8.02 (dt, *J* = 7.54, 1.85 Hz, 1H, HC(7)), 7.75 (ddd, *J*=7.60, 4.91, 1.00 Hz, 1H, HC(5)), 3.77 (s, 1H, HC(3)), 1.02 (s, 1H, HC(1))

^{13}C NMR: (126 MHz, CD_2Cl_2)

155.07 (s, C(6)), 151.73 (s, C(8)), 141.59 (s, C(7)), 123.33 (s, C(5)), 72.70 (s, C(3)), 32.23 (s, C(2)), 21.94 (s, C(1))

^{11}B NMR: (161 MHz, CD_2Cl_2)

27 ppm (br, BC(4))

IR: (neat, ATR)

3068 (w), 2949 (m), 2904 (m), 2823 (w), 1603 (m), 1472 (w), 1411 (m), 1398 (w), 1361 (w), 1317 (w), 1217 (s), 1186 (w), 1110 (s), 1071 (s), 1040 (s), 1008 (m), 957 (m), 827 (w), 757 (s), 718 (m), 693 (m), 669 (s), 629 (m), 618 (s), 578 (m), 549 (w), 480 (m)

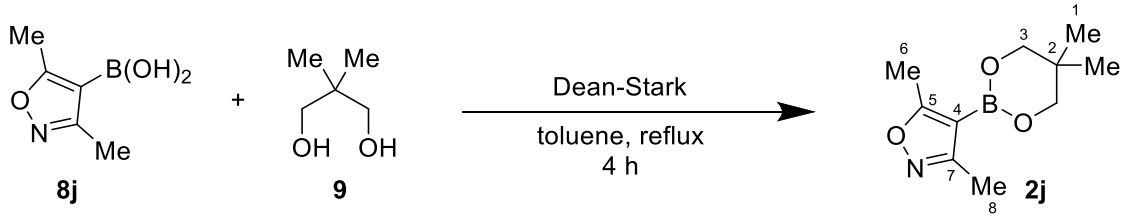
LRMS (ES^+): 233.1 (4), 193.1 (12), 192.1 (100, M+H), 191.1 (24), 124.1 (6)

HRMS (ES^+): Calcd for $C_{10}H_{15}BNO_2$ $(M+H)^+$: 192.1196 Found: 192.1194

Analysis: $C_{10}H_{14}BNO_2$ (191.04)

Calcd:	C, 62.87;	H, 7.39;	N, 7.33
Found:	C, 62.51;	H, 7.21;	N, 7.27

Preparation of 4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-3,5-dimethylisoxazole (2j)



A 100-mL, round-bottomed flask containing a 2.0-cm x 1.0-cm football-shaped magnetic stir bar was charged with (3,5-dimethylisoxazole-4-yl)boronic acid **8j** (1.45 g, 10.2 mmol), and neopentyl glycol **9** (1.04 g, 10.0 mmol, 1.00 equiv), followed by 50 mL of toluene. The flask was fitted with a Dean-Stark apparatus, and a reflux condenser. The mixture was heated at reflux and stirred for 4 h under nitrogen, at which point it was cooled to room temperature. The toluene was removed by rotary evaporation (30 ºC, 330 mm Hg to 15 mm Hg). The crude material was transferred to a sublimation apparatus which was heated at 65 °C under high vacuum (0.2 mm Hg). The sublimate was collected, to give 1.78g (85% yield, 8.5 mmol) of analytically pure product as a white crystalline solid.

Data for **2j:**

mp: 91.3-91.8°C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

3.70 (s, 4H, HC(3)), 2.47 (s, 3H, HC(6)), 2.30 (s, 3H, HC(8)), 1.00 (s, 6H, HC(1))

^{13}C NMR: (126 MHz, $CDCl_3$)

177.13 (s, C(8)), 164.02 (s, C(7)), 72.20 (s, C(3)), 32.00 (s, C(2)), 22.01 (s, C(1)),

12.96 (s, C(6)), 12.08 (s, C(8))

^{11}B NMR: (161 MHz, $CDCl_3$)

25.94 ppm, (br, BC(4))

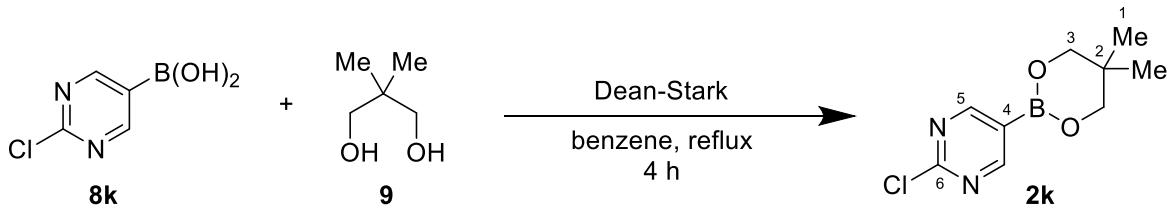
LRMS (ES^+): 262.1 (7), 233.1 (13), 210.1 (22, M+H), 149.0 (10), 142.1 (100), 141.1 (23), 124.1 (13)

HRMS (ES^+): Calcd for $C_{10}H_{17}BNO_3$ $(M+H)^+$: 210.1301 Found: 210.1311

Analysis: $C_{10}H_{16}BNO_3$ (209.05)

Calcd:	C, 57.45;	H, 7.71;	N, 6.70
Found:	C, 57.33;	H, 7.76;	N, 6.73

Preparation of 2-Chloro-5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)pyrimidine (2k)



A 100-mL, round-bottomed flask containing a 2.0-cm x 1.0-cm football-shaped magnetic stir bar was charged with (2-chloropyrimidin-5-yl)boronic acid **8k** (979.5 mg, 6.2 mmol), and neopentyl glycol **9** (520.8 mg, 5.0 mmol, 1.00 equiv), followed by 50 mL of benzene. The flask was fitted with a Dean-Stark apparatus, and a reflux condenser. The mixture was heated at reflux and stirred for 4 h under nitrogen, at which point it was cooled to room temperature. The benzene was removed by rotary evaporation (30 ºC, 330 mm Hg to 15 mm Hg). The crude material was transferred to a sublimation apparatus which was heated at 80 °C under high vacuum (0.2 mm Hg). The sublimate was collected, to give 972 mg (86% yield, 4.29 mmol) of analytically pure product as a white crystalline solid.

Data for **2k:**

mp: 113.8-115.3°C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

8.87 (s, 2H, HC(5)), 3.78 (s, 4H, HC(3)), 1.03 (s, 6H, HC(1))

^{13}C NMR: (126 MHz, $CDCl_3$)

164.97 (s, C(5)), 163.57 (s, C(6)), 72.58 (s, C(3)), 32.19 (s, C(2)), 21.97 (s, C(1))

^{11}B NMR: (161 MHz, $CDCl_3$)

26.13 ppm (br, BC(4))

IR: (neat, ATR)

2965 (w), 2944 (w), 2908 (w), 1572 (s), 1534 (s), 1493 (w), 1479 (m), 1429 (m), 1391 (m), 1378 (m), 1371 (m), 1340 (m), 1322 (s), 1309 (s), 1292 (m), 1267 (m), 1245 (s), 1217 (m), 1193 (w), 1160 (s), 1052 (m), 1024 (m), 954 (w), 933 (w), 914 (w), 815 (m), 799 (w), 775 (s), 696 (m), 680 (m), 656 (s), 643 (s), 575 (w), 500 (w), 471 (m)

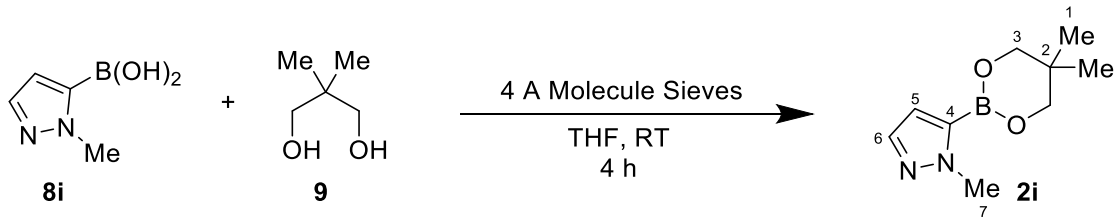
LRMS (ES^+): 322.1 (8), 233.1 (17), 229.1 (32), 227.1 (100, M+H), 226.1 (24), 161.0 (24), 159.0 (64), 158.0 (14)

HRMS (ES^+): Calcd for $C_9H_{13}BClN_2O_2$ $(M+H)^+$: 227.0759 Found: 227.0762

Analysis: $C_9H_{12}BClN_2O_2$ (226.47)

Calcd:	C, 47.73;	H, 5.34;	N, 12.37
Found:	C, 47.76;	H, 5.41;	N, 12.20

Preparation of 5-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (2i)



A 100-mL, round-bottomed flask containing a 2.0-cm x 1.0-cm football-shaped magnetic stir bar was charged with (1-methyl-1H-pyrazol-5-yl)boronic acid **8i** (1.56 g, 12.4 mmol), neopentyl glycol **9** (1.04 g, 10.0 mmol, 1.00 equiv) and 4 A molecular sieves (14 g). The flask was then fitted with a gas-line adapter and a septum. The vessel was purged 3 times with nitrogen, followed by the addition of 50 mL of THF (SDS). The mixture was stirred at room temperature for 4 h. The THF was removed by rotary evaporation (30 ºC, 450 mm Hg to 15 mm Hg). The crude material was transferred to a sublimation apparatus which was heated at 60 °C under high vacuum (0.2 mm Hg). The sublimate was collected and further recrystallized from boiling heptane (20 mL) to give 1.676 g (86% yield, 8.6 mmol) of analytically pure product as a white crystalline solid.

Data for **2i:**

mp: 77.4-78.3°C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

7.46 (d, *J* = 2.05 Hz, 1H, HC(6)), 6.65 (d, *J* = 2.05 Hz, 1H, HC(5)), 4.07 (s, 3H, HC(7)), 3.76 (s, 4H, HC(3)), 1.03 (s, 6H, HC(1))

^{13}C NMR: (126 MHz, $CDCl_3$)

138.22 (s, C(6)), 115.36 (s, C(5)), 72.67 (s, C(3)), 39.75 (s, C(7)), 32.30 (s, C(2)), 22.25 (s, C(1))

^{11}B NMR: (161 MHz, $CDCl_3$)

24.30 ppm (br, BC(4))

IR: (neat, ATR)

3097 (w), 2961 (w), 2875 (w), 1516 (m), 1476 (m), 1448 (m), 1417 (m), 1380 (m), 1341 (m), 1326 (s), 1308 (s), 1289 (m), 1246 (s), 1185 (m), 1124 (s), 1060 (w), 1036 (w), 1012 (m), 947 (m), 926 (m), 813 (m), 712 (m), 701 (s), 694 (s), 668 (w), 655 (m), 613 (w), 599 (m), 566 (w), 502 (m), 455 (m)

LRMS (ES^+):

196.1 (12), 195.1 (100, M+H), 194.1 (25), 141.1 (3), 127.1 (3)

HRMS (ES^+): Calcd for $C_9H_{16}BN_2O_2$ $(M+H)^+$: 195.1305 Found: 195.1304

Analysis: $C_9H_{15}BN_2O_2$ (194.04)

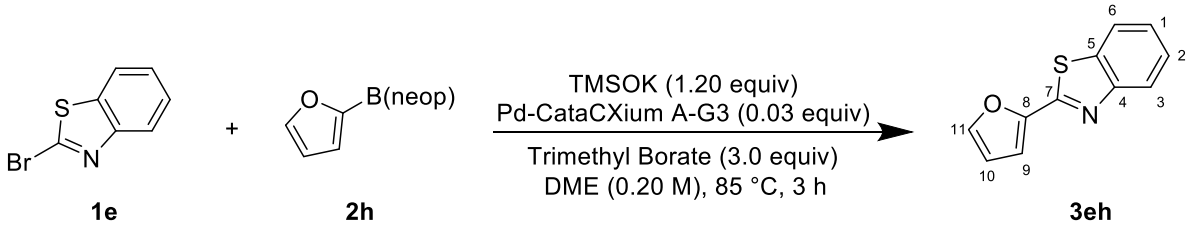
Calcd:	C, 55.71;	H, 7.79;	N, 14.44
Found:	C, 56.08;	H, 7.89;	N, 14.38

General Procedure for Cross-Coupling:

To a 15-mL, single-piece, round-bottomed flask with condenser containing a 1.5-cm x 0.7-cm rod-shaped magnetic stir bar was placed the aryl bromide (1.00 equiv), boronic ester (1.10 equiv), and Pd-CataXCium A-G3 precatalyst (0.03 equiv). The reaction vessel was evacuated and backfilled with argon two times. Still dried 1,2-dimethoxyethane (DME) (3.50 mL) was added via syringe, followed by 335 μL of trimethyl borate. In an oven-dried, 2-mL volumetric flask was placed 256 mg (2.00 mmol) of TMSOK followed by sufficient DME to give a 1.00 M solution. This solution was transferred to a 3-mL syringe equipped with a 0.2 micron syringe filter and filtered into a flame dried scintillation vial under argon. The reaction flask was then lowered into a pre-heated 110 °C oil bath for 5 min. At the 5 min time mark, 1.2 mL of the 1.00M TMSOK solution (1.20 equiv) was added to the heated reaction via syringe. The reaction mixture was stirred in the 110 °C oil bath until complete by TLC analysis. The reaction was then cooled to room temperature and transferred to a 125 mL separatory funnel using 50 mL of dichloromethane. The resulting organic layer was then washed with 1 M aqueous ethanolamine (1x50 mL) and brine (1x50 mL). The resulting aqueous layers were then extracted further with dichloromethane (2x25 mL). The combined organic layers were dried over sodium sulfate (5 g) and filtered. The sodium sulfate was further washed with dichloromethane to ensure quantitative transfer (2x25 mL). The resulting organic layer was then concentrated by rotary evaporation (35 ºC, 25 mm Hg). The crude material was then purified to furnish the desired product.

*Note: 1.00M TMSOK solutions were prepared using 1,2-dimethoxyethane that was dried over sodium metal and subsequently distilled. The resulting stock solution should be colorless to light yellow with minimal turbidity prior to syringe filtration.

Preparation of 2-(Furan-2-yl)benzo[d]thiazole (3eh)



1e **2h** **3eh**

Following the General Procedure, 2-bromobenzo[d]thiazole **1e** (214.0 mg, 1.00 mmol) was combined with boronic ester **2h** (198.3 mg, 1.10 mmol, 1.10 equiv) and Pd-CataCXium A-G3

precatalyst (21.8 mg, 0.03 mmol, 0.03 equiv). The total reaction time was 3 hr. After workup, the resulting solution was concentrated via rotary evaporation (35 ºC, 25 mm Hg) and loaded onto 0.7 g of celite. The crude product was purified by silica gel chromatography (2.0 cm, 10 g silica gel) eluting with 9:1 hexanes:EtOAc. The material was transferred to a sublimation apparatus which was heated at 100 °C using a silicone oil bath under high vacuum (0.1 mm Hg). The sublimate was collected to give 163.1 mg (0.81 mmol, 81% yield) of pure **3eh** as a white crystalline solid. Spectroscopic data was in agreement with literature values.[5]

Data for **3eh:**

^{1}H NMR: (500 MHz, $CDCl_3$)

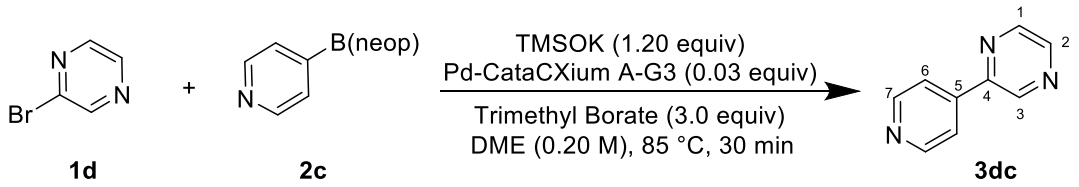
8.05 (d, *J*= 8.13 Hz 1H, HC(6)), 7.89 (d, *J*= 8.05 Hz 1H, HC(3)), 7.63-7.59 (m, 1H, HC(11)), 7.49 (t, *J* = 7.76 Hz, 1H, HC(1)), 7.38 (t, *J* = 7.67 Hz, 1H, HC(2)), 7.20 (d, *J* = 3.14 Hz, 1H, HC(9)), 6.60 (dd, *J*= 3.50, 1.80 Hz, 1H, HC(10))

^{13}C NMR: (126 MHz, $CDCl_3$)

157.58 (s, C(7)), 153.75 (s, C(4)), 148.76 (s, C(8)), 144.73 (s, C(11)), 134.29 (s, C(5)), 126.51 (s, C(1)), 125.22 (s, C(2)), 123.14 (s, C(6)), 121.59 (s, C(3)), 112.56 (s, C(10)), 111.47 (s, C(9))

HRMS (EI^+): Calcd for $C_{11}H_7NOS^+$: 201.0248 Found: 201.0253

Preparation of 2-(Pyridin-4-yl)pyrazine (3dc)



1d **2c** **3dc**

Following the General Procedure, 2-bromopyrazine **1d** (159.4 mg, 1.00 mmol) was combined with boronic ester **2c** (210.1 mg, 1.10 mmol, 1.10 equiv) and Pd-CataCXium A-G3 precatalyst (21.8 mg, 0.03 mmol, 0.03 equiv). The reaction was purged with argon using a needle for 5 min. The total reaction time was 30 min. After workup, the resulting solution was concentrated via rotary evaporation (35 ºC, 25 mm Hg) and loaded onto 0.5g of celite. The crude product was purified by silica gel chromatography (2.0 cm, 5g silica gel) eluting with EtOAc. The material was transferred to a sublimation apparatus which was heated at 75 °C using a silicone oil bath under high vacuum (0.1 mm Hg). The sublimate was collected to give 139.3 mg (0.88 mmol,

88% yield) of pure **3dc** as a white crystalline solid. Spectroscopic data was in agreement with literature values.[6]

Data for **3dc:**

^{1}H NMR: (500 MHz, $CDCl_3$)

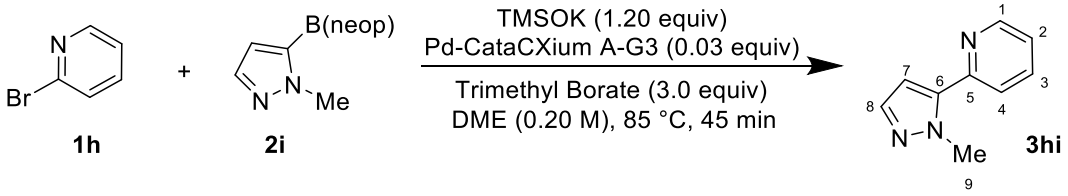
9.11 (d, *J*=1.52 Hz 1H, HC(1)), 8.78 (d, *J*=6.19 Hz 2H, HC(7)), 8.71 (t, *J*= 1.98 Hz, HC(2)), 8.63 (d, *J*= 2.44 Hz, 1H, HC(3)), 7.93 (d, *J*= 6.2Hz, 2H, HC(6))

^{13}C NMR: (126 MHz, $CDCl_3$)

150.77 (s, C(7)), 150.26 (s, C(4)), 144.92 (s, C(3)), 144.76 (s, C(2)), 143.75 (s, C(5)), 142.50 (s, C(1)), 121.06 (s, C(6))

HRMS (ES^+): Calcd for $C_9H_8N_3$ $(M+H)^+$: 158.0718 Found: 158.0711

Preparation of 2-(1-Methyl-1H-pyrazol-5-yl)pyridine (3hi)



Following the General Procedure, 2-bromopyridine **1h** (158.0 mg, 1.00 mmol) was combined with boronic ester **2i** (213.4 mg, 1.10 mmol, 1.10 equiv) and Pd-CataCXium A-G3 precatalyst (21.7 mg, 0.03 mmol, 0.03 equiv). The reaction was purged with argon using a needle for 5 min. The total reaction time was 45 min. After workup, the resulting solution was concentrated via rotary evaporation (35 ºC, 25 mm Hg), dissolved in 30 mL of THF, and loaded onto 0.85g of silica gel. The crude product was purified by silica gel chromatography (2.0 cm, 10 g silica gel) eluting with 9:1 hexanes:EtOAc to 7:3 hexanes:EtOAc. The material was concentrated via rotary evaporation (35 °C, 25 mm Hg) and transferred to a 25 mL round-bottomed flask which was heated at 40 °C under high vacuum (0.1 mm Hg) using a Kugelrohr apparatus to give 149.6 mg (0.94 mmol, 94% yield) of pure **3hi** as a yellow oil. Spectroscopic data was in agreement with literature values.[7]

Data for **3hi:**

^{1}H NMR: (500 MHz, $CDCl_3$)

8.67 (d, *J*=4.93 Hz 1H, HC(1)), 7.74 (dt, *J*=7.79,1.21 Hz 1H, HC(3)), 7.57 (d, *J*=

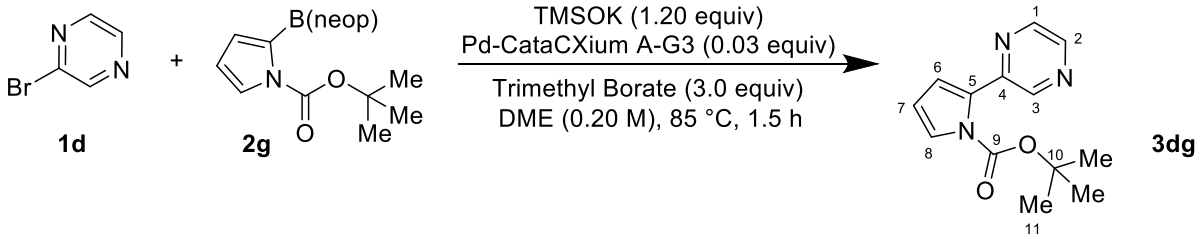
7.94 Hz, 1H, HC(4)), 7.51 (d, *J*= 1.91 Hz, 1H, HC(8)), 7.24 (dd, *J*=7.1,5.4 Hz, 1H, HC(2)), 6.58 (d, *J*= 1.93 Hz, 1H, HC(7)), 4.23 (s, 3H, HC(9))

^{13}C NMR: (126 MHz, $CDCl_3$)

150.19 (s, C(5)), 149.34 (s, C(1)), 141.41 (s, C(6)), 138.25 (s, C(8)), 136.83 (s, C(3)), 122.97 (s, C(4)), 122.46 (s, C(2)), 106.61 (s, C(7)), 39.51 (s, C(9))

HRMS (ES$^+$): Calcd for $C_9H_{10}N_3$ $(M+H)^+$: 160.0875 Found: 160.0870

Preparation of *tert*-Butyl 2-(Pyrazin-2-yl)-1H-pyrrole-1-carboxylate (3dg)



Following the General Procedure, 2-bromopyrazine **1d** (158.9 mg, 1.00 mmol) was combined with boronic ester **2g** (307.8 mg, 1.10 mmol, 1.10 equiv) and Pd-CataCXium A-G3 precatalyst (21.9 mg, 0.03 mmol, 0.03 equiv). The reaction was purged with argon using a needle for 5 min. The total reaction time was 1.5 h. After workup, the resulting solution was concentrated via rotary evaporation (35 ºC, 25 mm Hg) and loaded onto 0.5 g of celite. The crude product was purified by silica gel chromatography (2.0 cm, 10 g silica gel) eluting with neat hexanes to 1:1 EtOAc:hexanes. The material was concentrated via rotary evaporation (35 °C, 25 mm Hg) and transferred to a 25 mL round-bottomed flask which was heated at 40 °C under high vacuum (0.1 mm Hg) using a Kugelrohr apparatus to give 206.6 mg (0.84 mmol, 84% yield) of pure **3dg** as a yellow oil. Spectroscopic data was in agreement with literature values.[8]

Data for **3dg:**

^{1}H NMR: (500 MHz, $CDCl_3$)

8.68 (d, *J*=1.52 Hz, 1H, HC(3)), 8.56 (t, *J*=1.89 Hz, 1H, HC(1)), 8.45 (d, *J*=2.56 Hz, 1H, HC(2)), 7.43 (dd, *J*=3.32,1.74 Hz, 1H, HC(8)), 6.53 (dd, *J*=3.48,1.74 Hz, 1H, HC(6)), 6.30 (t, *J*=3.31 Hz, 1H, HC(7)), 1.40 (s, 9H, HC(11))

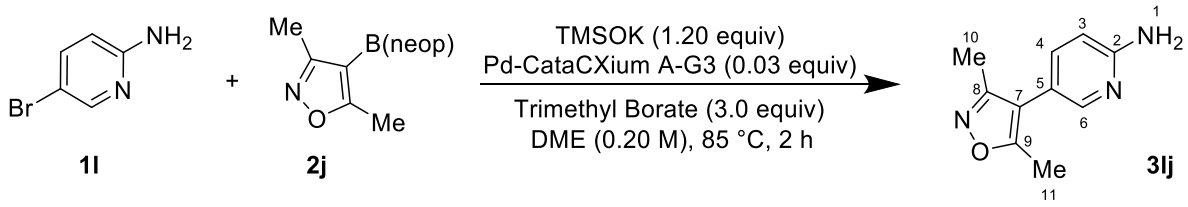
^{13}C NMR: (126 MHz, $CDCl_3$)

149.05 (s, C(9)), 148.97 (s, C(4)), 144.96 (s, C(3)), 143.51 (s, C(1)), 142.33 (s, C(2)), 130.86 (s, C(5)), 124.76 (s, C(8)), 117.41 (s, C(6)), 111.22 (s, C(7)), 84.50

(s, C(10)), 27.70 (s, C(11))

HRMS (EI$^+$): Calcd for $C_{13}H_{15}N_3O_2$ (M^+): 245.1164 Found: 245.1172

Preparation of 5-(3,5-Dimethylisoxazol-4-yl)pyridin-2-amine (3lj)



Following the General Procedure, 5-bromopyridin-2-amine **1l** (173.1 mg, 1.00 mmol) was combined with boronic ester **2j** (229.8 mg, 1.10 mmol, 1.10 equiv) and Pd-CataCXium A-G3 precatalyst (21.9 mg, 0.03 mmol, 0.03 equiv). The total reaction time was 2 h. After workup, the resulting solution was concentrated via rotary evaporation (35 ºC, 25 mm Hg) and loaded onto 0.5g of celite. The crude product was purified by silica gel chromatography (2.0 cm, 5 g silica gel) eluting with neat EtOAc. The product was concentrated via rotary evaporation (35 °C, 25 mm Hg). The material was transferred to a sublimation apparatus which was heated at 140 °C using a silicone oil bath under high vacuum (0.1 mm Hg). The sublimate was collected to give 147.1 mg (0.78 mmol, 78% yield) of pure **3lj** as a light yellow crystalline solid. Spectroscopic data was in agreement with literature values.[9]

Data for **3lj:**

^{1}H NMR: (500 MHz, $CDCl_3$)

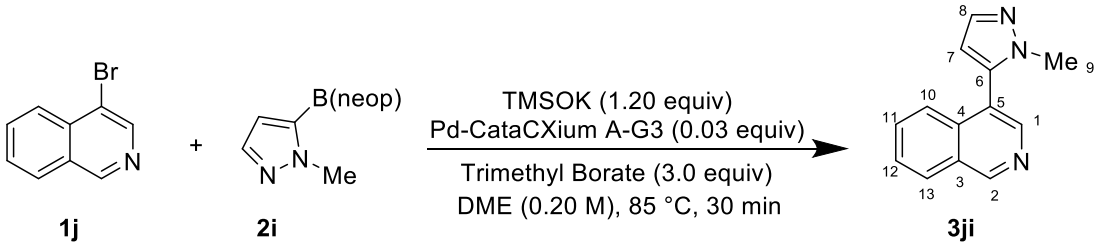
7.97 (d, *J*=2.44 Hz, 1H, HC(6)), 7.33 (dd, *J*=8.36,1.58 Hz, 1H, HC(4)), 6.85 (d, *J*=8.37 Hz, 1H, HC(3)), 4.53 (bs, 2H, H(1)), 2.38 (s, 3H, HC(11)), 2.24 (s, 3H, HC(10))

^{13}C NMR: (126 MHz, $CDCl_3$)

165.43 (s, C(9)), 159.04 (s, C(8)), 157.75 (s, C(2)), 148.44 (s, C(6)), 138.56 (s, C(4)), 116.56 (s, C(5)), 113.83 (s, C(7)), 108.63 (s, C(3)), 11.62 (s, C(11)), 10.85 (s, C(10))

HRMS (EI$^+$): Calcd for $C_{10}H_{11}N_3O$ (M^+): 189.0902 Found: 189.0899

Preparation of 4-(1-Methyl-1H-pyrazol-5-yl)isoquinoline (3ji)



Following the general procedure, 4-bromoisoquinoline **1j** (208.0 mg, 1.00 mmol) was combined with boronic ester **2i** (213.5 mg, 1.10 mmol, 1.10 equiv) and Pd-CataCXium A-G3 precatalyst (21.9 mg, 0.03 mmol, 0.03 equiv). The total reaction time was 30 min. After workup, the crude product was purified by silica gel chromatography (2.0 cm, 10 g silica gel) eluting with 4:1 hexanes:EtOAc to neat EtOAc. The resulting yellow oil was transferred to a 25 mL round-bottomed flask and heated at 70°C at 0.1 mmHg in a Kugelrohr apparatus to furnish 183.5 mg (0.88 mmol, 88% yield) of pure **3ji** as a yellow oil. Spectroscopic data was in agreement with literature values.[10]

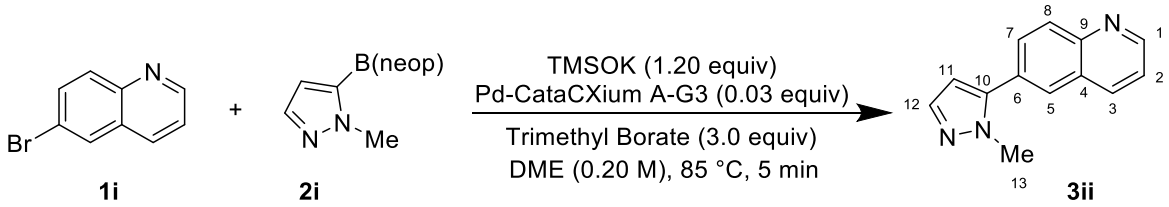
Data for **3ji:**

^{1}H NMR: (500 MHz, $CDCl_3$)
9.35 (s, 1H, HC(2)), 8.51 (s, 1H, HC(1)), 8.10 (d, *J*= 8.11 Hz, 1H, HC(13)), 7.78-7.74 (m, 1H, HC(11)), 7.72-7.68 (m, 1H, HC(12)), 7.68 (d, *J*=1.84 Hz, 1H, HC(8), 7.66 (d, *J*=7.93 Hz, 1H, HC(10), 6.45 (d, *J*= 1.81 Hz, 1H, HC(7)), 3.71 (s, 3H, HC(9))

^{13}C NMR: (126 MHz, $CDCl_3$)
153.45 (s, C(2)), 143.67 (s, C(1)), 139.09 (s, C(8)), 138.08 (s, C(6)), 135.04 (s, C(4)), 131.81 (s, C(11)), 128.38 (s, C(13)), 128.35 (s, C(3)), 128.09 (s, C(12)), 124.56 (s, C(10)), 122.72 (s, C(5)), 108.70 (s, C(7)), 37.37 (s, C(9))

HRMS (ES^+): Calcd for $C_{13}H_{12}N_3$ $(M+H)^+$: 210.1031 Found: 210.1027

Preparation of 6-(1-Methyl-1H-pyrazol-5-yl)quinoline (3ii)



Following the General Procedure, 6-bromoquinoline **1i** (208.2 mg, 1.00 mmol) was combined with boronic ester **2i** (213.3 mg, 1.10 mmol, 1.10 equiv) and Pd-CataCXium A-G3 precatalyst (21.8 mg, 0.03 mmol, 0.03 equiv). The total reaction time was 5 min. After workup, the crude product was loaded onto 0.3g celite and purified by silica gel chromatography (2.0 cm, 10 g silica gel) eluting with 5:1 hexanes:EtOAc to neat EtOAc. The material was transferred to a sublimation apparatus which was heated at 60 °C using a silicone oil bath under high vacuum (0.1 mm Hg). The sublimate was collected to give 146.5 mg (0.70 mmol, 70% yield) of pure **3ii** as a white crystalline solid. Spectroscopic data was in agreement with literature values.[11]

Data for **3ii:**

^{1}H NMR: (500 MHz, $CDCl_3$)

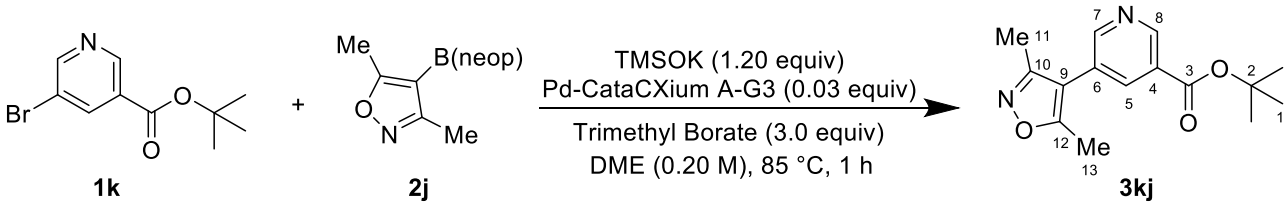
8.98 (dd, *J*=4.27,1.67 Hz, 1H, HC(1)), 8.26-8.18 (m, 2H, HC(3,8)), 7.88 (d, *J*=1.94 Hz, 1H, HC(5)), 7.79 (dd, *J*=8.73,1.99 Hz, 1H, HC(7)), 7.58 (d, *J*=1.87 Hz, 1H, HC(12)), 7.49 (dd, *J*=8.33,4.24 Hz, 1H, HC(2)), 6.44 (d, *J*=1.85 Hz, 1H, HC(11)), 3.97 (s, 3H, HC(13))

^{13}C NMR: (126 MHz, $CDCl_3$)

151.17 (s, C(1)), 147.75 (s, C(9)), 142.90 (s, C(10)), 138.91 (s, C(12)), 136.52 (s, C(3 or 8)), 130.23 (s, C(7)), 130.08 (s, C(3 or 8)), 129.20 (s, C(6)), 128.24 (s, C(4)), 127.85 (s, C(5)), 122.03 (s, C(2)), 106.83 (s, C(11)), 37.86 (s, C(13))

HRMS (EI$^+$): Calcd for $C_{13}H_{11}N_3$ (M^+): 209.0953 Found: 209.0959

Preparation of *tert*-Butyl 5-(3,5-Dimethylisoxazol-4-yl)nicotinate (3kj)



Following the General Procedure, *tert*-butyl 5-bromonicotinate **1k** (258.2 mg, 1.00 mmol)

was combined with boronic ester **2j** (229.9 mg, 1.10 mmol, 1.10 equiv) and Pd-CataCXium A-G3 precatalyst (21.8 mg, 0.03 mmol, 0.03 equiv). The total reaction time was 1 hr. After workup, the crude product was purified by silica gel chromatography (2.0 cm, 10g silica gel) eluting with 4:1 hexanes:EtOAc. The resulting solution was concentrated via rotary evaporation (35 ºC, 25 mm Hg). The material was transferred to a sublimation apparatus which was heated at 90 °C using a silicone oil bath under high vacuum (0.1 mm Hg). The sublimate was collected to give 245.3 mg (0.89 mmol, 89% yield) of analytically pure **3kj** as a white crystalline solid.

Data for **3kj:**

mp: 109.5-111.7°C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

9.15 (d, *J*= 2.02 Hz, 1H, HC(8)), 8.67 (d, *J*=2.15 Hz, 1H, HC(7)), 8.16 (t, *J*= 2.13 Hz, 1H, HC(5)), 2.45 (s, 3H, HC(13)), 2.30 (s, 3H, HC(11)), 1.63 (s, 9H, HC(1))

^{13}C NMR: (126 MHz, $CDCl_3$)

166.63 (s, C(12), 164.02 (s, C(3)), 158.54 (s, C(10)), 152.65 (s, C(7)), 149.58 (s, C(8)), 137.33 (s, C(5)), 128.09 (s, C(6)), 126.71 (s, C(4)), 112.91 (s, C(9)), 82.78 (s, C(2)), 28.30 (s, C(1)), 11.80 (s, C(13)), 10.90 (s, C(11))

IR: (neat, ATR)

2978 (w), 1710 (s), 1639 (w), 1595 (w), 1456 (m), 1414 (m), 1367 (m), 1314 (s), 1274 (s), 1240 (s), 1158 (s), 1124 (s), 1027 (m), 1010 (w), 919 (w), 879 (s), 845 (m), 774 (s), 709 (s), 653 (w), 617 (w), 585 (w), 560 (w), 474 (w)

LRMS (EI^+):

274.1 (57), 260.1 (15), 219.1 (12), 218.1 (100, M), 203.0 (23), 201.1 (36), 176.1 (22), 131.1 (17), 57.1 (32)

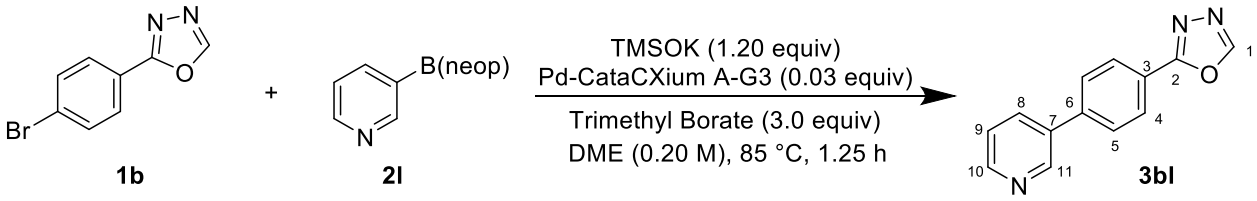
HRMS (EI^+): Calcd for $C_{15}H1_8N_2O_3$ (M^+): 274.1317 Found: 274.1322

TLC: R_f 0.28 (hexanes/EtOAc 5:1, UV)

Analysis: $C_{15}H1_8N_2O_3$ (274.32)

Calcd:	C, 65.68;	H, 6.61;	N, 10.21
Found:	C, 65.63;	H, 6.58;	N, 10.19

Preparation of 2-(4-(Pyridin-3-yl)phenyl)-1,3,4-oxadiazole (3bl)



Following the General Procedure, 2-(4-bromophenyl)-1,3,4-oxadiazole **1b** (225.1 mg, 1.00 mmol) was combined with boronic ester **2l** (210.3 mg, 1.10 mmol, 1.10 equiv) and Pd-CataCXium A-G3 precatalyst (21.9 mg, 0.03 mmol, 0.03 equiv). The total reaction time was 1.25 hr. After workup, the resulting solution was concentrated via rotary evaporation (35 ºC, 25 mm Hg). The material was transferred to a sublimation apparatus which was heated at 95 °C using a silicone oil bath under high vacuum (0.1 mm Hg). The sublimate was collected to give 172.3 mg (0.77 mmol, 77% yield) of pure **3bl** as a white crystalline solid. A portion of this material was further purified by recrystallizing 30 mg from 10 mL of heptane to give 28 mg (93% recovery) after filtration. The recrystallized material was transferred to a sublimation apparatus which was heated at 95 °C using a silicone oil bath under high vacuum (0.1 mm Hg). The sublimate was collected to give 14 mg (50% recovery) of pure **3bl** as a white crystalline solid.

Data for **3bl:**

mp: 141.1-141.5°C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

8.91 (s, 1H, HC(11)), 8.66 (d, *J*=4.45 Hz, 1H, HC(10)), 8.51 (s, 1H, HC(1)), 8.21 (d, *J*=8.09 Hz, 2H, HC(4)), 7.94 (d, *J*=8.18 Hz, 1H, HC(8)), 7.76 (*J*=8.12 Hz, 2H, HC(5)) (d 7.42 (dd, J=7.90, 4.18 1H, HC(9))

^{13}C NMR: (126 MHz, $CDCl_3$)

164.56 (s, C(2), 152.86 (s, C(1)), 149.53 (s, C(10)), 148.41 (s, C(11)), 141.55 (s, C(6)), 135.45 (s, C(7)), 134.56 (s, C(8)), 128.00 (s, C(4 or 5)), 127.97 (s, C(4 or 5)), 123.87 (s, C(9)), 123.29 (s, C(3))

IR: (neat, ATR)

3080 (w), 1614 (w), 1585 (w), 1573 (w), 1553 (w), 1509 (w), 1478 (m), 1428 (m), 1403 (m), 1333 (w), 1246 (w), 1198 (w), 1135 (w), 1098 (m), 1062 (m), 1026 (w), 1002 (m), 972 (w), 953 (m), 940 (m), 884 (w), 862 (w), 851 (m), 805 (m), 743 (s), 706 (s), 639 (s), 621 (w), 556 (m), 516 (w), 452 (m)

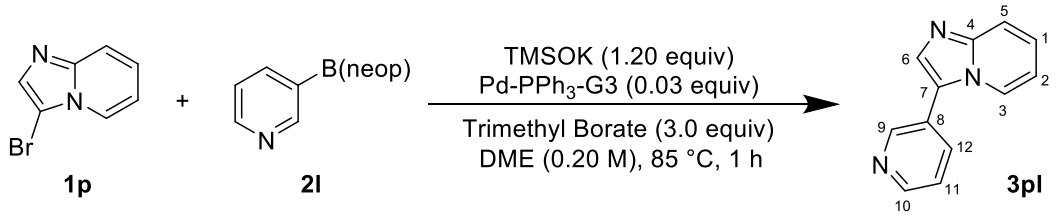
LRMS (EI$^+$): 224.1 (16), 223.1 (100, M), 182.1 (83), 180.1 (95), 179.1 (36), 154.1 (23), 127.0 (24)

HRMS (EI$^+$): Calcd for $C_{13}H_9N_3O$ (M^+): 223.0746 Found: 223.0750

TLC: R_f 0.32 (EtOAc, UV)

qNMR: 100% Purity (1,3,5-trimethoxybenzene int. std.)

Preparation of 3-(Pyridin-3-yl)imidazo[1,2-a]pyridine (3pl)



Following a modified version of the General Procedure, 3-bromoimidazo[1,2-a]pyridine **1p** (197.0 mg, 1.00 mmol) was combined with boronic ester **2l** (210.2 mg, 1.10 mmol, 1.10 equiv) and Pd-PPh$_3$-G3 precatalyst (18.9 mg, 0.03 mmol, 0.03 equiv). The total reaction time was 1 hr. After workup, the resulting solution was concentrated via rotary evaporation (35 ºC, 25 mm Hg) and loaded into a single piece Kugelrohr bulb. The crude product was purified by Kugelrohr distillation (130°C, 0.1 mmHg) to give 149.0 mg (0.76 mmol, 76%) of pure **3pl** as a light yellow oil. Spectroscopic data was in agreement with literature values.[12]

Data for **3pl:**

^{1}H NMR: (500 MHz, $CDCl_3$)

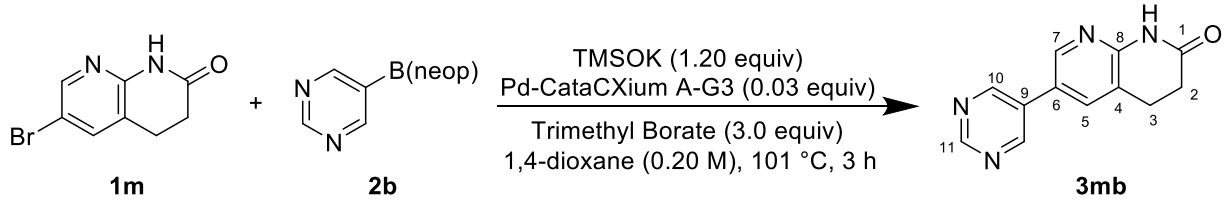
8.86 (d, *J*= 2.30 Hz, 1H, HC(9)), 8.68 (dd, *J*= 4.87,1.69 Hz, 1H, HC(10)), 8.30 (d, *J*= 6.93 Hz, 1H, HC(3)), 7.89 (dt, *J*= 7.87,1.95 1H, HC(11)), 7.77 (s, 1H, HC(6)), 7.74 (d, *J*=9.16 1H, HC(5)), 7.47 (dd *J*= 7.83,4.80 1H, HC(**12**)), 7.31-7.27 (m, 1H, HC(1)), 6.89 (t, *J*= 6.76 1H, HC(2))

^{13}C NMR: (126 MHz, $CDCl_3$)

149.53 (s, C(10)), 149.10 (s, C(9)), 146.61 (s, C(4)), 135.37 (s, C(11)), 133.14 (s, C(6)), 125.64 (s, C(**7**)), 125.27 (s, C(1)), 124.12 (s, C(12)), 123.16 (s, C(3)), 122.52 (s, C(8)), 118.57 (s, C(5)), 113.43 (s, C(2))

HRMS (ES$^+$): Calcd for $C_{12}H_{10}N_3$ $(M+H)^+$: 196.0875 Found: 196.0873

Preparation of 6-(Pyrimidin-5-yl)-3,4-dihydro-1,8-naphthyridin-2(1H)-one (3mb)



Following a modified version of the General Procedure, 6-bromo-3,4-dihydro-1,8-naphthyridin-2(1H)-one **1m** (227.0 mg, 1.00 mmol) was combined with boronic ester **2b** (211.5 mg, 1.10 mmol, 1.10 equiv) and Pd-CataCXium A-G3 precatalyst (21.8 mg, 0.03 mmol, 0.03 equiv). 3.5 mL of 1,4-dioxane was used in place of 1,2-dimethoxyethane and the 1.00M TMSOK solution was also prepared in 1,4-dioxane. The reaction was heated in a 130 °C silicon oil bath. The total reaction time was 3 h. The reaction was then cooled to room temperature and transferred to a 500 mL separatory funnel using 200 mL of dichloromethane. The resulting organic layer was then washed with 1M aqueous ethanolamine (1x50 mL) and brine (1x50mL). The resulting aqueous layers were then extracted further with dichloromethane (2x50 mL). The combined organic layers were dried over sodium sulfate (5 g) and filtered. The sodium sulfate was further washed with dichloromethane to ensure quantitative transfer (2x25 mL). The resulting organic layer was then concentrated by rotary evaporation (35 ºC, 25 mm Hg). After workup, the crude product was passed through a silica gel plug (3.0 cm, 10 g silica gel) eluting with 5:1 CH_2Cl_2/MeOH. The resulting solution was concentrated by rotary evaporation (35 ºC, 25 mm Hg) and subsequently recrystallized from 50 mL of acetonitrile to furnish 165.0 mg (0.73 mmol, 73% yield) of pure **3mb** as a light yellow crystalline solid. A portion of the material (65 mg) was further purified by sublimation in a diffusion pump (175°C, 4.0×10^{-5} mm Hg) to furnish 44 mg (68% recovery) of analytically pure product as a white crystalline solid.

Data for **3mb:**

mp: >260°C (sealed tube)

^{1}H NMR: (500 MHz, DMSO-d6)
10.67 (s, 1H, H(N)), 9.18 (s, 1H, HC(11)), 9.16 (s, 2H, HC(10)), 8.57 (d, *J*= 2.33, 1H, HC(7)), 8.10 (d, *J*= 2.37, 1H, HC(5)), 2.97 (t, *J*=7.61 2H, HC(3)), 2.56 (t, *J*=7.64 2H, HC(2))

^{13}C NMR: (126 MHz, DMSO-d6)
171.02 (s, C(1)), 157.18 (s, C(11)), 154.28 (s, C(10)), 152.06 (s, C(8)), 144.32 (s,

C(7)), 134.13 (s, C(5)), 130.60 (s, C(9)), 123.90 (s, C(6)), 119.24 (s, C(4)), 30.04 (s, C(2)), 23.41 (s, C(3))

IR: (neat, ATR)

3037 (m), 2885 (m), 1665 (s), 1614 (m), 1594 (m), 1559 (m), 1506 (m), 1462 (w), 1448 (m), 1417 (s), 1366 (m), 1353 (s), 1330 (s), 1312 (s), 1297 (s), 1207 (s), 1183 (s), 1035 (m), 998 (w), 944 (m), 922 (m), 908 (s), 856 (s), 786 (m), 750 (m), 741 (m), 720 (s), 691 (m), 637 (s), 606 (m), 576 (m), 535 (s), 497 (m), 465 (m)

LRMS (EI^+): 227.1 (15), 226.1 (100, M), 198.1 (24), 197.1 (69), 171.1 (23), 60.0 (17), 57.1 (23)

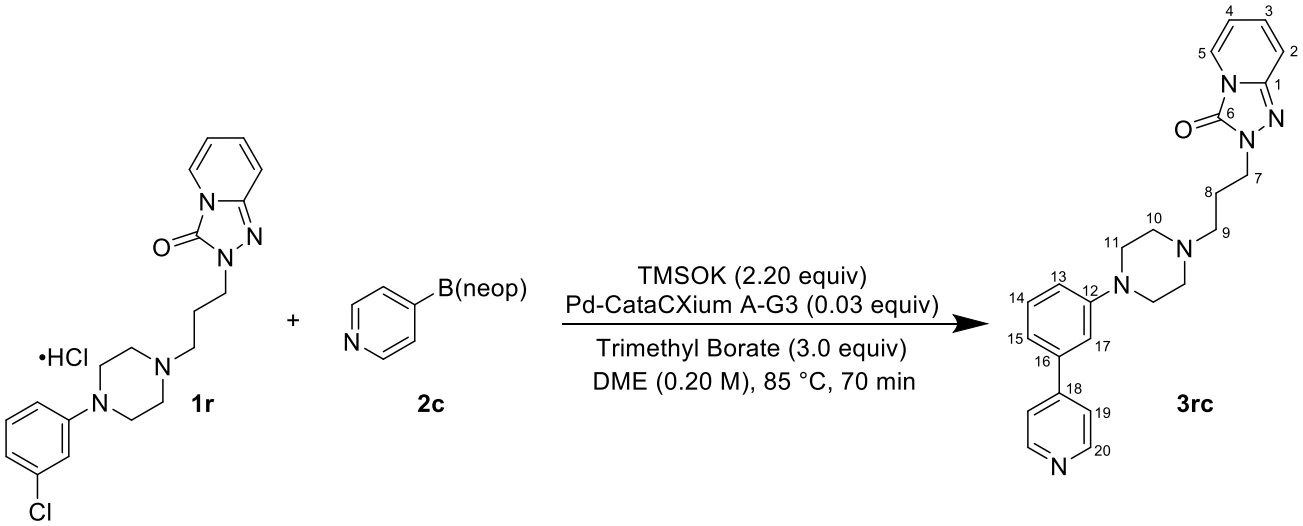
HRMS (EI^+): Calcd for $C_{12}H_{10}N_4O$ (M^+): 226.0855 Found: 226.0853

TLC: R_f 0.51 (EtOAc/MeOH 5:1, UV)

Analysis: $C_{12}H_{10}N_4O$ (226.24)

Calcd:	C, 63.71;	H, 4.46;	N, 24.76
Found:	C, 63.53;	H, 4.28;	N, 24.43

Preparation of 2-(3-(4-(3-(Pyridin-4-yl)phenyl)piperazin-1-yl)propyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one (3rc)



Following a modified version of the General Procedure, Trazodone•HCl **1r** (408.4 mg, 1.00 mmol) was combined with boronic ester **2c** (210.2 mg, 1.10 mmol, 1.10 equiv) and Pd-CataCXium A-G3 precatalyst (21.8 mg, 0.03 mmol, 0.03 equiv). 2.5 mL of 1,2-dimethoxyethane and 2.2 mL of 1.00 M TMSOK solution were used. The total reaction time was 70 min. After workup, the resulting solution was concentrated via rotary evaporation (35 ºC, 25 mm Hg). The

crude product was purified by silica gel chromatography (2.0 cm, 10 g silica gel) eluting with neat EtOAc to 4:1 EtOAc/MeOH. The purified product was transferred to a 50 mL round-bottomed flask and dried for 60 min at 70°C (0.1 mmHg) and 30 min at 85 °C (0.1 mmHg) using a Kugelrohr apparatus to remove residual EtOAc to furnish 402.7 mg of **3rc** as a glassy yellow oil. (0.91 mmol, 91%)

*Note: **3rc** was found to be thermally unstable and underwent partial decomposition during heating to remove EtOAc and was therefore not further purified beyond column chromatography. The reported yield accounts for the trace EtOAc still present by ^{1}H NMR after drying.

Data for **3rc:**

^{1}H NMR: (500 MHz, $CDCl_3$)

8.63 (d, *J* = 6.15 Hz, 2H, HC(20)), 7.76 (d, *J* = 7.05 Hz, 1H, HC(5)), 7.48 (d, *J* = 6.16 Hz, 1H, HC(19)), 7.35 (t, *J* = 7.92 Hz, 1H, HC(14)), 7.15-7.02 (m, 4H, HC(2,3,15,17)), 6.97 (dd, *J* = 8.32, 2.43 Hz, 1H, HC(13)), 6.48 (t, *J* = 6.40 Hz, 1H, HC(4)), 4.10 (t, *J* = 6.94 Hz, 2H, HC(7)), 3.22 (t, *J* = 4.97 Hz, 4H, HC(11)), 2.62 (t, *J* = 4.95 Hz, 4H, HC(10)), 2.52 (t, *J* = 7.08 Hz, 2H, HC(9)), 2.07 (t, *J* = 7.04 Hz, 2H, HC(8))

^{13}C NMR: (126 MHz, $CDCl_3$)

152.06 (s, C(12)), 150.29 (s, C(20)), 149.13 (s, C(1)), 148.78 (s, C(6)), 141.61 (s, C(18)), 139.33 (s, C(16)), 129.96 (s, C(14)), 129.91 (s, C(3)), 123.88 (s, C(5)), 121.94 (s, C(19)), 118.41 (s, C(15)), 116.62 (s, C(13)), 115.53 (s, C(2)), 114.68 (s, C(17)), 110.63 (s, C(4)), 55.70 (s, C(9)), 53.22 (s, C(10)), 49.19 (s, C(11)), 44.56 (s, C(7)), 26.23 (s, C(8))

IR: (neat, ATR)

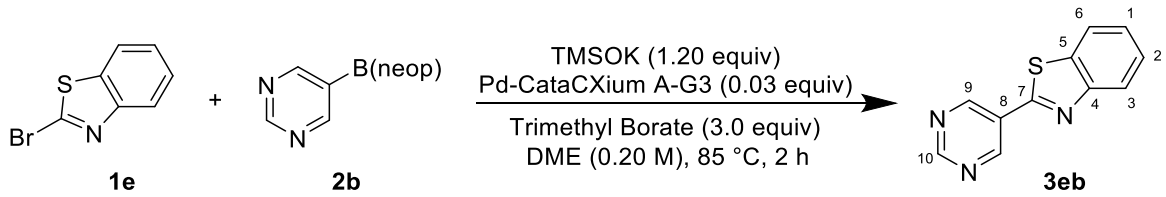
3406 (w), 3030 (w), 2941 (w), 2880 (w), 2817 (w), 1939 (w), 1702 (s), 1638 (m), 1592 (s), 1542 (s), 1481 (m), 1439 (m), 1405 (m), 1380 (m), 1355 (m), 1315 (m), 1274 (m), 1224 (s), 1143 (m), 1067 (w), 1025 (w), 1009 (w), 991 (m), 944 (m), 889 (w), 824 (m), 778 (m), 747 (s), 712 (m), 689 (m), 650 (w), 612 (m), 589 (m), 559 (w), 540 (w), 472 (w)

LRMS (EI^+): 70.1 (52), 78.0 (34), 154.1 (45), 176.1 (50), 181.1 (39), 205.1 (100), 209.1 (56), 231.1 (41), 252.1 (54), 321.2 (51), 399.2 (52), 414.2 (35, M)

HRMS (EI$^+$): Calcd for $C_{24}H_{26}N_6O$ (M^+): 414.2168 Found: 414.2166

TLC: R_f 0.22 (4:1 EtOAc/MeOH, UV)

Preparation of 2-(Pyrimidin-5-yl)benzo[d]thiazole (3eb)



Following the General Procedure, 2-bromobenzo[d]thiazole **1e** (214.1 mg, 1.00 mmol) was combined with boronic ester **2b** (211.2 mg, 1.10 mmol, 1.10 equiv) and Pd-CataCXium A-G3 precatalyst (21.8 mg, 0.03 mmol, 0.03 equiv). The total reaction time was 2 hr. After workup, the resulting solution was concentrated via rotary evaporation (35 ºC, 25 mm Hg). The material was transferred to a sublimation apparatus which was heated at 90 °C using a silicone oil bath under high vacuum (0.1 mm Hg). The sublimate was collected to give 158.0 mg (0.74 mmol, 74% yield) of **3eb** as a yellow crystalline solid. Spectroscopic data was in agreement with literature values.[13]

Data for **3eb:**

^{1}H NMR: (500 MHz, $CDCl_3$)

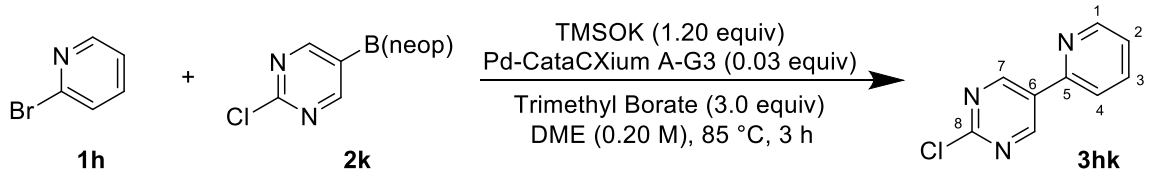
9.40 (s, 2H, HC(9)), 9.32 (s, 1H, HC(10)), 8.14 (d, J = 8.17, 1H, HC(3)), 7.97 (d, J = 8.01 Hz , 1H, HC(2)), 7.57 (t, J = 8.26 Hz, 1H, HC(6)), 7.48 (t, J = 8.14 Hz, 1H, HC(5))

^{13}C NMR: (126 MHz, $CDCl_3$)

161.18 (s, C(8)), 159.99 (s, C(10)), 155.35 (s, C(9)), 154.03 (s, C(5)), 135.07 (s, C(4)), 128.12 (s, C(7)), 127.15 (s, C(2)), 126.42 (s, C(1)), 123.99 (s, C(3)), 122.03 (s, C(6))

HRMS (ES$^+$): Calcd for $C_{11}H_8N_3S$ $(M+H)^+$: 214.0439 Found: 214.0433

Preparation of 2-Chloro-5-(pyridin-2-yl)pyrimidine (3kh)



Following the General Procedure, 2-bromopyridine **1h** (158.0 mg, 1.00 mmol) was combined with boronic ester **2k** (249.0 mg, 1.10 mmol, 1.10 equiv) and Pd-CataCXium A-G3 precatalyst (21.8 mg, 0.03 mmol, 0.03 equiv). The total reaction time was 3 hr. After workup, the crude product was purified by silica gel chromatography (2.0 cm, 5 g silica gel) eluting with isopropyl alcohol/CH_2Cl_2/petroleum ether in a 1:10:125 ratio. The resulting solution was concentrated via rotary evaporation (35 ºC, 25 mm Hg) to furnish 147.0 mg (0.77 mmol, 77% yield) of pure **3hk** as a white crystalline solid. Spectroscopic data was in agreement with literature values.[14]

Data for **3hk:**

^{1}H NMR: (500 MHz, DMSO-d_6)

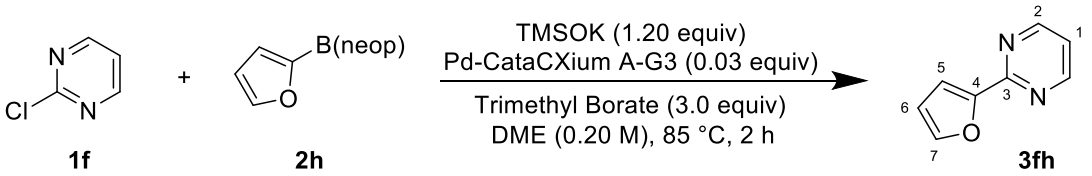
9.41 (s, 2H, HC(7)), 8.75 (d, *J* = 4.82 Hz, 1H, HC(1)), 8.16 (d, *J* = 7.93 Hz, 1H, HC(4)), 7.99 (dt, *J* = 7.80, 1.80 Hz, 1H, HC(3)), 7.50 (dd, *J* = 7.58, 4.80 Hz, 1H, HC(2))

^{13}C NMR: (126 MHz, DMSO-d_6)

160.13 (s, C(8)), 158.16 (s, C(7)), 150.19 (s, C(5)), 150.13 (s, C(1)), 137.74 (s, C(3)), 130.89 (s, C(6)), 124.28 (s, C(2)), 121.25 (s, C(4))

HRMS (ES$^+$): Calcd for $C_9H_7N_3Cl$ $(M+H)^+$: 192.0329 Found: 192.0324

Preparation of 2-(Furan-2-yl)pyrimidine (3fh)



Following the general procedure, 2-chloropyrimidine **1f** (137.0 mg, 1.20 mmol) was combined with boronic ester **2h** (238.0 mg, 1.32 mmol, 1.10 equiv) and Pd-CataCXium A-G3 precatalyst (22.0 mg, 0.03 mmol, 0.03 equiv). The total reaction time was 2 hr. After workup, the crude product was passed through a silica gel plug (3.0 cm, 20 g silica gel) eluting with 99:1

DCM:MeOH. The resulting solution was concentrated via rotary evaporation (35 ºC, 25 mm Hg). The material was transferred to a sublimation apparatus which was heated at 50 °C using a silicone oil bath under high vacuum (0.1 mm Hg). The sublimate was collected to furnish a white crystalline solid. The resulting crystals were then recrystallized from 5 mL of heptane to furnish 155.0 mg (1.06 mmol, 88% yield) of analytically pure **3fh** as a white crystalline solid.

Data for **3fh:**

mp: 69.0-70.0°C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)
8.75 (d, J = 4.8 Hz, 2H, HC(2)), 7.63 (t, J = 0.83 Hz, 1H, HC(7)), 7.33 (d, J = 3.44 Hz, 1H, HC(5)), 7.13 (t, J = 4.86 Hz, 1H, HC(1)), 6.58 (dd, J = 3.45, 1.76 Hz, 1H, HC(6))

^{13}C NMR: (126 MHz, $CDCl_3$)
157.96 (s, C(3)), 157.49 (s, C(2)), 152.13 (s, C(4)), 145.31 (s, C(7)), 118.80 (s, C(1)), 113.65 (s, C(5)), 112.42 (s, C(6))

IR: (neat, ATR)
3112 (w), 1635 (w), 1585 (m), 1564 (s), 1552 (s), 1489 (s), 1437 (m), 1410 (s), 1387 (m), 1317 (m), 1272 (w), 1220 (m), 1169 (m), 1106 (m), 1093 (w), 1075 (w), 1007 (m), 987 (m), 913 (m), 882 (m), 800 (s), 757 (s), 722 (s), 659 (m), 633 (s), 594 (s), 496 (w), 455 (w)

LRMS (ES^+): 200.2 (3), 169.1 (4), 149.0 (4), 148.1 (13), 147.1 (100, M+H), 119.1 (5)

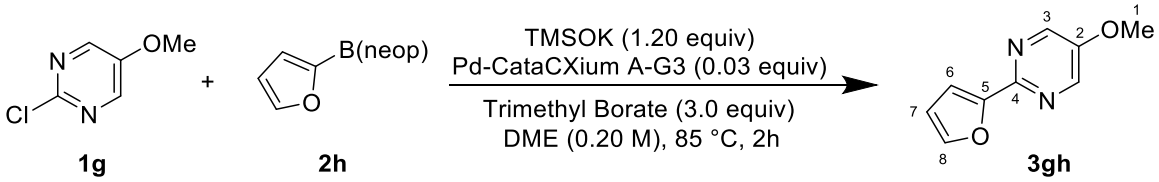
HRMS (ES^+): Calcd for $C_8H_7N_2O$ $(M+H)^+$: 147.0558 Found: 147.0552

TLC: R_f 0.58 (EtOAc, UV)

Analysis: $C_8H_6N_2O$ (146.15)

Calcd:	C, 65.75;	H, 4.14;	N, 19.17
Found:	C, 65.62;	H, 4.10;	N, 18.77

Preparation of 2-(Furan-2-yl)-5-methoxypyrimidine (3gh)



Following the General Procedure, 2-chloro-5-methoxypyrimidine **1g** (144.6 mg, 1.00 mmol) was combined with boronic ester **2h** (198.0 mg, 1.10 mmol, 1.10 equiv) and Pd-CataCXium A-G3 precatalyst (21.8 mg, 0.03 mmol, 0.03 equiv). The total reaction time was 2h. After workup, the resulting solution was concentrated via rotary evaporation (35 ºC, 25 mm Hg). The material was transferred to a sublimation apparatus which was heated at 90 °C using a silicone oil bath under high vacuum (0.1 mm Hg). The sublimate was collected to give 160.0 mg (0.89 mmol, 89% yield) of analytically pure **3gh** as a white, crystalline solid.

Data for **3gh:**

mp: 106.7-107.8°C (sealed tube)

^{1}H NMR: (500 MHz, CD_2Cl_2)
8.41 (s, 2H, HC(3)) 7.58 (dd, *J* = 1.70, 0.80 Hz, 1H, HC(8)), 7.15 (d, *J* = 3.34 Hz, 1H, HC(6)), 6.55 (dd, *J* = 3.36, 1.78 Hz, 1H, HC(7)) 3.94 (s, 3H, HC(1))

^{13}C NMR: (126 MHz, CD_2Cl_2)
152.27 (s, C(5)), 151.64 (s, C(2)), 151.15 (s, C(4)), 144.14 (s, C(8)), 143.42 (s, C(3)),111.91 (s, C(7)), 111.21 (s, C(6)), 56.13 (s, C(1))

IR: (neat, ATR)
3112 (w), 2985 (w), 1589 (m), 1549 (m), 1495 (m), 1453 (m), 1427 (s), 1393 (s), 1319 (w), 1274 (s), 1209 (m), 1175 (m), 1093 (w), 1074 (w), 1003 (s), 953 (w), 915 (s), 884 (m), 824 (w), 788 (m), 761 (s), 661 (w), 638 (m), 623 (s), 596 (m), 501 (m)

LRMS (ES^+): 178.1 (12), 177.1 (100, M+H), 149.1 (13)

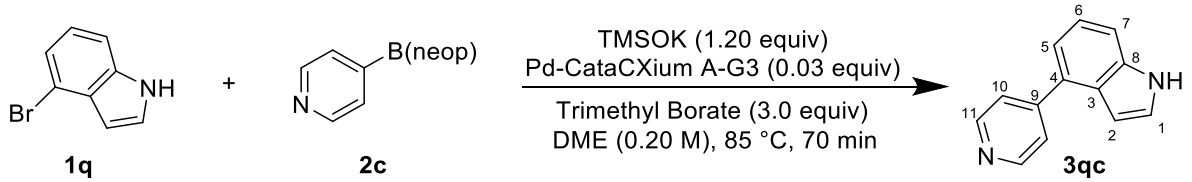
HRMS (ES^+): Calcd for $C_9H_9N_2O_2$ $(M+H)^+$: 177.0664 Found: 177.0658

TLC: R_f 0.74 (EtOAc, UV)

Analysis: $C_9H_8N_2O_2$ (176.18)

Calcd:	C, 61.36;	H, 4.58;	N, 15.90
Found:	C, 61.42;	H, 4.52;	N, 15.57

Preparation of 4-(Pyridin-4-yl)-1H-indole (3qc)



Following the General Procedure, 4-bromoindole **1q** (195.7 mg, 1.00 mmol) was combined with boronic ester **2c** (210.1 mg, 1.10 mmol, 1.10 equiv) and Pd-CataCXium A-G3 precatalyst (21.7 mg, 0.03 mmol, 0.03 equiv). The total reaction time was 70 min. The reaction was then cooled to room temperature and transferred to a 500-mL separatory funnel using 100 mL of EtOAc. The resulting organic layer was then washed with 1 M aqueous ethanolamine (1x50 mL) and brine (1x50mL). The resulting aqueous layers were then extracted further with EtOAc (2x50 mL). The combined organic layers were dried over sodium sulfate (6.5 g) and filtered. The sodium sulfate was further washed with EtOAc to ensure quantitative transfer (3x50 mL). After workup, the crude product was purified by silica gel chromatography (2.0 cm, 10g silica gel) eluting with 1:1 EtOAc/hexanes to 3:1 EtOAc/hexanes. The resulting solution was concentrated via rotary evaporation (35 ºC, 25 mm Hg) and triturated with 50 mL of hexanes. The suspended product was filtered and placed into a sublimation apparatus. The sublimation apparatus was heated at 70 °C using a silicone oil bath under high vacuum (0.1 mm Hg) to remove a crystalline impurity. The residual, unsublimed material was collected to furnish 157.4 mg (0.81 mmol, 81% yield) of pure **3qc** as a white powder. Spectroscopic data was in agreement with literature values.[15]

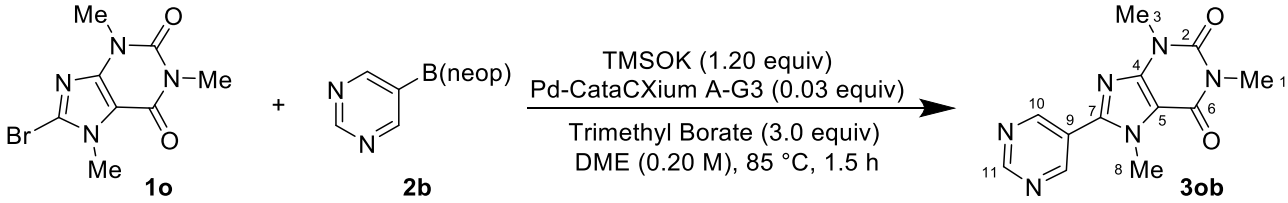
Data for **3qc:**

^{1}H NMR: (500 MHz, DMSO-d_6)
11.39 (bs, 1H, H(N)), 8.66 (d, J = 6.09 Hz, 2H, HC(11)), 7.68 (d, J = 6.07 Hz, 2H, HC(10)), 7.51 (dd, J = 5.8, 1.6 Hz, 1H, HC(7)), 7.48 (t, J = 2.83 Hz, 1H, HC(1)), 7.27-7.18 (m, 2H, HC(5,6)), 6.63 (s, 1H, HC(2))

^{13}C NMR: (126 MHz, DMSO-d_6)
149.95 (s, C(11)), 148.21 (s, C(9)), 136.48 (s, C(8)), 129.86 (s, C(4)), 126.64 (s, C(1)), 125.23 (s, C(3)), 122.97 (s, C(10)), 121.37 (s, C(5 or 6)), 118.92 (s, C(5 or 6)), 112.39 (s, C(7)), 99.78 (s, C(2))

HRMS (EI$^+$): Calcd for $C_{13}H_{10}N_2$ (M^+): 194.0844 Found: 194.0845

Preparation of 1,3,7-Trimethyl-8-(pyrimidin-5-yl)-3,7-dihydro-1H-purine-2,6-dione (3ob)



Following the General Procedure, 8-bromocaffeine **1o** (273.1 mg, 1.00 mmol) was combined with boronic ester **2b** (211.1 mg, 1.10 mmol, 1.10 equiv) and Pd-CataCXium A-G3 precatalyst (21.9 mg, 0.03 mmol, 0.03 equiv). The total reaction time was 1.5 h. After workup, the resulting solution was concentrated via rotary evaporation (35 ºC, 25 mm Hg). The yellow solid was dissolved in 50 mL of boiling acetonitrile and the volume was reduced to 45 mL. The solution was cooled to 23 °C and then stored in a -20 °C freezer for 30 min. The resulting white crystals were filtered and then transferred to a sublimation apparatus which was heated at 145 °C using a silicone oil bath under high vacuum (0.1 mm Hg). The sublimate was collected to give 175.9 mg (0.65 mmol, 65% yield) of pure **3ob** as a white solid.

Data for **3ob:**

mp: sublimes (sealed tube)

^{1}H NMR: (500 MHz, DMSO-d_6)
9.36 (s, 1H, HC(11)) 9.25 (s, 2H, HC(10)), 4.08 (s, 3H, HC(8)), 3.49 (s, 3H, HC(3)) 3.27 (s, 3H, HC(1))

^{13}C NMR: (126 MHz, DMSO-d_6)
158.88 (s, C(11)), 156.59 (s, C(10)), 154.79 (s, C(6)), 150.89 (s, C(2)), 147.75 (s, C(4)), 145.89 (s, C(7)), 123.45 (s, C(9)), 108.58 (s, C(5)), 33.53 (s, C(8)), 29.53 (s, C(3)), 27.70 (s, C(1))

IR: (neat, ATR)
3045 (w), 1703 (s), 1660 (s), 1606 (m), 1591 (m), 1559 (m), 1540 (s), 1496 (m), 1452 (s), 1424 (m), 1407 (s), 1340 (m), 1286 (m), 1234 (m), 1213 (m), 1190 (m), 1129 (w), 1067 (w), 1041 (m), 1024 (m), 974 (m), 926 (w), 803 (w), 761 (m), 744 (s), 734 (m), 722 (m), 717 (m), 678 (m), 631 (m), 592 (w), 530 (m), 523 (m), 472 (m)

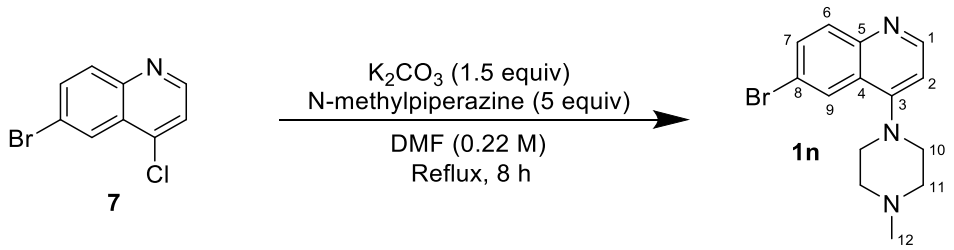
LRMS (EI$^+$): 60 (100), 64.0 (74), 77.0 (88), 91.1 (), 105.1 (56), 117.1 (92), 131.1 (47), 149.0 (75), 272.1 (82, M)

HRMS (EI$^+$): Calcd for $C_{12}H_{12}N_6O_2$ (M^+): 272.1022 Found: 272.1020

TLC: R_f 0.18 (EtOAc, UV)

qNMR: 97% Purity (1,3,5-trimethoxybenzene int. std.)

Preparation of 6-Bromo-4-(4-methylpiperazin-1-yl)quinoline (1n)



To a flame-dried, 50-mL, round-bottomed flask fitted with a reflux condenser, gas adaptor, and septum, containing a 1.0- cm x 0.5-cm rod-shaped stir bar was placed 6-bromo-4-chloroquinoline **7** (1.21 g, 5.0 mmol) and potassium carbonate (1.04 g, 7.5 mmol, 1.5 equiv). The reaction vessel was evacuated and backfilled with nitrogen three times. Dry, degassed DMF (20.0 mL) and *N*-methylpiperazine (2.50 g, 25 mmol, 5.00 equiv) were added by syringe. The reaction mixture was heated using a silicon oil bath and stirred at 130 °C for 8 h. Once the reaction was complete, the reactions contents were cooled to room temperature and then transferred to a separatory funnel with 50 mL of DCM and 50 mL of water. The biphasic mixture was extracted with DCM (3 x 20 mL). The combined organic layers were dried over sodium sulfate (10 g), then filtered and concentrated by rotary evaporation (30 ºC, 76 mm Hg). The crude product was further purified by recrystallization. The product was dissolved in 20 mL of refluxing hexane, and the solution was cooled in the freezer (-20 °C) for 24 h. The crystals were collected by vacuum filtration and were washed with 5 mL of cold hexane. The crystals were dried under high vacuum (0.2 mmHg) for 12 h to give 1.22 g of analytically pure **1n** (3.98 mmol, 79 % yield) as light orange needles.

Data for **1n:**

mp: 124.5-125.5 °C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

8.69 (d, J = 4.90 Hz, 1H, HC(1)), 8.18 (d, J = 2.30 Hz, 1H, HC(9)), 7.89 (d, J = 8.90 Hz, 1H, HC(6)), 7.71 (dd, J = 8.92, 2.27 Hz, 1H, HC(7)), 6.89 (d, J = 4.92 Hz, 1H, HC(2)), 3.43-3.09 (m, 4H, HC(10)), 2.88-2.57 (m, 4H, HC(11)) , 2.38 (s, 3H,

HC(12))

^{13}C NMR: (126 MHz, $CDCl_3$)

56.47 (s, C(3)), 151.66 (s, C(1)), 148.74 (s, C(5)), 132.57 (s, C(7)), 132.26 (s, C(6)), 126.55 (s, C(9)), 125.35 (s, C(4)), 119.46 (s, C(8)), 110.11 (s, C(2)), 55.35 (s, C(11)), 52.55 (s, C(10)), 46.24 (s, C(12))

IR: (neat, ATR)

2965 (w), 2933 (w), 2842 (w), 2792 (m), 1914 (w), 1578 (s), 1493 (s), 1453 (s), 1420 (w), 1374 (s), 1358 (m), 1291 (s), 1254 (m), 1239 (m), 1227 (m), 1198 (m), 1157 (m), 1140 (s), 1111 (m), 1076 (m), 1063 (m), 1027 (m), 1011 (s), 938 (m), 920 (s), 885 (s), 863 (s), 854 (m), 842 (s), 822 (s), 774 (m), 727 (m), 673 (m), 644 (w), 613 (s), 590 (w), 549 (m), 526 (w), 506 (m), 494 (s)

LRMS (ES^+): 309.1 (16), 308.1 (99, M+H), 306.1 (100, M+H), 154.5 (17)

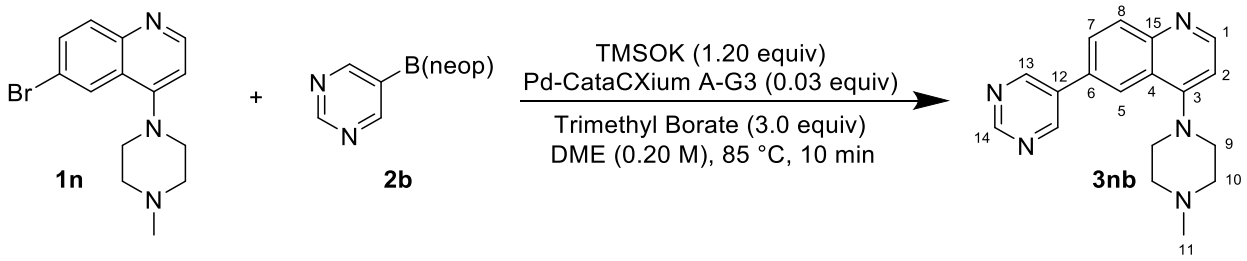
HRMS (ES^+): Calcd for $C_{14}H_{17}BrN_3$ $(M+H)^+$: 306.0606 Found: 306.0616

TLC: R_f 0.64 (Basic Aluminum Oxide, EtOAc, UV)

Analysis: $C_{14}H_{16}BrN_3$ (306.21)

Calcd:	C, 54.92;	H, 5.27;	N, 13.72
Found:	C, 55.01;	H, 5.37;	N, 13.42

Preparation of 4-(4-Methylpiperazin-1-yl)-6-(pyrimidin-5-yl)quinoline (3nb)



Following the General Procedure, 6-bromo-4-(4-methylpiperazin-1-yl)quinoline **1n** (306.2 mg, 1.00 mmol) was combined with boronic ester **2b** (210.8 mg, 1.10 mmol, 1.10 equiv) and Pd-CataCXium A-G3 precatalyst (21.9 mg, 0.03 mmol, 0.03 equiv). The total reaction time was 10 min. After workup, the resulting solution was concentrated via rotary evaporation (35 ºC, 25 mm Hg). The resulting yellow solid was recrystallized from acetonitrile to furnish 257.0 mg of product. The material was then transferred to a sublimation apparatus which was heated at 140 °C using a silicone oil bath under high vacuum (0.1 mm Hg). The sublimate was collected to give 220.0 mg

(0.72 mmol, 72% yield) of **3nb** as a yellow, crystalline solid.

Data for **3nb:**

mp: 180.6-182.4°C

^{1}H NMR: (500 MHz, CD_2Cl_2)

9.20 (s, 1H, HC(14)), 9.08 (s, 2H, HC(13)), 8.74 (d, *J* = 4.96 Hz, 1H, HC(1)), 8.26 (d, *J* = 2.08 Hz, 1H, HC(5)), 8.15 (d, J = 8.7 Hz, 1H, HC(8)), 7.89 (dd, *J*=8.70, 2.12 Hz, 1H, HC(7)), 6.93 (d, *J*=4.97 Hz, 1H, HC(2)), 3.45-3.12 (m, 4H, HC(9)), 2.87-2.54 (m, 4H, HC(10)), 2.38 (s, 3H, HC(11))

^{13}C NMR: (126 MHz, CD_2Cl_2)

157.99 (s, C(14)), 157.53 (s, C(3)), 155.45 (s, C(13)), 152.12 (s, C(1)), 150.01 (s, C(15)), 134.38 (s, C(12)), 131.75 (s, C(8)), 131.42 (s, C(6)), 127.71 (s, C(7)), 124.21 (s, C(4)), 122.73 (s, C(5)), 110.06 (s, C(2)), 55.38 (s, C(10)), 52.64 (s, C(9)), 46.23 (s, C(11))

IR: (neat, ATR)

3014 (w), 2965 (w), 2925 (w), 2844 (w), 2820 (w), 2792 (w), 2745 (w), 1574 (m), 1553 (s), 1503 (w), 1450 (s), 1438 (m), 1407 (s), 1371 (s), 1334 (m), 1288 (s), 1276 (m), 1260 (w), 1239 (m), 1228 (m), 1195 (m), 1140 (s), 1123 (m), 1104 (m), 1077 (m), 1066 (m), 1050 (m), 1027 (m), 1007 (s), 926 (s), 900 (s), 861 (s), 829 (s), 786 (m), 724 (s), 695 (m), 632 (m), 609 (w), 558 (m), 544 (m), 522 (m), 496 (m), 471 (w)

LRMS (EI$^+$): 306.2 (22), 305.2 (100, M), 304.2 (26), 290.1 (14), 261.1 (12), 234.1 (19), 206.1 (12), 152.1 (12), 71.1 (25), 70.1 (36)

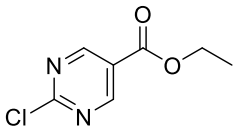
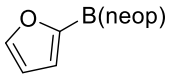
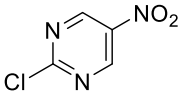
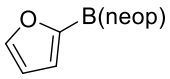
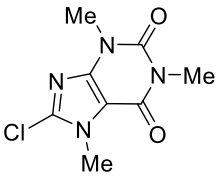
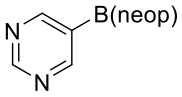
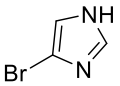
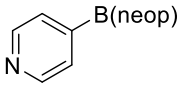
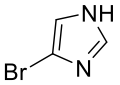
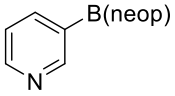
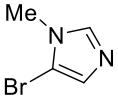
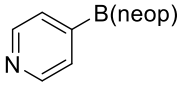
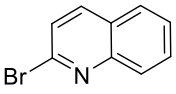
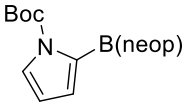
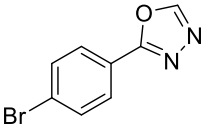
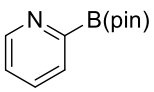
HRMS (EI$^+$): Calcd for $C_{18}H_{19}N_5$ (M^+): 305.1640 Found: 305.1646

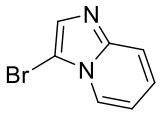
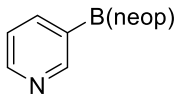
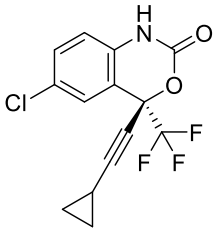
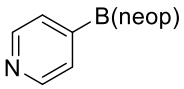
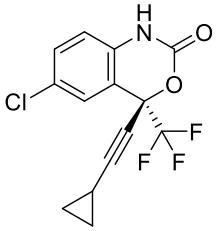
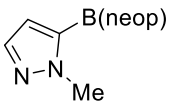
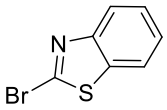
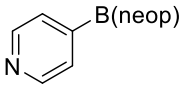
TLC: R_f 0.36 (Basic Aluminum Oxide, EtOAc, UV)

Analysis: $C_{18}H_{19}N_5$ (305.39)

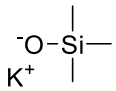
Calcd:	C, 70.80;	H, 6.27;	N, 22.93
Found:	C, 70.70;	H, 6.23;	N, 22.54

Problematic Substrate Pairs:

Entry	Electrophile	Nucleophile	Comments
1			Ethyl ester deprotection
2			S_NAR
3			S_NAR
4			No reaction
5			No reaction
6			Reaction stalling
7			Slow reactivity
8			Protodeboronation

Entry	Electrophile	Nucleophile	Comments
9			Slow reactivity with CataCXium A ligand
10			Underwent decarboxylative Larock-type quinoline formation
11			Underwent decarboxylative Larock-type quinoline formation
12			>5 species by TLC analysis

Analytical Analysis of Working TMSOK Batch:



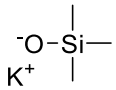
CH Analysis: C_3H_9KOSi (128.29)

Calcd:	C, 28.09;	H, 7.07;
Found:	C, 26.73;	H, 7.24;

ICP Analysis: C_3H_9KOSi (128.29)

Calcd:	K, 30.48
Found:	K, 28.86

Analytical Analysis of Problematic TMSOK Batch:



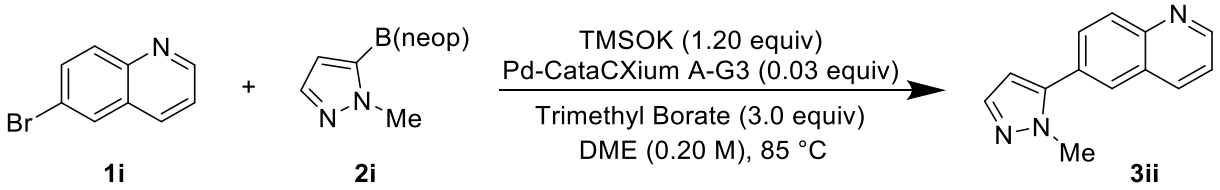
CH Analysis: C_3H_9KOSi (128.29)

Calcd:	C, 28.09;	H, 7.07;
Found:	C, 23.05;	H, 7.20;

ICP Analysis: C_3H_9KOSi (128.29)

Calcd:	K, 30.48
Found:	K, 24.82

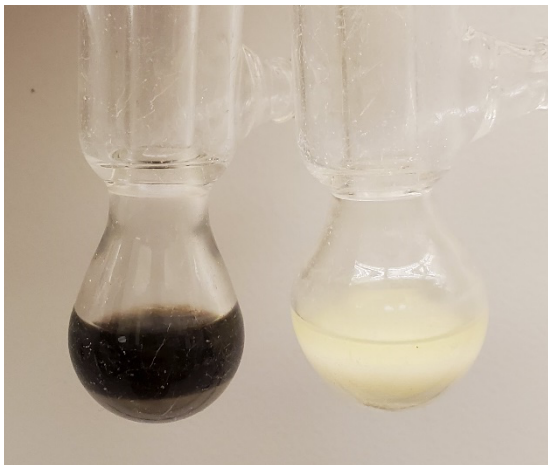
Demonstration of Reaction Stalling Using Impure TMSOK:



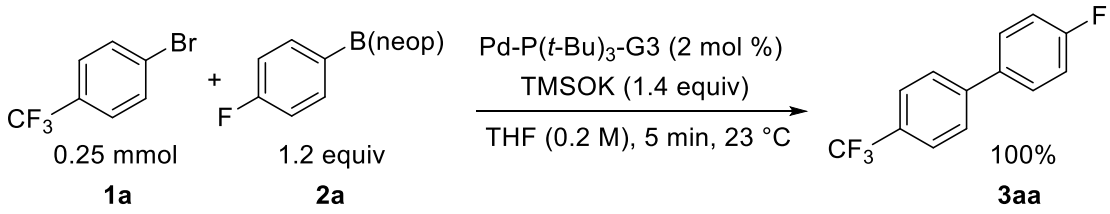
1i **2i** **3ii**

A 1.00 M TMSOK solution was prepared using the problematic batch of TMSOK by weighing 256.5 mg of TMSOK into a 2-mL volumetric flask and filling to dilution with 1,2-dimethoxyethane. The resulting solution was syringe-filtered (0.2 micron) into a flame-dried dram vial under argon. A 1.00 M TMSOK solution was prepared using the working batch of TMSOK by the same process. To two flame-dried, 5-mL, single-necked, round-bottomed flasks containing 3-mm x 8-mm magnetic stir bars was added 6-bromoquinoline **1i** (103.8 mg, 0.50 mmol), boronic

ester **2i** (106.5 mg, 0.55 mmol, 1.1 equiv), and Pd-CataCXium A-G3 precatalyst (10.8 mg, 0.015 mmol, 0.03 equiv). The round-bottomed flasks were equipped with a gas adapter and septum and evacuated with high vacuum and backfilled with argon two times. To the reaction flasks was added 1.75 mL of 1,2-dimethoxyethane and 170 μL of trimethyl borate. The reaction flasks were placed into a pre-heated 110 °C oil bath and stirred for 5 min. Then, 0.6 mL of the problematic 1.00 M TMSOK solution was added to one flask and 0.6 mL of the working 1.00 M TMSOK solution was added to the other flask. After 5 min, the reaction treated with working base had formed Pd-black, signaling the reaction had gone to completion (left reaction, shown below). After 80 min, the reaction treated with problematic base had not gone to completion (right reaction, shown below).



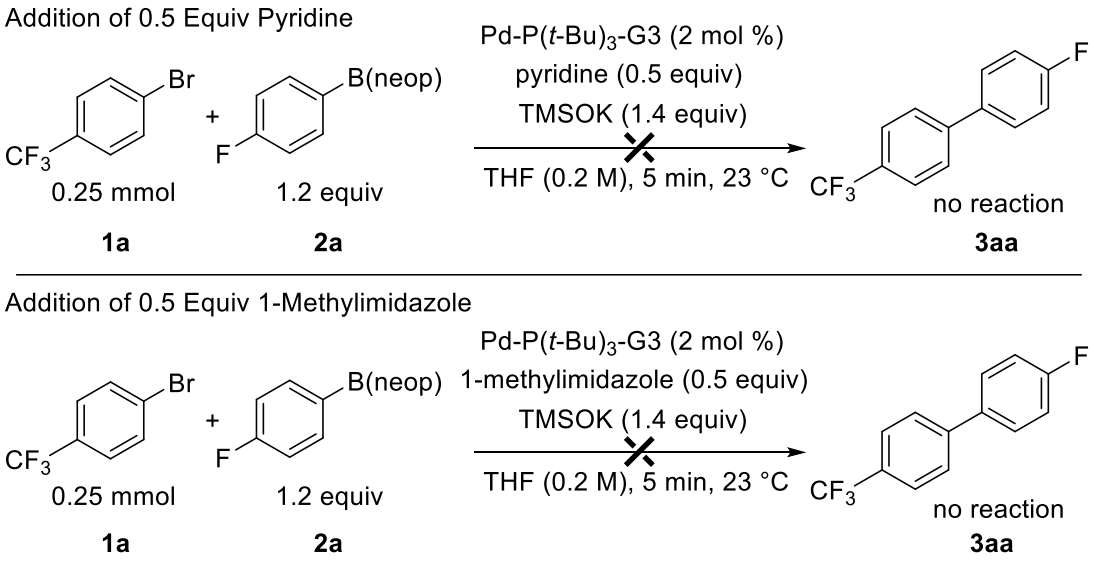
Control Experiment of Previously Optimized Cross-Coupling:



To a flame-dried, 15-mL, single-necked, round-bottomed flask containing a 2.0-cm x 1.0-cm magnetic stir bar was added 62.2 mg (1.2 equiv) of neopentyl 4-fluorophenyl boronic ester **2a**. The round-bottomed flask was equipped with a gas adapter and septum and evacuated with high vacuum and backfilled with argon two times. To the reaction flask was added 0.8 mL of SDS THF via syringe. Next, 0.1 mL of a Pd-P(*t*-Bu)$_3$-G3 stock solution in THF (2.89 mg/0.1 mL), 25 μL of 1,2-difluorobenzene (1.0 equiv), and 35 μL of 4-CF_3-bromobenzene were added using Hamilton gastight syringes. 0.35 mL of a 1.0 M TMSOK stock solution in THF was added via syringe. After

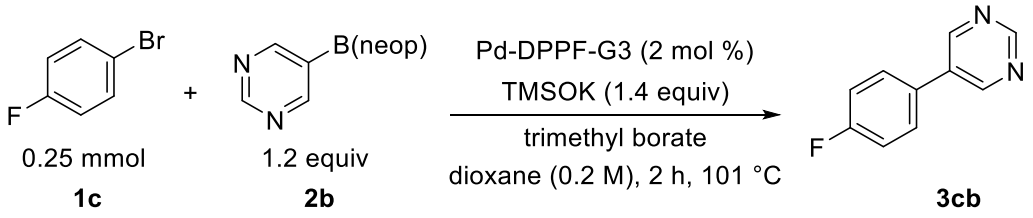
5 min, 0.7 mL of 1.0 M HCl in Et_2O was added to quench the reaction mixture. The reaction mixture was directly analyzed (unlocked) by ^{19}F NMR using 1,2-difluorobenzene as an internal standard showing 100% product formation.

Investigation of 1-Methylimidazole and Pyridine Deactivation (Without Trimethyl Borate):



To a flame-dried, 15-mL, single-necked, round-bottomed flask containing a 2.0-cm x 1.0-cm magnetic stir bar was added 62.2 mg (1.2 equiv) of neopentyl 4-fluorophenyl boronic ester **2a**. The round-bottomed flask was equipped with a gas adapter and septum and evacuated with high vacuum and backfilled with argon two times. To the reaction flask was added 0.8 mL of SDS THF via syringe. Next, 0.1 mL of a Pd-P(*t*-Bu)$_3$-G3 stock solution in THF (2.89 mg/0.1 mL), 25 μL of 1,2-difluorobenzene (1.0 equiv), 35 μL of *p*-CF_3-bromobenzene (1.0 equiv), and 0.5 equiv of 1-methylimidazole (10 μL) or 0.5 equiv of pyridine (10 μL) were added using Hamilton gastight syringes. 0.35 mL of a 1.0 M TMSOK stock solution in THF was added via syringe. After 5 min, 0.7 mL of 1.0 M HCl in Et_2O was added to quench the reaction mixture. The reaction mixture was directly analyzed (unlocked) by ^{19}F NMR using 1,2-difluorobenzene as an internal standard showing no product formation for either reaction.

Trimethyl Borate Loadings Studies Using 5-Pyrimidyl Neopentyl Boronic Ester:

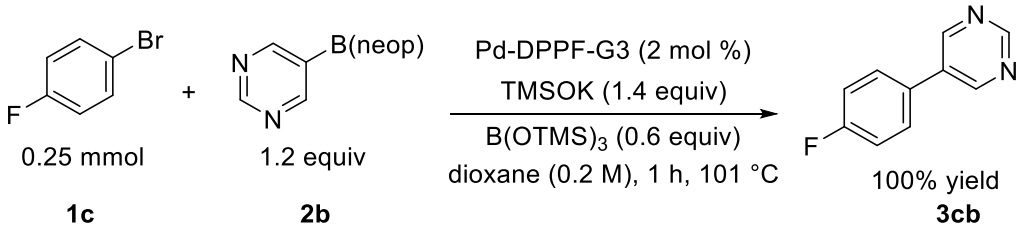


0.25 mmol **1c** + 1.2 equiv **2b** → **3cb**

vial	trimethyl borate (equiv)	yield (%)
1	0.0	0
2	0.6	100
3	1.2	100
4	2.4	100

To a 1-mL volumetric flask was added 23 mg of Pd-DPPF-G3 precatalyst, 137.3 μL of 1-bromo-4-fluorobenzene **1c**, 161 μL of 1-fluoronaphthalene, and 288.0 mg of 5-pyrimidyl neopentyl boronic ester **2b**. The volumetric flask was diluted to 1 mL using 1,4-dioxane. Four dram vials with Teflon caps were equipped with a 3-mm x 8-mm magnetic stir bar and the vials were evacuated with high vacuum and backfilled with argon two times via needle. To each vial was added 0.2 mL of stock solution and 0.8 mL of 1,4-dioxane. To vial 1 was added no trimethyl borate. To vial 2 was added 17 μL of trimethyl borate. To vial 3 was added 33 μL of trimethyl borate. To vial 4 was added 67 μL of trimethyl borate. To each vial was then added 0.35 mL of a 1.0 M TMSOK solution in 1,4-dioxane and the vials were placed into a pre-heated 120°C fitted aluminum block with stirring. After 2 h, the reactions were cooled to 23°C and the reaction mixtures were directly analyzed (unlocked) by ^{19}F NMR using 1-fluoronaphthalene as an internal standard.

Tris(Trimethylsilyl) Borate Study Using 5-Pyrimidyl Neopentyl Boronic Ester:

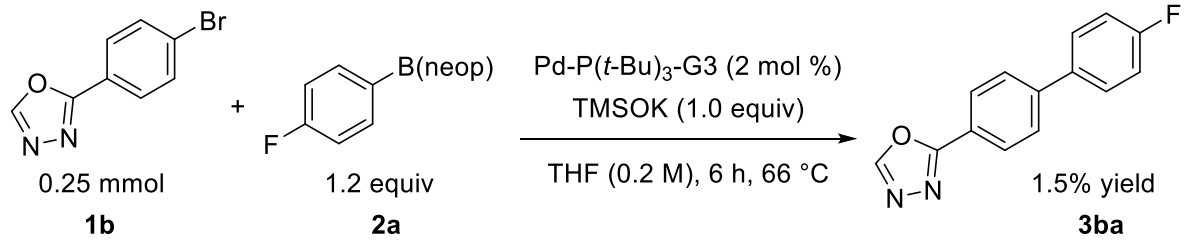


0.25 mmol **1c** + 1.2 equiv **2b** → 100% yield **3cb**

To a 1 mL volumetric flask was added 23 mg of Pd-DPPF-G3 precatalyst, 137.3 μL of 1-

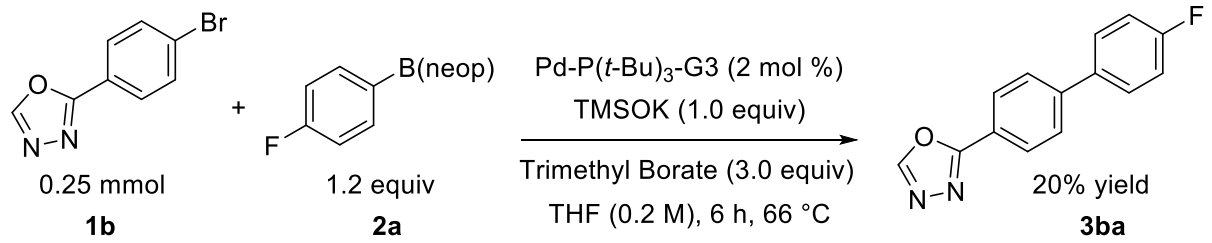
bromo-4-fluorobenzene **1c**, 161 μL of 1-fluoronaphthalene, and 288.0 mg of 5-pyrimidyl neopentyl boronic ester **2b**. The volumetric flask was diluted to 1 mL using 1,4-dioxane. A dram vials with Teflon cap was equipped with a 3-mm x 8-mm magnetic stir bar and the vial was evacuated with high vacuum and backfilled with argon two times via needle. To the vial was added 0.2 mL of stock solution and 0.8 mL of 1,4-dioxane. To the vial was then added 50 μL of tris(trimethylsilyl) borate, followed by 0.35 mL of a 1.0 M TMSOK solution in 1,4-dioxane and the vial was placed into a pre-heated 120°C fitted aluminum block with stirring. After 1h, the reaction was cooled to 23°C and directly analyzed (unlocked) by ^{19}F NMR using 1-fluoronaphthalene as an internal standard.

Control Experiment with Heterocyclic Substrate Using Originally Developed Conditions (0.0 Equiv Trimethyl Borate)



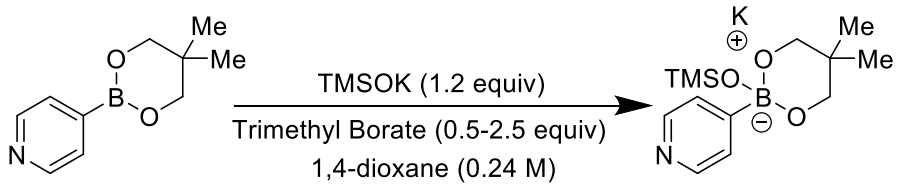
To a 5-mL, single-piece, round-bottomed flask with condenser containing a 3-mm x 8-mm magnetic stir bar was added 56.4 mg (0.25 mmol) of 2-(4-bromophenyl)-1,3,4-oxadiazole **1b**, 62.4 mg (0.3 mmol) of boronic ester **2a**, 41.6 mg of 1,3,5-trimethoxybenzene (internal standard), and 2.7 mg (2 mol %) of Pd-P(*t*-Bu)$_3$ precatalyst. The reaction vessel was evacuated and backfilled with argon two times. 0.925 mL of THF was added via syringe and the reaction flask was placed into a pre-heated 90°C oil bath under argon. After 5 min, 0.25 mL of 1.0 M TMSOK in THF was added. After 6 h, 100 μL of the reaction solution was sampled via Hamilton syringe and cooled to room temperature in a dram vial. The reaction solvent was removed via high vacuum (0.1 mmHg) for 15 min. Then, the crude reaction mixture was dissolved in 0.6 mL of $CDCl_3$ and analyzed by ^{1}H NMR. The extent of cross-coupling was quantified against the internal standard.

Control Experiment with Heterocyclic Substrate Using Originally Developed Conditions (3.0 Equiv Trimethyl Borate)



To a 5-mL, single-piece, round-bottomed flask with condenser containing a 3-mm x 8-mm magnetic stir bar was added 56.3 mg (0.25 mmol) of 2-(4-bromophenyl)-1,3,4-oxadiazole **1b**, 62.5 mg (0.3 mmol) of boronic ester **2a**, 41.8 mg of 1,3,5-trimethoxybenzene (internal standard), and 2.8 mg (2 mol %) of Pd-P(*t*-Bu)$_3$ precatalyst. The reaction vessel was evacuated and backfilled with argon two times. 0.925 mL of THF and 85 μL of trimethyl borate were added via syringe and the reaction flask was placed into a pre-heated 90 °C oil bath under argon. After 5 min, 0.25 mL of 1.0 M TMSOK in THF was added. After 6 h, 100 μL of the reaction solution was sampled via Hamilton syringe and cooled to room temperature in a dram vial. The reaction solvent was removed via high vacuum (0.1 mmHg) for 15 min. Then, the crude reaction mixture was dissolved in 0.6 mL of $CDCl_3$ and analyzed by ^{1}H NMR. The extent of cross-coupling was quantified against the internal standard.

Evaluation of 4-Pyridyl Boronate Solubility at Different Trimethyl Borate Loadings

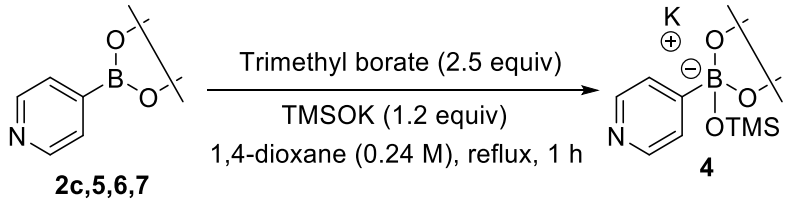


Four, 1-dram vials with Teflon caps were each equipped with a 3-mm x 8-mm magnetic stir bar. To each vial was added 57.2 mg (0.3 mmol) of 4-pyridyl neopentyl boronic ester. The vials were evacuated with high vacuum and backfilled with argon two times via needle. To each vial was added 0.9 mL of 1,4-dioxane. To vial 1 was added 17 μL of trimethyl borate (0.5 equiv). To vial 2 was added 35 μL of trimethyl borate (1.0 equiv). To vial 3 was added 65 μL of trimethyl borate (2.0 equiv). To vial 4 was added 85 μL of trimethyl borate (2.5 equiv). To each vial was then added 0.35 mL of a 1.0 M TMSOK solution in 1,4-dioxane and the vials were placed into a

pre-heated 120°C fitted aluminum block with stirring. The solubility was monitored after 60 min.
Results:

- Vial 1: Heterogeneous white suspension.
- Vial 2: Heterogeneous white suspension.
- Vial 3: Heterogeneous white suspension.
- Vial 4: Homogeneous bi-phase.

Evaluation of 4-Pyridyl Boronate Solubility Using Different Boronic Esters

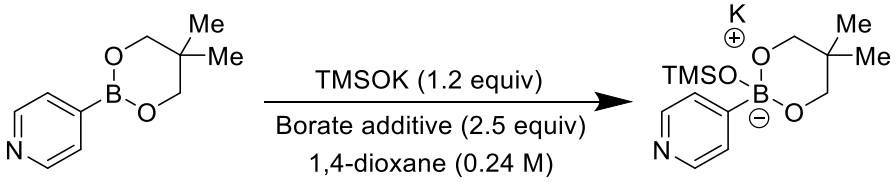


2c,5,6,7 **4**

Four, 1-dram vials with Teflon caps were each equipped with a 3-mm x 8-mm magnetic stir bar. To vial 1 was added 57.3 mg (0.3 mmol) of 4-pyridyl neopentyl boronic ester **2c**. To vial 2 was added 56.8 mg (0.3 mmol) of 4-pyridyl cyclopentyl boronic ester **6**. To vial 3 was added 57.2 mg (0.3 mmol) of 4-pyridyl THF boronic ester **5**. To vial 4 was added 60.6 mg (0.3 mmol) of 4-pyridyl cyclohexyl boronic ester **7**. The vials were evacuated with high vacuum and backfilled with argon two times via needle. To each vial was added 0.9 mL of 1,4-dioxane. To each vial was added 85 μL of trimethyl borate (2.5 equiv), followed by 0.35 mL of a 1.0 M TMSOK solution in 1,4-dioxane and the vials were placed into a pre-heated 120°C fitted aluminum block with stirring. The solubility was monitored after 60 min.
Results:

- Vial 1: Homogeneous biphase.
- Vial 2: Homogeneous biphase.
- Vial 3: Oil biphase with insoluble solids.
- Vial 4: Heterogeneous white suspension.

Evaluation of 4-Pyridyl Boronate Solubility Using Different Borate Additives



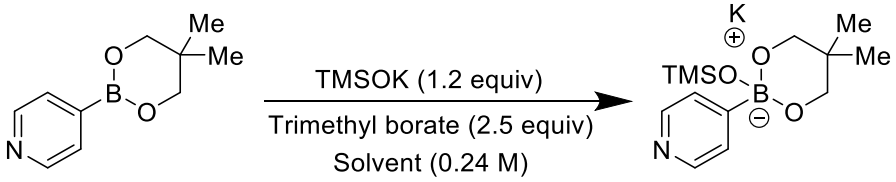
2c **4**

Four, 1-dram vials with Teflon caps were each charged with 57.2 mg (0.3 mmol) of 4-pyridyl neopentyl boronic ester **2c** and a 3-mm x 8-mm magnetic stir bar was added. The vials were evacuated with high vacuum and backfilled with argon two times via needle. To each vial was added 0.9 mL of 1,4-dioxane. To vial 1 was added 200 μL of tri-*n*-butyl borate (2.5 equiv). To vial 2 was added 175 μL of triisopropyl borate (2.5 equiv). To vial 3 was added 250 μL of tris(trimethylsilyl) borate (2.5 equiv). To vial 4 was added 85 μL of trimethyl borate (2.5 equiv). To each vial was then added 0.35 mL of a 1.0 M TMSOK solution in 1,4-dioxane and the vials were placed into a pre-heated 120 °C fitted aluminum block with stirring. The solubility was monitored after 60 min.

Results:

- Vial 1: Heterogeneous white suspension.
- Vial 2: Heterogeneous white suspension.
- Vial 3: Heterogeneous white suspension.
- Vial 4: Homogeneous biphasic mixture.

Evaluation of 4-Pyridyl Boronate Solubility Using Different Reaction Solvents



2c **4**

Three, 1-dram vials with Teflon caps were charged with 57.2 mg (0.3 mmol) of 4-pyridyl neopentyl boronic ester **2c** and a 3-mm x 8-mm stir bar was added. The vials were evacuated with high vacuum and backfilled with argon two times through a syringe needle. To vial 1 was added 0.9 mL of acetonitrile. To vial 2 was added 0.9 mL of 1,4-dioxane. To vial 3 was added 0.9 mL of

1,2-dimethoxyethane (DME). The vials were then treated with 85 μL of trimethyl borate (2.5 equiv). To each vial was added 0.35 mL of a 1.0 M TMSOK solution prepared in the respective solvent and the vials were placed into a pre-heated (20 °C above boiling point) aluminum block with stirring. The solubility was monitored after 60 min.

Results:

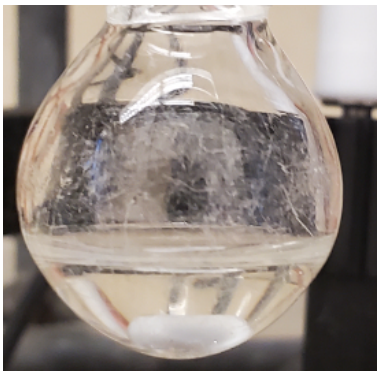
- Vial 1: Fully homogeneous solution with trace solids on vial walls.
  *Note: Stock solutions generated from MeCN were found to react with TMSOK over time.
- Vial 2: Homogeneous biphasic mixture.
- Vial 3: Fully homogeneous solution with trace solids on vial walls.
- Preparation of a 1.0 M TMSOK solution in diglyme resulted in exothermic decomposition. This solvent was therefore not tested due to incompatibility with TMSOK.
- Preparation of a 1.0 M TMSOK solution in NMP resulted in a purple-colored mixture. This solvent was therefore not tested due to incompatibility with TMSOK.
- Preparation of a 0.5 M TMSOK solution in toluene was found to be largely insoluble. Therefore, this solvent was not tested.

To ensure that 1,2-dimethoxyethane was fully homogenous under active reflux, the following experiment was performed:

To a 5-mL, single-piece, round-bottomed flask with condenser containing a 3-mm x 8-mm magnetic stir bar was placed 57.2 mg (0.3 mmol) of 4-pyridyl neopentyl boronic ester **2c**. The reaction vessel was evacuated and backfilled with argon two times. 0.9 mL of 1,2-dimethoxyethane was added via syringe, followed by 85 μL of trimethyl borate (2.5 equiv). To the reaction mixture was added 0.35 mL of 1.0 M TMSOK in 1,2-dimethoxyethane. The reaction flask was placed into a 110°C pre-heated oil bath for 60 min and then cooled to 23°C.

Results:

The reaction was fully homogeneous, including upon cooling to 23°C (shown below). The reaction remained fully homogenous for 48 h at 23°C.



Evaluation of Neopentyl 4-Pyridylboronate Solubility at 0.5 mmol Without Trimethyl Borate:

To a 15-mL, single-piece, round-bottomed flask with condenser containing a 3-mm x 8-mm magnetic stir bar was placed 95.4 mg (0.5 mmol) of neopentyl 4-pyridylboronic ester **2c**. The reaction vessel was evacuated and backfilled with argon two times. 1.75 mL of 1,2-dimethoxyethane was added via syringe. The reaction flask was placed into a 110°C pre-heated oil bath for 5 min. Then, 0.6 mL of 1.0 M TMSOK in 1,2-dimethoxyethane was added via syringe. After 5 min, the reaction was removed from heating and a picture was quickly taken while still hot.

Results:

In the absence of trimethyl borate, the reaction was highly heterogeneous with concomitant loss of agitation (shown below).

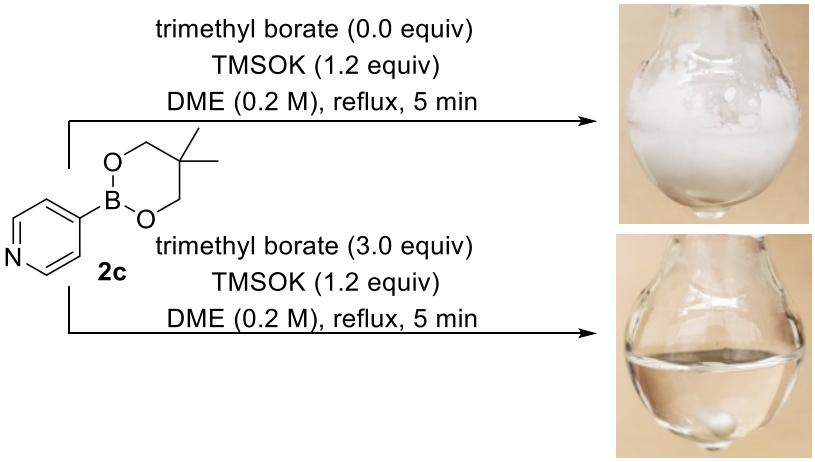
Evaluation of Neopentyl 4-Pyridylboronate Solubility at 0.5 mmol with Trimethyl Borate:

To a 15-mL, single-piece, round-bottomed flask with condenser containing a 3-mm x 8-mm magnetic stir bar was placed 95.6 mg (0.5 mmol) of neopentyl 4-pyridylboronic ester **2c**. The reaction vessel was evacuated and backfilled with argon two times. 1.75 mL of 1,2-dimethoxyethane was added via syringe, followed by 165 μL of trimethyl borate (3.0 equiv). The reaction flask was placed into a 110°C pre-heated oil bath for 5 min. Then, 0.6 mL of 1.0 M TMSOK in 1,2-dimethoxyethane was added via syringe. After 5 min, the reaction was removed from heating and a picture was quickly taken while still hot.

Results:

In the presence trimethyl borate (3.0 equiv), the reaction mixture was fully homogeneous

and remained homogeneous upon cooling to 23°C.



Evaluation of 1-Methyl Pyrazolyl Neopentyl Boronate Solubility at 0.5 mmol without Trimethyl Borate:

To a 5-mL, single-piece, round-bottomed flask with condenser containing a 3-mm x 8-mm magnetic stir bar was placed 97.1 mg (0.5 mmol) of 1-methyl pyrazolyl neopentyl boronic ester **2i**. The reaction vessel was evacuated and backfilled with argon two times. 1.75 mL of 1,2-dimethoxyethane was added via syringe. The reaction flask was placed into a 110°C pre-heated oil bath for 5 min. Then, 0.6 mL of 1.0 M TMSOK in 1,2-dimethoxyethane was added via syringe. After 5 min, the reaction was removed from heating and a picture was quickly taken while still hot.

Results:

In the absence of trimethyl borate, the reaction was highly heterogeneous with concomitant loss of agitation (shown below).

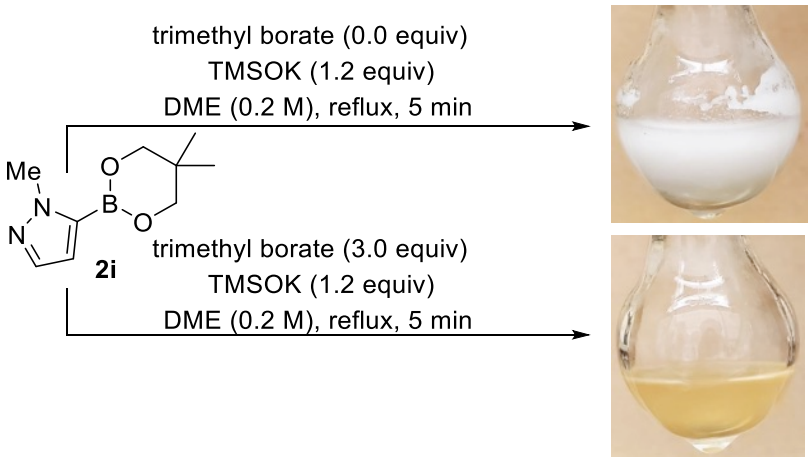
Evaluation of Neopentyl 1-Methylpyrazolylboronate Solubility at 0.5 mmol with Trimethyl Borate:

To a 5-mL, single-piece, round-bottomed flask with condenser containing a 3-mm x 8-mm magnetic stir bar was placed 97.2 mg (0.5 mmol) of 1-methyl pyrazolyl neopentyl boronic ester **2i**. The reaction vessel was evacuated and backfilled with argon two times. 1.75 mL of 1,2-dimethoxyethane was added via syringe, followed by 165 μL of trimethyl borate (3.0 equiv). The reaction flask was placed into a 110°C pre-heated oil bath for 5 min. Then, 0.6 mL of 1.0 M TMSOK in 1,2-dimethoxyethane was added via syringe. After 5 min, the reaction was removed

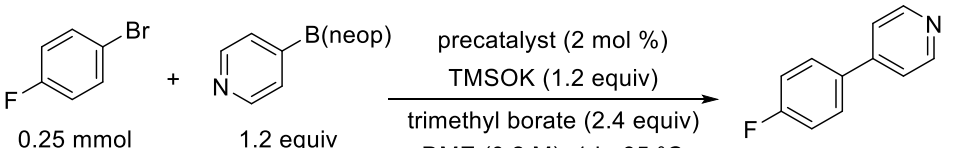
from heating and a picture was quickly taken while still hot.

Results:

In the presence trimethyl borate (3.0 equiv), the reaction was fully homogeneous and remained homogeneous upon cooling to 23°C.



Precatalyst Ligand Survey:



0.25 mmol **1c** | 1.2 equiv **2c** | **3cc**

entry	precatalyst	yield (%)[a]
1	Pd-P(Cy)$_3$-G3	25
2	Pd-P(t-Bu)$_3$-G3	4
3	Pd-CataCXium A-G3	100
4	Pd-dppb-G3	17
5	Pd-dppf-G3	34
6	Pd-JosiPhos-G3	0
7	Pd-SPhos-G3	10
8	Pd-XPhos-G3	32

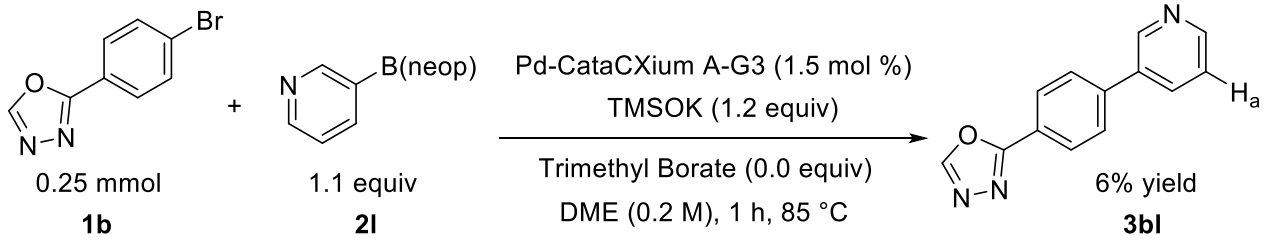
[a] Yields determined by ^{19}F NMR using 1.0 equiv of 1-fluoronaphthalene as an internal standard.

To a 5-mL volumetric flask was added 0.686 mL of 1-bromo-4-fluorobenzene **1c**, 0.807 mL of 1-fluoronaphthalene, and 1.67 mL of trimethyl borate. The volumetric flask was diluted to

5 mL using 1,2-dimethoxyethane. Eight dram vials with Teflon caps were equipped with a 3-mm x 8-mm magnetic stir bar and the vials were each treated with 57.3 mg (0.3 mmol) of 4-pyridyl neopentyl boronic ester **2c** and 2 mol% of precatalyst. The vials were evacuated with high vacuum and backfilled with argon two times. Then, 0.8 mL of 1,2-dimethoxyethane and 0.2 mL of stock solution was added to each vial. The vials were placed into a pre-heated 120°C fitted aluminum block with stirring. After 5 min, to each vial was then added 0.30 mL of a 1.00 M TMSOK solution in 1,2-dimethoxyethane. After 1 h, the reactions were cooled to 23 °C and 0.5 mL of the reaction mixture added to an NMR tube along with 0.1 mL of ethanol[a] and the reaction was directly analyzed (unlocked) by ^{19}F NMR using 1-fluoronaphthalene as an internal standard.

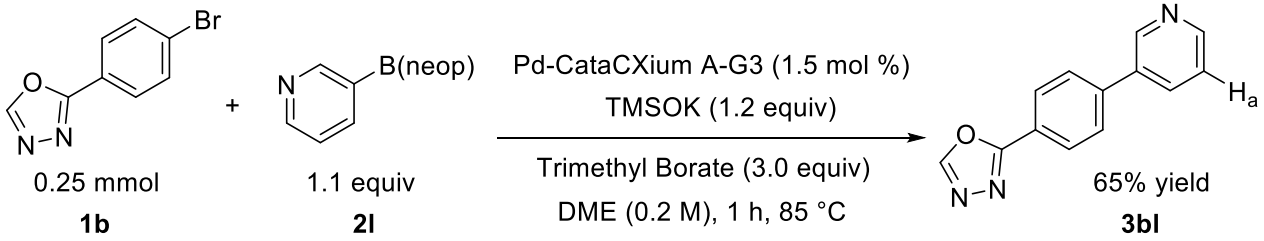
[a]The ^{19}F NMR resonances for cross-coupled product **3cc** and protodehalogenated product fluorobenzene were found to overlap. The addition of ethanol enables baseline separation and proper quantification of the product **3cc**.

Effect of Trimethyl Borate on Base Inhibition (0.0 Equiv Trimethyl Borate)



To a 5-mL, single-piece, round-bottomed flask with condenser containing a 3-mm x 8-mm magnetic stir bar was added 56.2 mg (0.25 mmol) of 2-(4-bromophenyl)-1,3,4-oxadiazole **1b**, 52.6 mg (0.275 mmol) of boronic ester **2l**, 42.0 mg of 1,3,5-trimethoxybenzene (internal standard), and 2.6 mg (1.5 mol %) of Pd-CataCXium A-G3 precatalyst. The reaction vessel was evacuated and backfilled with argon two times. 0.9 mL of 1,2-dimethoxyethane was added via syringe and the reaction flask was placed into a pre-heated 110 °C oil bath under argon. After 5 min, 0.30 mL of 1.0 M TMSOK in 1,2-dimethoxyethane was added. After 1h, 100 μL of the reaction solution was sampled via Hamilton syringe and cooled to room temperature in a dram vial. The reaction solvent was removed via high vacuum (0.1 mmHg) for 15 min. Then, the crude reaction mixture was dissolved in 0.6 mL of $CDCl_3$ and analyzed by ^1H NMR. The extent of cross-coupling was quantified against the internal standard using proton resonance H_a.

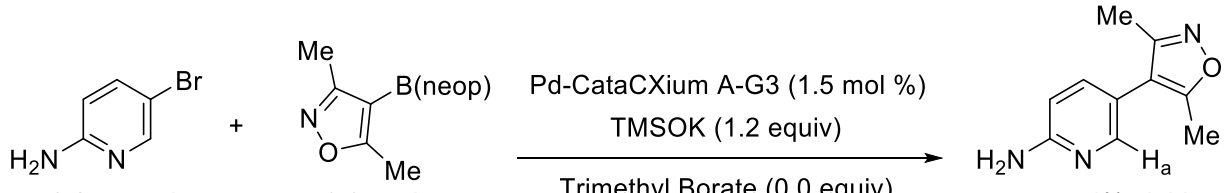
Effect of Trimethyl Borate on Base Inhibition (3.0 Equiv Trimethyl Borate)



0.25 mmol **1b** | 1.1 equiv **2l** | 65% yield **3bl**

To a 5-mL, single-piece, round-bottomed flask with condenser containing a 3-mm x 8-mm magnetic stir bar was added 56.2 mg (0.25 mmol) of 2-(4-bromophenyl)-1,3,4-oxadiazole **1b**, 52.5 mg (0.275 mmol) of boronic ester **2l**, 41.8 mg of 1,3,5-trimethoxybenzene (internal standard), and 2.6 mg (1.5 mol %) of Pd-CataCXium A-G3 precatalyst. The reaction vessel was evacuated and backfilled with argon two times. 0.9 mL of 1,2-dimethoxyethane and 85 μL of trimethyl borate were added via syringe and the reaction flask was placed into a pre-heated 110 °C oil bath under argon. After 5 min, 0.30 mL of 1.0 M TMSOK in 1,2-dimethoxyethane was added. After 1 h, 100 μL of the reaction solution was sampled via Hamilton syringe and cooled to room temperature in a dram vial. The reaction solvent was removed via high vacuum (0.1 mmHg) for 15 min. Then, the crude reaction mixture was dissolved in 0.6 mL of $CDCl_3$ and analyzed by ^1H NMR. The extent of cross-coupling was quantified against the internal standard using proton resonance H_a.

Formation of Product 3lj Without Trimethyl Borate

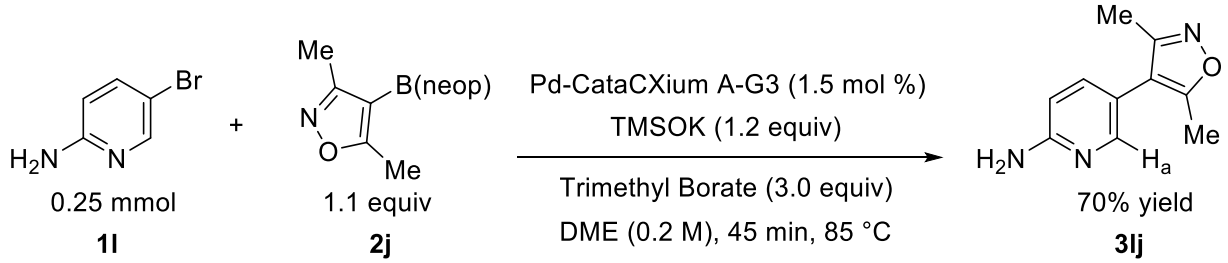


0.25 mmol **1l** | 1.1 equiv **2j** | 4% yield **3lj**

To a 5-mL, single-piece, round-bottomed flask with condenser containing a 3-mm x 8-mm magnetic stir bar was added 43.3 mg (0.25 mmol) of 5-bromopyridin-2-amine **1l**, 57.6 mg (0.275 mmol) of boronic ester **2j**, 41.2 mg of 1,3,5-trimethoxybenzene (internal standard), and 2.6 mg (1.5 mol %) of Pd-CataCXium A-G3 precatalyst. The reaction vessel was evacuated briefly and backfilled with argon two times. 0.9 mL of 1,2-dimethoxyethane was added via syringe and the reaction flask was placed into a pre-heated 110 °C oil bath under argon. After 5 min, 0.30 mL of 1.0 M TMSOK in 1,2-dimethoxyethane was added. After 45 min, 100 μL of the reaction solution

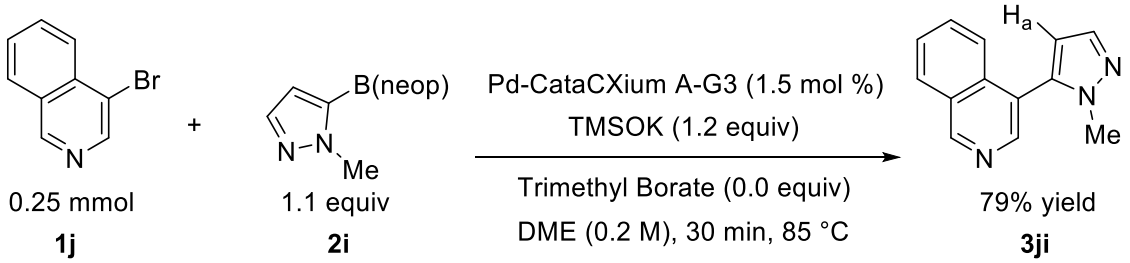
was sampled via Hamilton syringe and cooled to room temperature in a dram vial. The reaction solvent was removed via high vacuum (0.1 mmHg) for 15 min. Then, the crude reaction mixture was dissolved in 0.6 mL of $CDCl_3$ and analyzed by ^1H NMR. The extent of cross-coupling was quantified against the internal standard using proton resonance H_a.

Formation of Product 3lj With Trimethyl Borate



To a 5-mL, single-piece, round-bottomed flask with condenser containing a 3-mm x 8-mm magnetic stir bar was added 43.3 mg (0.25 mmol) of 5-bromopyridin-2-amine **1l**, 57.6 mg (0.275 mmol) of boronic ester **2j**, 41.5 mg of 1,3,5-trimethoxybenzene (internal standard), and 2.6 mg (1.5 mol %) of Pd-CataCXium A-G3 precatalyst. The reaction vessel was evacuated briefly and backfilled with argon two times. 0.9 mL of 1,2-dimethoxyethane and 85 μL of trimethyl borate were added via syringe and the reaction flask was placed into a pre-heated 110 °C oil bath under argon. After 5 min, 0.30 mL of 1.0 M TMSOK in 1,2-dimethoxyethane was added. After 45 min, 100 μL of the reaction solution was sampled via Hamilton syringe and cooled to room temperature in a dram vial. The reaction solvent was removed via high vacuum (0.1 mmHg) for 15 min. Then, the crude reaction mixture was dissolved in 0.6 mL of $CDCl_3$ and analyzed by ^1H NMR. The extent of cross-coupling was quantified against the internal standard using proton resonance H_a.

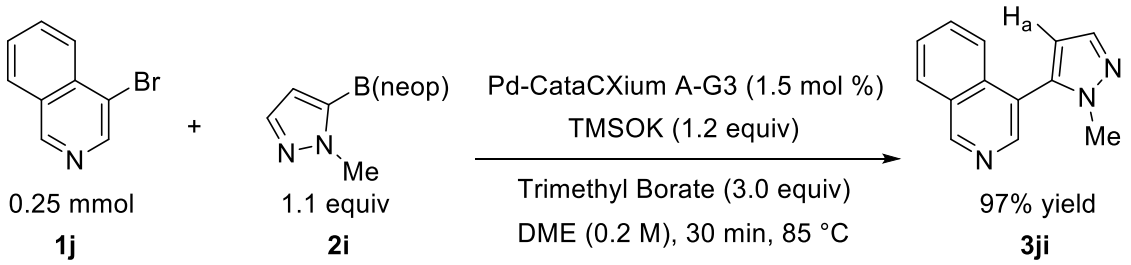
Formation of Product 3ji Without Trimethyl Borate



To a 5-mL, single-piece, round-bottomed flask with condenser containing a 3-mm x 8-mm magnetic stir bar was added 52.0 mg (0.25 mmol) of 4-bromoisoquinoline **1j**, 53.4 mg (0.275

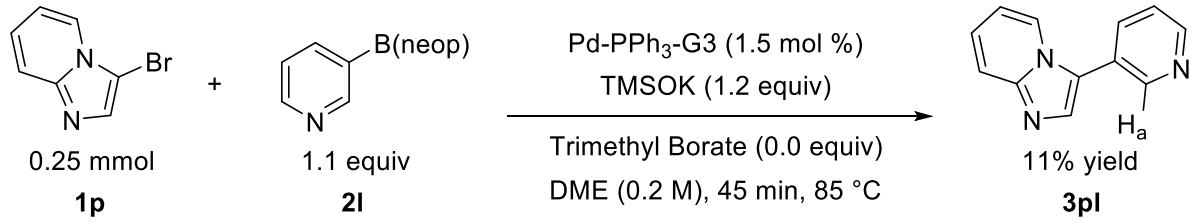
mmol) of boronic ester **2j**, 41.4 mg of 1,3,5-trimethoxybenzene (internal standard), and 2.6 mg (1.5 mol %) of Pd-CataCXium A-G3 precatalyst. The reaction vessel was evacuated briefly and backfilled with argon two times. 0.9 mL of 1,2-dimethoxyethane was added via syringe and the reaction flask was placed into a pre-heated 110 °C oil bath under argon. After 5 min, 0.30 mL of 1.0 M TMSOK in 1,2-dimethoxyethane was added. After 30 min, 100 μL of the reaction solution was sampled via Hamilton syringe and cooled to room temperature in a dram vial. The reaction solvent was removed via high vacuum (0.1 mmHg) for 15 min. Then, the crude reaction mixture was dissolved in 0.6 mL of $CDCl_3$ and analyzed by ^1H NMR. The extent of cross-coupling was quantified against the internal standard using proton resonance H_a.

Formation of Product 3ji With Trimethyl Borate



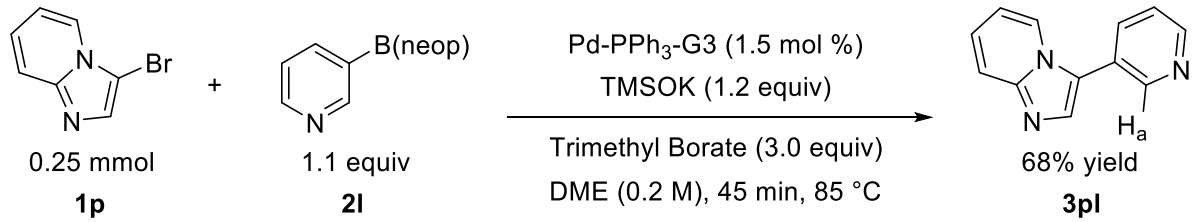
To a 5-mL, single-piece, round-bottomed flask with condenser containing a 3-mm x 8-mm magnetic stir bar was added 52.0 mg (0.25 mmol) of 4-bromoisoquinoline **1j**, 53.3 mg (0.275 mmol) of boronic ester **2j**, 41.3 mg of 1,3,5-trimethoxybenzene (internal standard), and 2.6 mg (1.5 mol %) of Pd-CataCXium A-G3 precatalyst. The reaction vessel was evacuated briefly and backfilled with argon two times. 0.9 mL of 1,2-dimethoxyethane and 85 μL of trimethyl borate were added via syringe and the reaction flask was placed into a pre-heated 110 °C oil bath under argon. After 5 min, 0.30 mL of 1.0 M TMSOK in 1,2-dimethoxyethane was added. After 30 min, 100 μL of the reaction solution was sampled via Hamilton syringe and cooled to room temperature in a dram vial. The reaction solvent was removed via high vacuum (0.1 mmHg) for 15 min. Then, the crude reaction mixture was dissolved in 0.6 mL of $CDCl_3$ and analyzed by ^1H NMR. The extent of cross-coupling was quantified against the internal standard using proton resonance H_a.

Formation of Product 3pl Without Trimethyl Borate



To a 5-mL, single-piece, round-bottomed flask with condenser containing a 3-mm x 8-mm magnetic stir bar was added 49.3 mg (0.25 mmol) of 3-bromoimidazo[1,2-a]pyridine **1p**, 52.5 mg (0.275 mmol) of boronic ester **2l**, 41.1 mg of 1,3,5-trimethoxybenzene (internal standard), and 2.4 mg (1.5 mol %) of Pd-PPh_3-G3 precatalyst. The reaction vessel was evacuated briefly and backfilled with argon two times. 0.9 mL of 1,2-dimethoxyethane was added via syringe and the reaction flask was placed into a pre-heated 110 °C oil bath under argon. After 5 min, 0.30 mL of 1.0 M TMSOK in 1,2-dimethoxyethane was added. After 45 min, 100 μL of the reaction solution was sampled via Hamilton syringe and cooled to room temperature in a dram vial. The reaction solvent was removed via high vacuum (0.1 mmHg) for 45 min. Then, the crude reaction mixture was dissolved in 0.6 mL of $CDCl_3$ and analyzed by ^1H NMR. The extent of cross-coupling was quantified against the internal standard using proton resonance H_a.

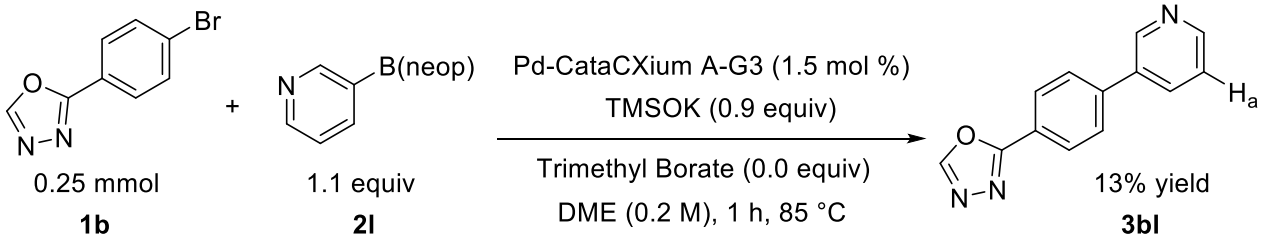
Formation of Product 3pl With Trimethyl Borate



To a 5-mL, single-piece, round-bottomed flask with condenser containing a 3-mm x 8-mm magnetic stir bar was added 49.3 mg (0.25 mmol) of 3-bromoimidazo[1,2-a]pyridine **1p**, 52.5 mg (0.275 mmol) of boronic ester **2l**, 41.3 mg of 1,3,5-trimethoxybenzene (internal standard), and 2.4 mg (1.5 mol %) of Pd-PPh_3-G3 precatalyst. The reaction vessel was evacuated briefly and backfilled with argon two times. 0.9 mL of 1,2-dimethoxyethane and 85 μL of trimethyl borate were added via syringe and the reaction flask was placed into a pre-heated 110 °C oil bath under argon. After 5 min, 0.30 mL of 1.0 M TMSOK in 1,2-dimethoxyethane was added. After 45 min, 100 μL of the reaction solution was sampled via Hamilton syringe and cooled to room temperature

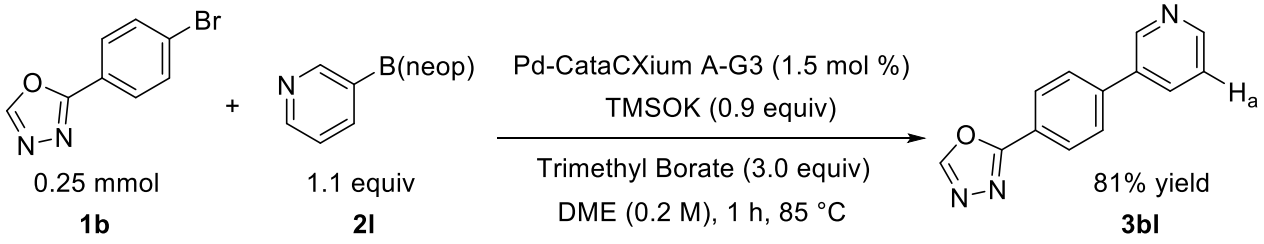
in a dram vial. The reaction solvent was removed via high vacuum (0.1 mmHg) for 45 min. Then, the crude reaction mixture was dissolved in 0.6 mL of $CDCl_3$ and analyzed by ^1H NMR. The extent of cross-coupling was quantified against the internal standard using proton resonance H_a.

Effect of Trimethyl Borate on Reaction Rate (0.0 Equiv Trimethyl Borate)



To a 5-mL, single-piece, round-bottomed flask with condenser containing a 3-mm x 8-mm magnetic stir bar was added 56.2 mg (0.25 mmol) of 2-(4-bromophenyl)-1,3,4-oxadiazole **1b**, 52.6 mg (0.275 mmol) of boronic ester **2l**, 41.3 mg of 1,3,5-trimethoxybenzene (internal standard), and 2.6 mg (1.5 mol %) of Pd-CataCXium A-G3 precatalyst. The reaction vessel was evacuated and backfilled with argon two times. 0.975 mL of 1,2-dimethoxyethane was added via syringe and the reaction flask was placed into a pre-heated 110 °C oil bath under argon. After 5 min, 0.225 mL of 1.0 M TMSOK in 1,2-dimethoxyethane was added. After 1h, 100 µL of the reaction solution was sampled via Hamilton syringe and cooled to room temperature in a dram vial. The reaction solvent was removed via high vacuum (0.1 mmHg) for 15 min. Then, the crude reaction mixture was dissolved in 0.6 mL of $CDCl_3$ and analyzed by ^1H NMR. The extent of cross-coupling was quantified against the internal standard using proton resonance H_a.

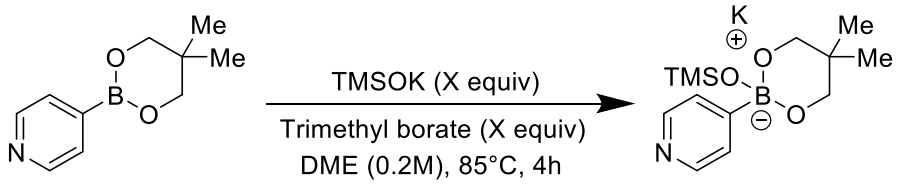
Effect of Trimethyl Borate on Reaction Rate (3.0 Equiv Trimethyl Borate)



To a 5-mL, single-piece, round-bottomed flask with condenser containing a 3-mm x 8-mm magnetic stir bar was added 56.2 mg (0.25 mmol) of 2-(4-bromophenyl)-1,3,4-oxadiazole **1b**, 52.6 mg (0.275 mmol) of boronic ester **2l**, 41.4 mg of 1,3,5-trimethoxybenzene (internal standard), and

2.6 mg (1.5 mol %) of Pd-CataCXium A-G3 precatalyst. The reaction vessel was evacuated and backfilled with argon two times. 0.975 mL of 1,2-dimethoxyethane and 85 µL of trimethyl borate were added via syringe and the reaction flask was placed into a pre-heated 110 °C oil bath under argon. After 5 min, 0.225 mL of 1.0 M TMSOK in 1,2-dimethoxyethane was added. After 1h, 100 µL of the reaction solution was sampled via Hamilton syringe and cooled to room temperature in a dram vial. The reaction solvent was removed via high vacuum (0.1 mmHg) for 15 min. Then, the crude reaction mixture was dissolved in 0.6 mL of $CDCl_3$ and analyzed by ^1H NMR. The extent of cross-coupling was quantified against the internal standard using proton resonance H_a.

Evaluation of 4-Pyridyl Neopentyl Boronate Solubility



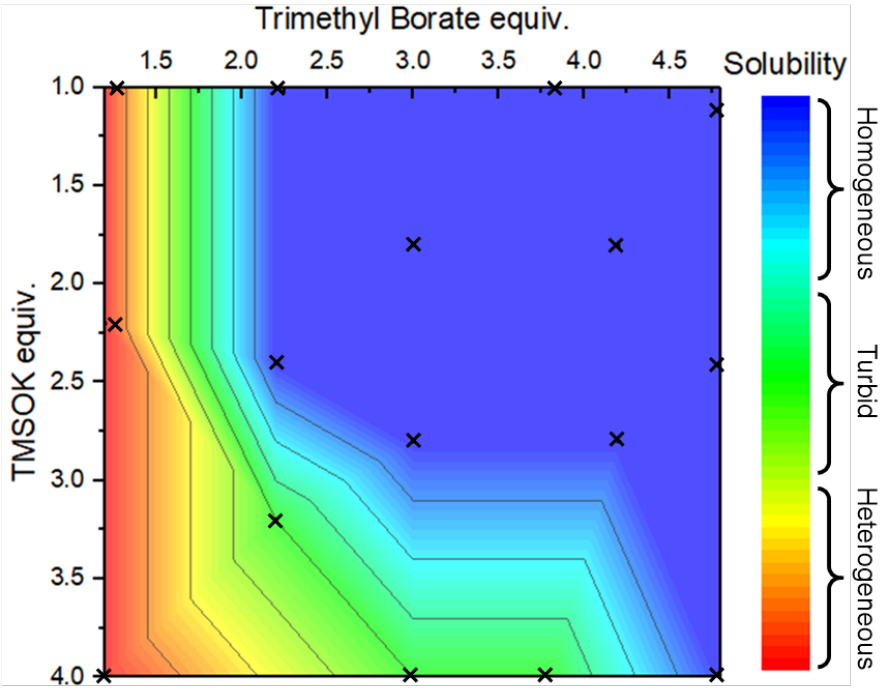
0.2 mmol

2c

4

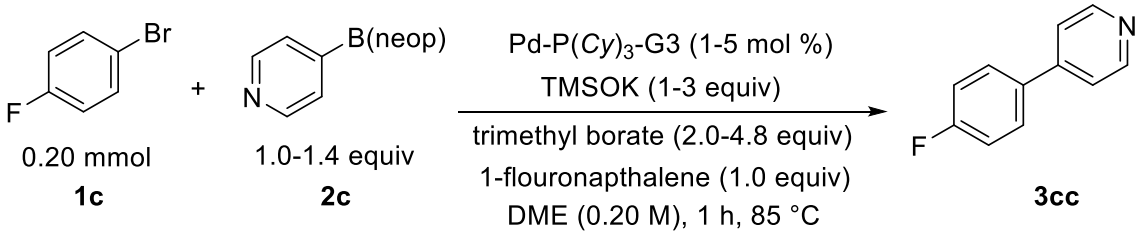
Prior to Design of Experiment planning, a solubility study was performed to inform the space in which 4-pyridyl neopentyl boronate complex **4** was homogeneous. 15 1-dram vials containing 3-mm x 8-mm magnetic stir bars were dried in a 150 °C oven and then transferred to a glovebox along with 15 corresponding Teflon caps. 32.8 mg (0.2 mmol) of 4-pyridyl neopentyl boronic ester **2c** was weighed into vials 1-15. The dram vials were then capped and removed from the glovebox. To each vial was then added the corresponding volumes of 1,2-dimethoxyethane, 1.0 M trimethyl borate stock solution (DME), and 1.0 M TMSOK stock solution (DME) shown in the loading table below. The vials were then placed into a pre-heated 85 °C hotplate and the solubility was noted after 4 h. The solubility observations are summarized pictorially below.

Solubility Study Loading Table				
Run	Ester (mg)	1.0 M TMB in DME (μL)	DME (μL)	1.0 M TMSOK in DME (μL)
1	38.2	0.120	0.780	0.100
2	38.2	0.120	0.660	0.220
3	38.2	0.220	0.680	0.100
4	38.2	0.220	0.540	0.240
5	38.2	0.220	0.460	0.320
6	38.2	0.300	0.520	0.180
7	38.2	0.300	0.420	0.280
8	38.2	0.300	0.300	0.400
9	38.2	0.380	0.520	0.100
10	38.2	0.380	0.220	0.400
11	38.2	0.420	0.400	0.180
12	38.2	0.420	0.300	0.280
13	38.2	0.480	0.420	0.100
14	38.2	0.480	0.280	0.240
15	38.2	0.480	0.120	0.400



Pictorial Representation of 4-Pyridyl Neopentyl Boronate **4** Solubility Space Varying Trimethyl Borate and TMSOK Loadings.

Design of Experiment (DOE)



0.20 mmol **1c** | 1.0-1.4 equiv **2c** | **3cc**

Experimental Design:

A DOE was planned using DesignExpert (Version 9) software. A response surface/central composite design was selected and optimized for 4 continuous variables: (A) boronic ester loading (1.0-1.4 equiv); (B) catalyst loading (1-5 mol%);(C) TMSOK loading (1-3 equiv); and (D) trimethyl borate loading (2.0-4.8 equiv). 30 experiments were planned based on 1 response (yield). Pd-P(*Cy*)$_3$-G3 was chosen as the precatalyst due to its higher solubility compared with Pd-CataCXium A-G3, enabling the preparation of stock solutions. Yields were determined by ^{19}F NMR quantitating against the internal standard 1-fluoronaphthalene. The corresponding equivalency table is shown below.

Equivalents Table					
Vial	Ester **2c** (equiv)	Catalyst (mol%)	Base-TMSOK (equiv)	Additive-TMB (equiv)	Std/Bromide (equiv)
1	1.2	1	2	3.4	1
2	1.1	2	2.5	4.1	1
3	1.2	3	2	3.4	1
4	1.3	4	2.5	4.1	1
5	1.1	2	1.5	2.7	1
6	1.2	3	2	4.8	1
7	1.1	4	1.5	2.7	1
8	1.3	2	2.5	4.1	1
9	1.3	2	1.5	4.1	1
10	1.2	5	2	3.4	1
11	1	3	2	3.4	1
12	1.2	3	1	3.4	1
13	1.2	3	2	3.4	1
14	1.3	2	1.5	2.7	1
15	1.2	3	2	3.4	1
16	1.3	2	2.5	2.7	1

17	1.3	4	1.5	4.1	1
18	1.2	3	2	3.4	1
19	1.1	4	2.5	4.1	1
20	1.1	2	2.5	2.7	1
21	1.3	4	1.5	2.7	1
22	1.4	3	2	3.4	1
23	1.1	4	2.5	2.7	1
24	1.1	2	1.5	4.1	1
25	1.2	3	2	2	1
26	1.2	3	2	3.4	1
27	1.2	3	2	3.4	1
28	1.2	3	3	3.4	1
29	1.3	4	2.5	2.7	1
30	1.1	4	1.5	4.1	1

Preparation of Catalyst Stock Solution:

A 10 mL volumetric flask was charged with 129.83 mg of Pd-P(*Cy*)$_3$-G3 precatalyst and diluted with 9 mL of 1,2-dimethoxyethane. The suspension was sonicated to dissolution and then diluted to 10 mL to generate a 0.02 M stock solution. The resulting stock solution was transferred to a 20 mL scintillation vial with Teflon cap under nitrogen via syringe.

Preparation of Bromide/1-Fluoronaphthalene Stock Solution:

A 5 mL volumetric flask was charged with 1.098 mL (10.0 mmol) of bromide **1c** and 1.290 mL (10.0 mmol) of 1-fluoronapthalene using 2.5 mL Hamilton gas-tight syringes. 4 mL of 1,2-dimethoxyethane was added to the mixture and shaken. Then, the solution was diluted to 5 mL to generate a 2.0 M solution relative to the bromide and internal standard. The resulting stock solution was transferred to a 20 mL scintillation vial with Teflon cap under nitrogen via syringe.

Preparation of TMSOK Stock Solution:

A 10 mL volumetric flask was charged with 2566 mg (20.0 mmol) of TMSOK. To the volumetric flask was added 9 mL of 1,2-dimethoxyethane and the mixture was shaken. Then, the solution was diluted to 10 mL to furnish a mildly turbid solution. The resulting 2.0 M stock solution was syringe-filtered using a 0.2 micron filter into a 20 mL scintillation vial with Teflon cap under nitrogen via syringe.

Preparation of Trimethyl Borate Stock Solution:

A 10 mL volumetric flask was charged with 4460 μL (40.0 mmol) of trimethyl borate using a Hamilton gas-tight syringe. To the volumetric flask was added 9 mL of 1,2-dimethoxyethane and the mixture was shaken. Then, the solution was diluted to 10 mL. The resulting 4.0 M solution was transferred to a 20 mL scintillation vial with Teflon cap under nitrogen via syringe.

Execution of Reactions:

30 1-dram vials containing 3-mm x 8-mm magnetic stir bars were dried in a 150 °C oven and then transferred to a glovebox along with 30 corresponding Teflon caps. 4-pyridyl neopentyl boronic ester **2c** was weighed into vials 1-30 according to the loading table shown below. The dram vials were then capped and removed from the glovebox. To each vial was added 100 μL (0.2 mmol) of 1-fluoronaphthalene/**1c** bromide stock solution via Hamilton gas-tight syringe. Then, the indicated volume of trimethyl borate stock solution was added to each vial as shown in the loading table below. Each vial was then charged with the indicated amount of 1,2-dimethoxyethane to render the total volume of each reaction 1.0 mL (0.20 M). Next, each vial was charged with the indicated volume of TMSOK solution. The vials were then placed into a pre-heated 85 °C hotplate and stirred for 10 min. To each vial was then added the indicated volume of catalyst stock solution. After 1h, each vial was cooled to 23°C and 0.5 mL of the reaction mixture was removed using a 1 mL syringe and transferred directly to an NMR tube. 0.1 mL of ethanol[a] was added to each NMR tube and the reaction mixture was analyzed by ^{19}F NMR unlocked quantitating against the internal standard 1-fluoronaphthalene.

[a]The ^{19}F NMR resonances for cross-coupled product **3cc** and protodehalogenated product fluorobenzene were found to overlap. The addition of ethanol enables baseline separation and proper quantification of the product **3cc**.

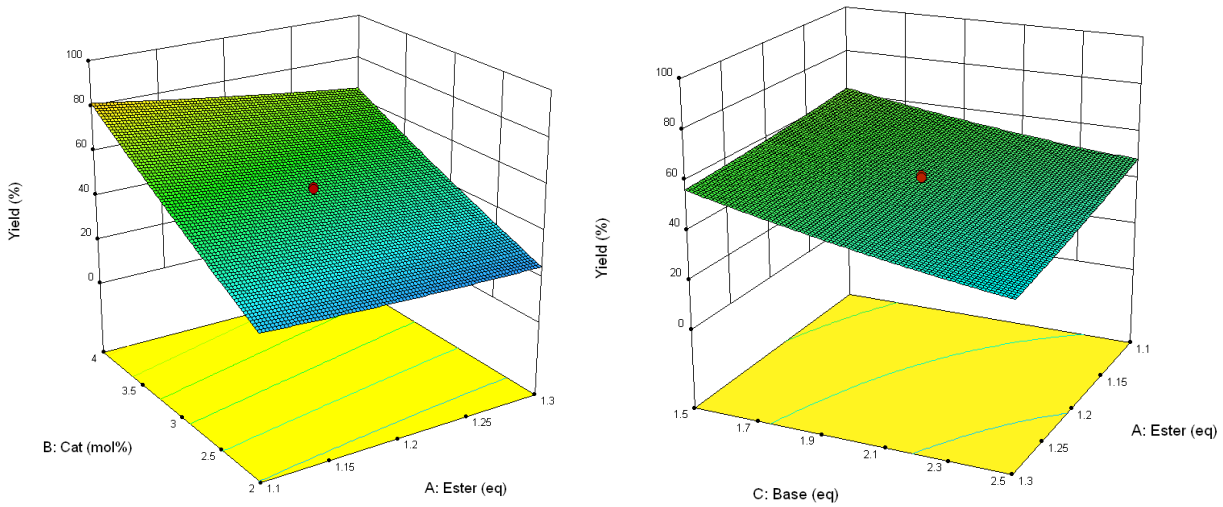
Loading Table						
Vial	Ester **2c** (mg)	Catalyst Stock Soln. (μL)	Base-TMSOK (μL)	Additive-TMB Stock Solution (μL)	Std/Bromide **1c** (μL)	DME (μL)
1	45.84	100	200	170	100	430

2	42.02	200	250	205	100	245
3	45.84	300	200	170	100	230
4	49.67	400	250	205	100	45
5	42.02	200	150	135	100	415
6	45.84	300	200	240	100	160
7	42.02	400	150	135	100	215
8	49.67	200	250	205	100	245
9	49.67	200	150	205	100	345
10	45.84	500	200	170	100	30
11	38.20	300	200	170	100	230
12	45.84	300	100	170	100	330
13	45.84	300	200	170	100	230
14	49.67	200	150	135	100	415
15	45.84	300	200	170	100	230
16	49.67	200	250	135	100	315
17	49.67	400	150	205	100	145
18	45.84	300	200	170	100	230
19	42.02	400	250	205	100	45
20	42.02	200	250	135	100	315
21	49.6704	400	150	135	100	215
22	53.4912	300	200	170	100	230
23	42.0288	400	250	135	100	115
24	42.0288	200	150	205	100	345
25	45.8496	300	200	100	100	300
26	45.8496	300	200	170	100	230
27	45.8496	300	200	170	100	230
28	45.8496	300	300	170	100	130
29	49.6704	400	250	135	100	115
30	42.0288	400	150	205	100	145

Results:

Yield of 3cc						
Vial	Ester **2c** (equiv)	Catalyst (mol%)	Base-TMSOK (equiv)	Additive-TMB (equiv)	Std/Bromide **1c** (equiv)	Yield (%)
1	1.2	1	2	3.4	1	13
2	1.1	2	2.5	4.1	1	27
3	1.2	3	2	3.4	1	48
4	1.3	4	2.5	4.1	1	56
5	1.1	2	1.5	2.7	1	33

6	1.2	3	2	4.8	1	48
7	1.1	4	1.5	2.7	1	99
8	1.3	2	2.5	4.1	1	23
9	1.3	2	1.5	4.1	1	29
10	1.2	5	2	3.4	1	99
11	1	3	2	3.4	1	69
12	1.2	3	1	3.4	1	83
13	1.2	3	2	3.4	1	52
14	1.3	2	1.5	2.7	1	33
15	1.2	3	2	3.4	1	48
16	1.3	2	2.5	2.7	1	26
17	1.3	4	1.5	4.1	1	83
18	1.2	3	2	3.4	1	51
19	1.1	4	2.5	4.1	1	77
20	1.1	2	2.5	2.7	1	28
21	1.3	4	1.5	2.7	1	89
22	1.4	3	2	3.4	1	39
23	1.1	4	2.5	2.7	1	72
24	1.1	4	1.5	4.1	1	99
25	1.2	3	2	2	1	73
26	1.2	3	2	3.4	1	47
27	1.2	3	2	3.4	1	46
28	1.2	3	3	3.4	1	33
29	1.3	4	2.5	2.7	1	54
30	1.1	4	1.5	4.1	1	83



Response Surfaces for Catalyst/Ester and Base/Ester Continuous Variables.

Anova Output:

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	17787.0527	14	1270.50376	28.7178351	2.78E-08	significant
A-Ester	599.453754	1	599.453754	13.5497544	0.00222399	
B-Cat	11973.6236	1	11973.6236	270.645832	5.24E-11	
C-Base	1966.24207	1	1966.24207	44.4439577	7.52E-06	
D-Additive	186.178814	1	186.178814	4.2082933	0.05811432	
AB	111.90554	1	111.90554	2.52945716	0.13258955	
AC	41.100685	1	41.100685	0.92901944	0.35040054	
AD	0.62378928	1	0.62378928	0.01409982	0.90705485	
BC	327.632813	1	327.632813	7.40564912	0.01576912	
BD	0.05497196	1	0.05497196	0.00124256	0.97234525	
CD	35.175922	1	35.175922	0.79509904	0.3866432	
A^2	11.8737185	1	11.8737185	0.26838763	0.61197205	
B^2	36.7135137	1	36.7135137	0.829854	0.376722	
C^2	75.2124164	1	75.2124164	1.70006404	0.21193539	
D^2	142.544165	1	142.544165	3.22199739	0.09282738	
Residual	663.613967	15	44.2409312			
Lack of Fit	508.280634	9	56.475626	2.18146195	0.17733556	not significant
Pure Error	155.333333	6	25.8888889			
Cor Total	18450.6667	29				

The Model F-value of 28.72 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

Values of "Prob > F" less than 0.0500 indicate model terms are significant.
In this case A, B, C, BC are significant model terms.
Values greater than 0.1000 indicate the model terms are not significant.
If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Comments:

A statistically significant relationship between three out of four continuous variables (A, B, and C) and the response variable (yield) was observed. A small, but statistically significant, 2nd order dependence between base and catalyst was also observed – no other 2nd order dependences were observed. Given the small influence of base and boronic ester stoichiometry on reaction yield, the

reaction was developed using the minimal necessary loadings for each variable (i.e. 1.1 equiv boronic ester, 3 mol% catalyst, and 1.2 equiv TMSOK). Variable D (additive loading) was found to influence the response variable less – by design, all loadings tested (i.e. 2.0-4.8 equiv) promote reactivity as seen previously in trimethyl borate loading studies (see page S39). Therefore, 3.0 equiv of additive was chosen as the preferred reaction loading to maximize reaction homogeneity.

References

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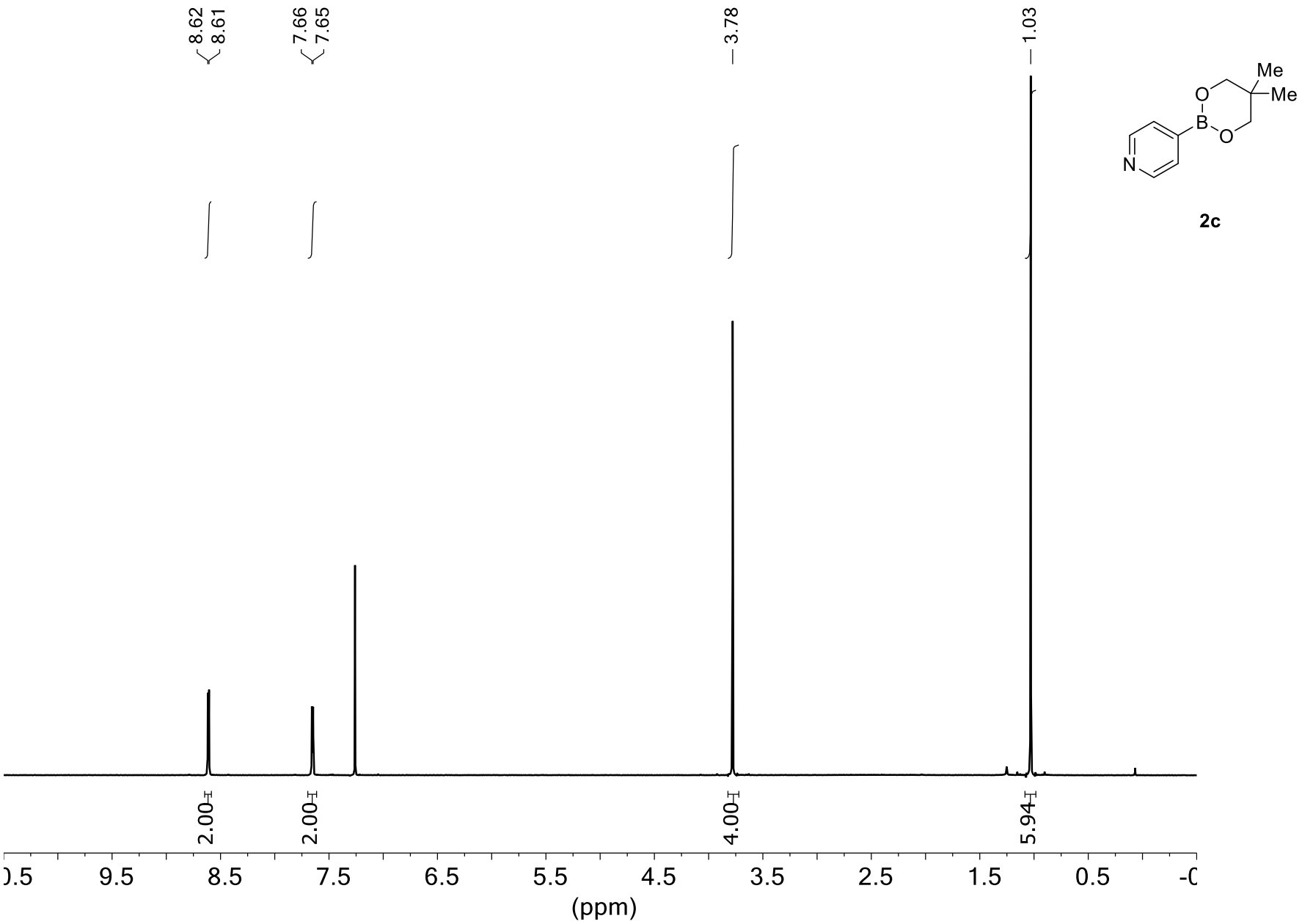
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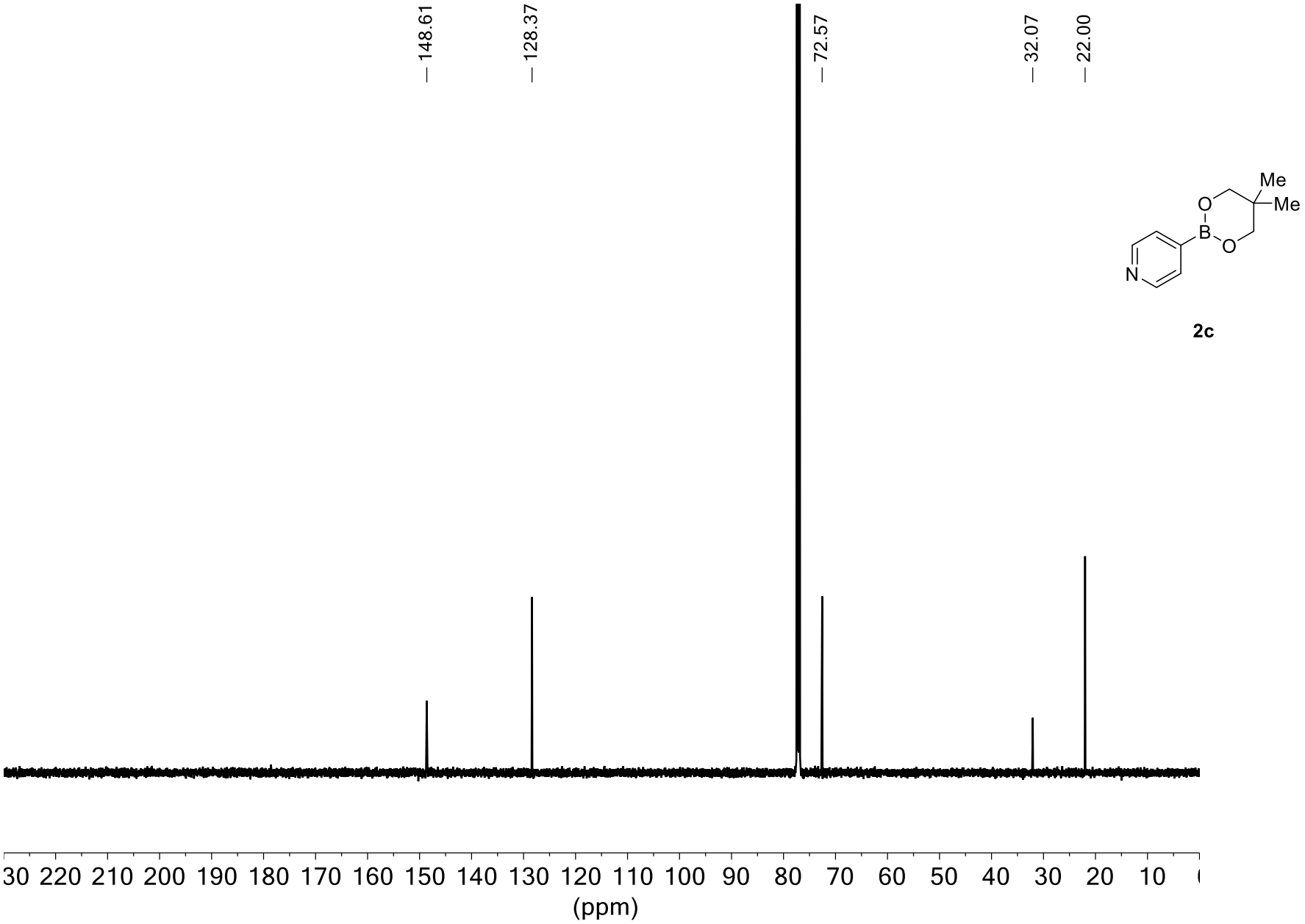
8.61
7.66
7.65
3.78
1.03
Me
Me
O
B
O
N
2c
2.00
2.00
4.00
5.94
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
(ppm)


148.61
128.37
72.57
32.07
22.00
Me
Me
O
B
O
N
2c
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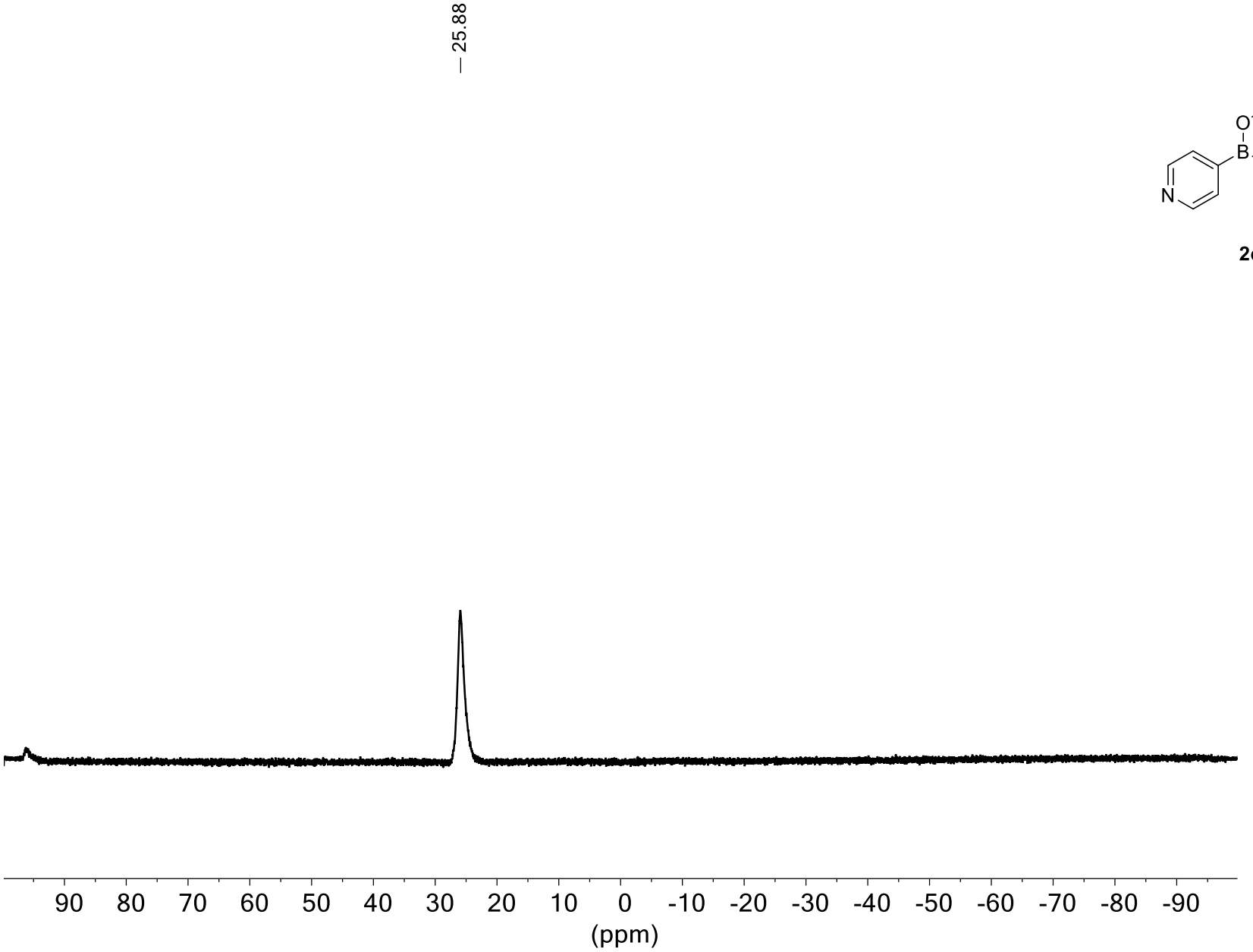
(ppm)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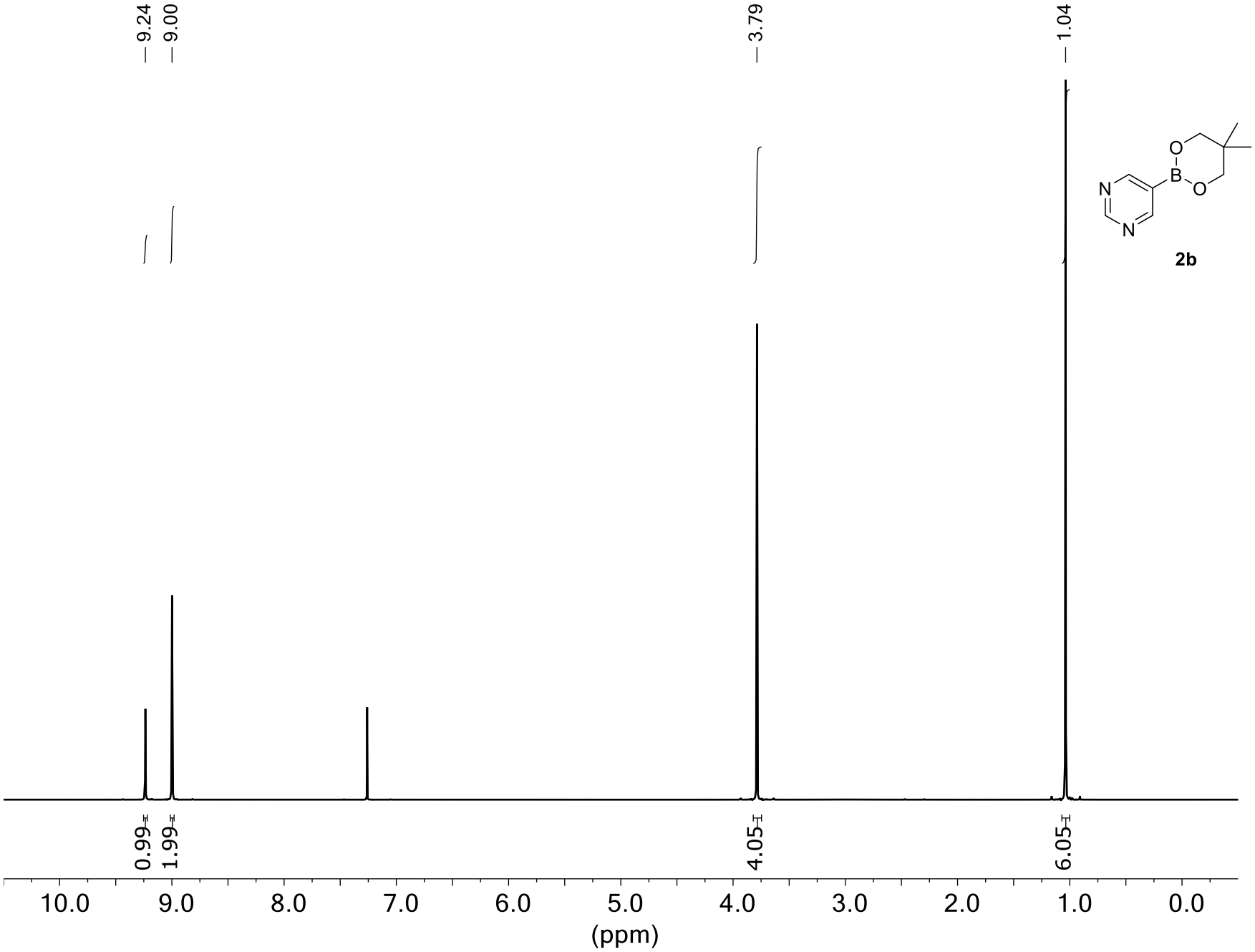
(ppm)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9.00
3.79
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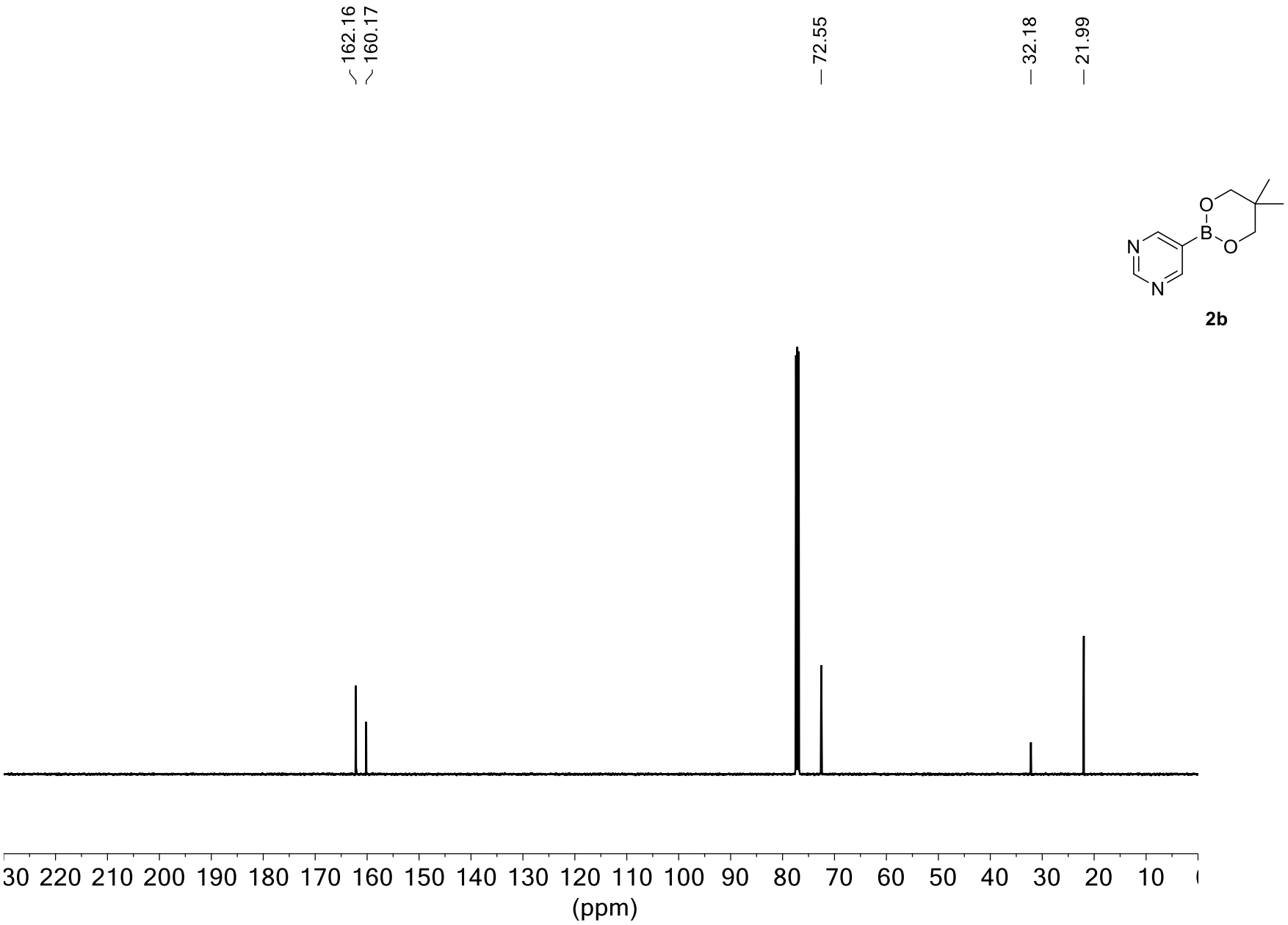
0.99
1.99
4.05
6.05
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)
O
B
O
N
N
2b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160.17
72.55
32.18
21.99
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B
O
N
N
2b
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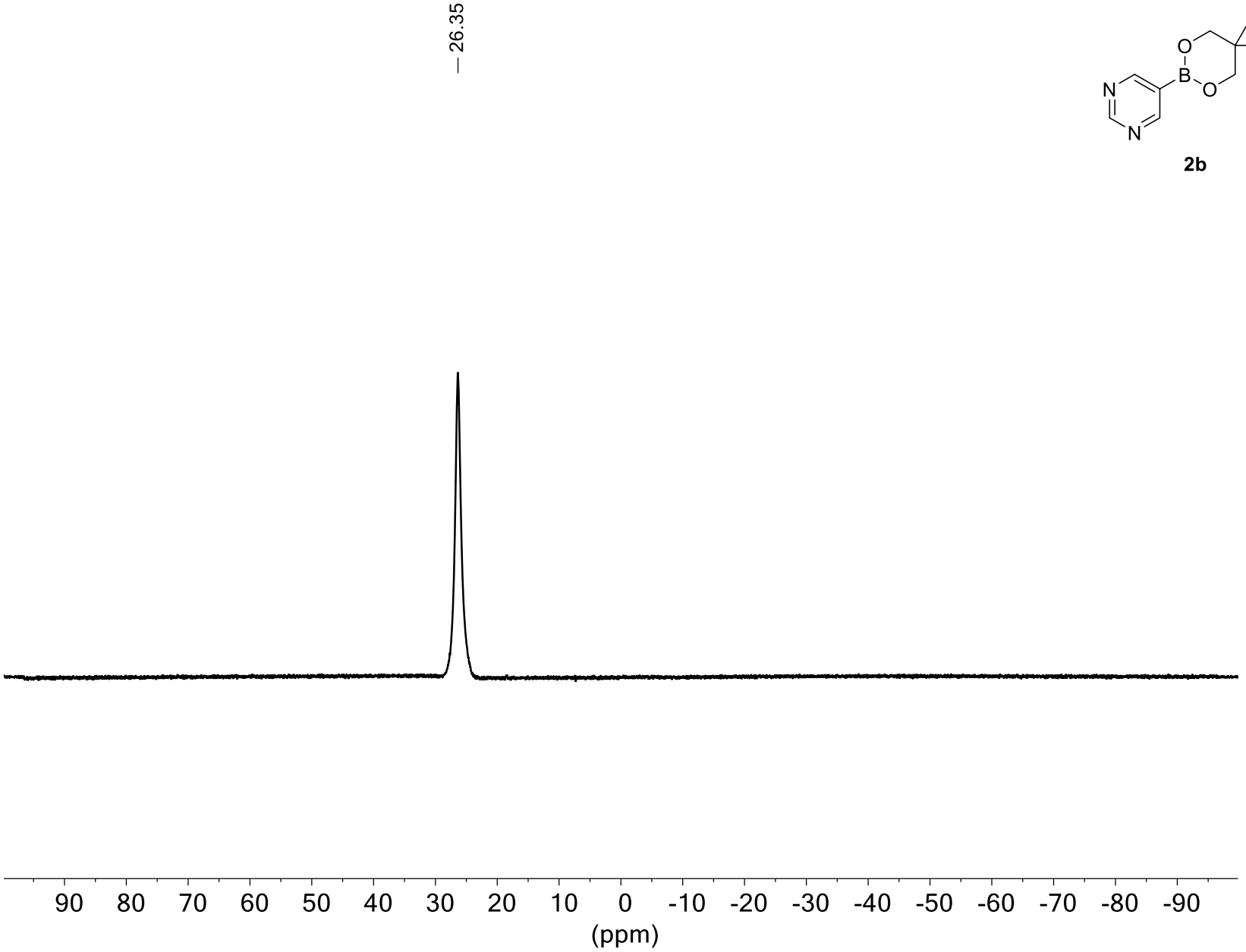
(ppm)



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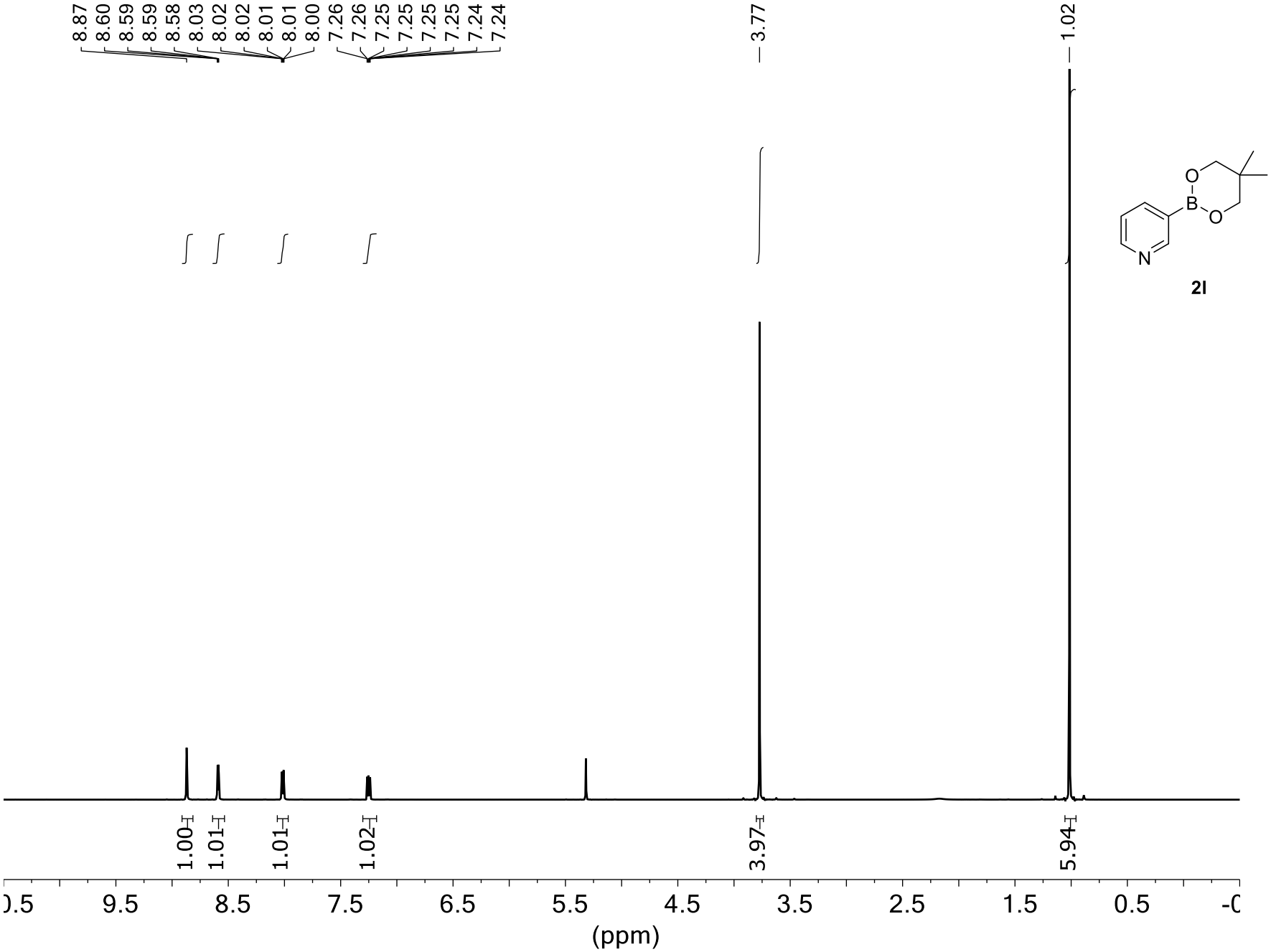
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8.59
8.59
8.58
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8.02
8.02
8.01
8.01
8.00
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7.26
7.25
7.25
7.25
7.25
7.24
7.24
3.77
1.02
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B
O
N
2l
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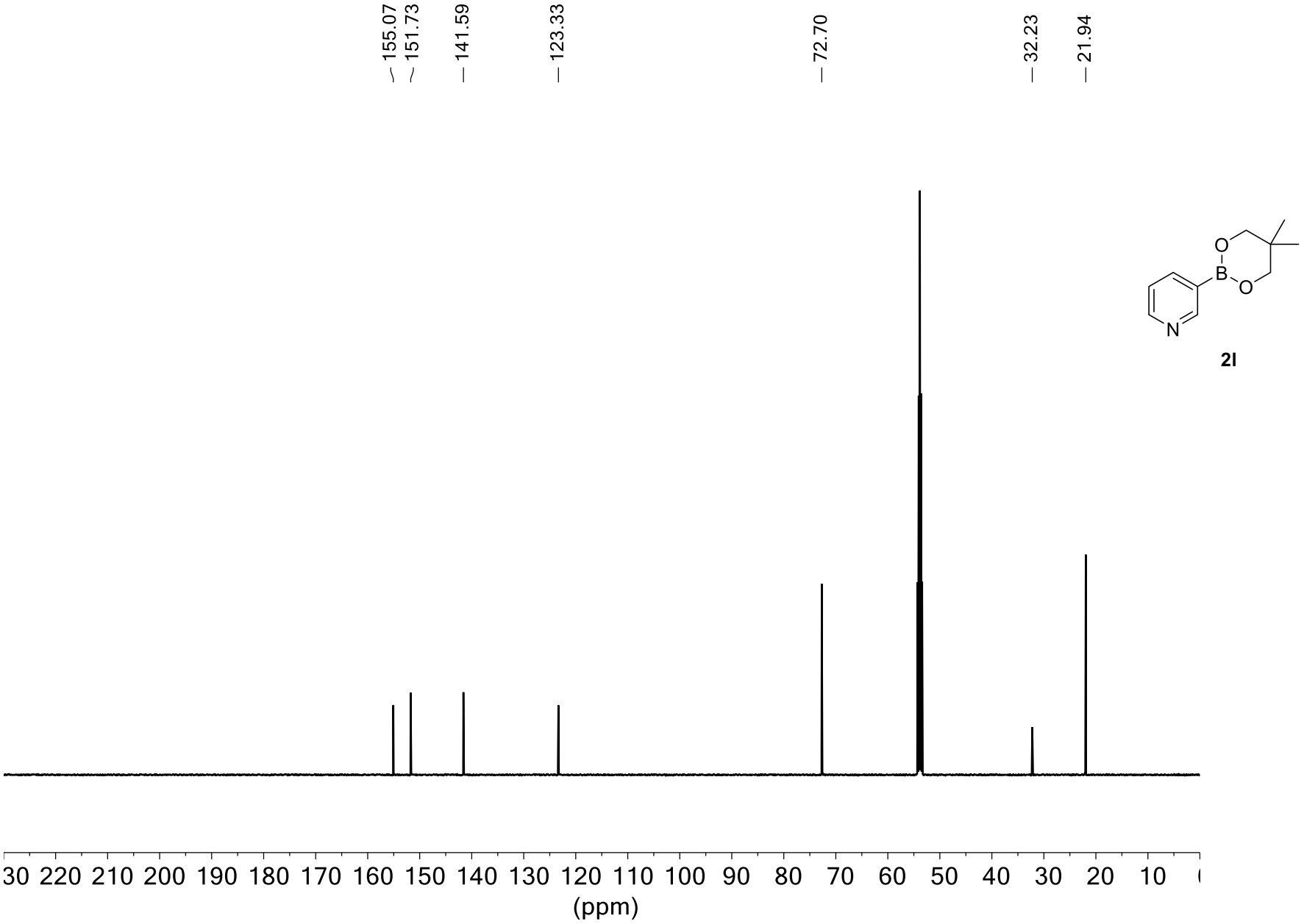
1.01
1.01
1.02
3.97
5.94
(ppm)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151.73
141.59
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72.70
32.23
21.94
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B
O
N
2l
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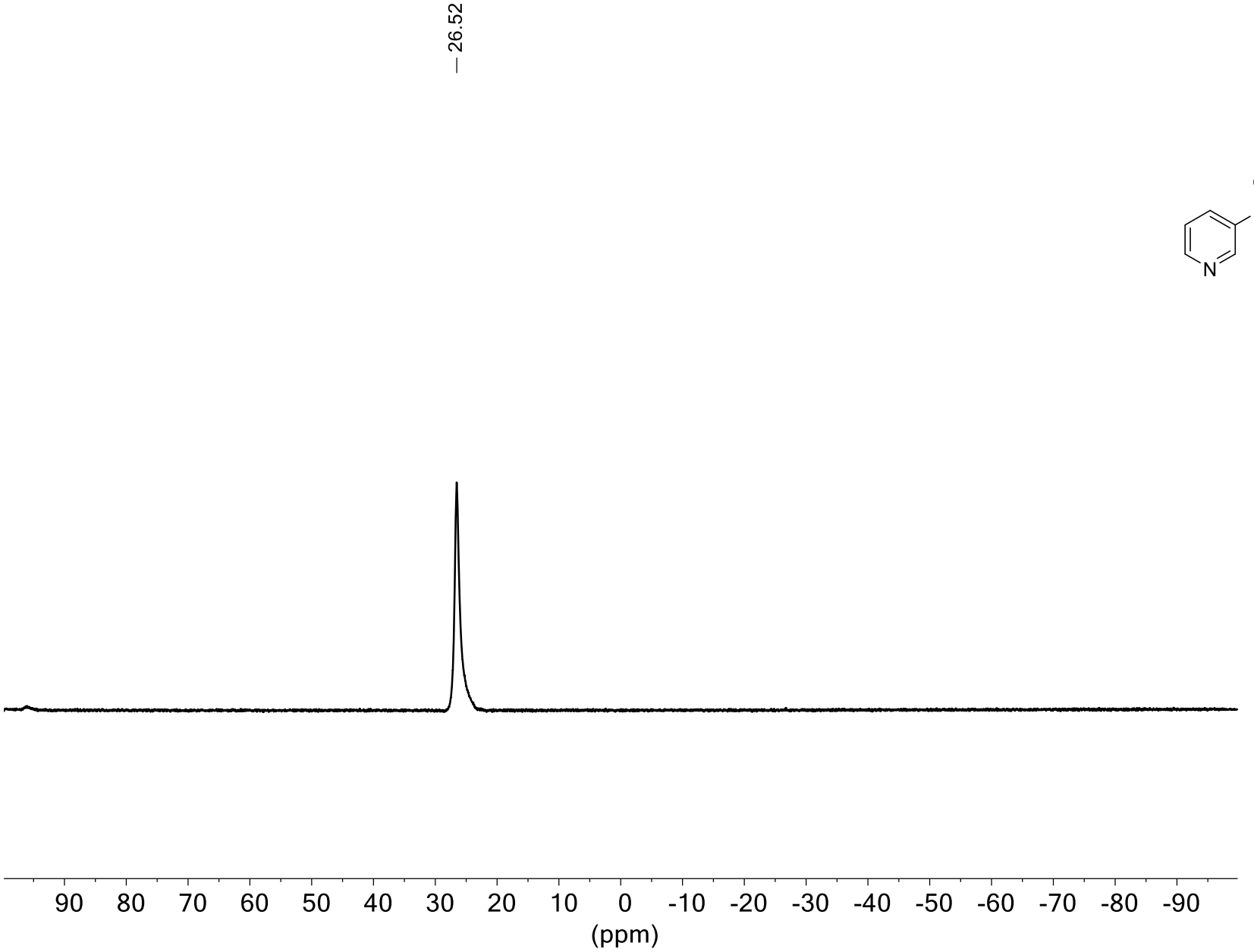
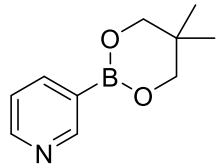
(ppm)





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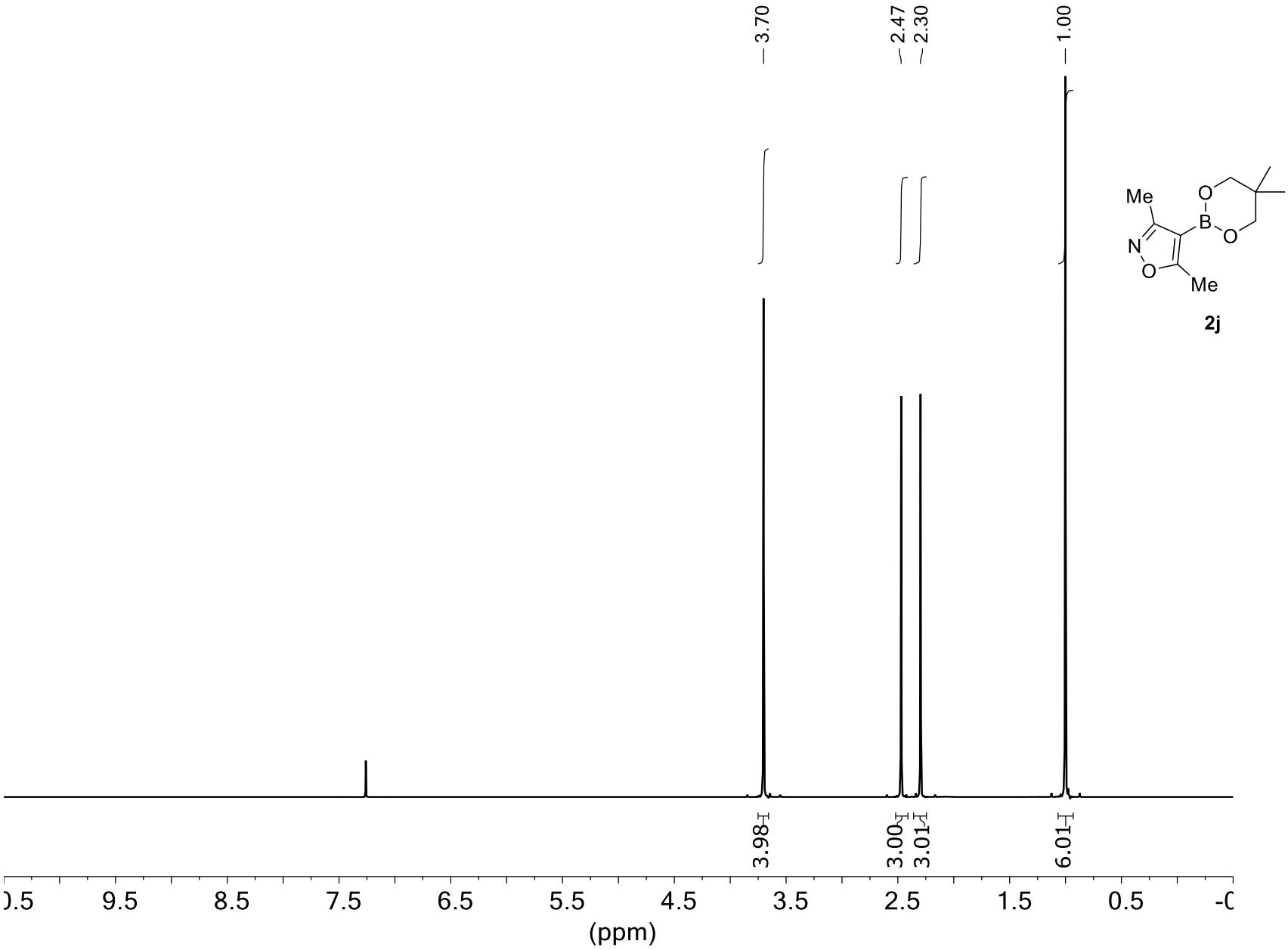
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O
B
O
N
O
Me
2j
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3.00
3.01
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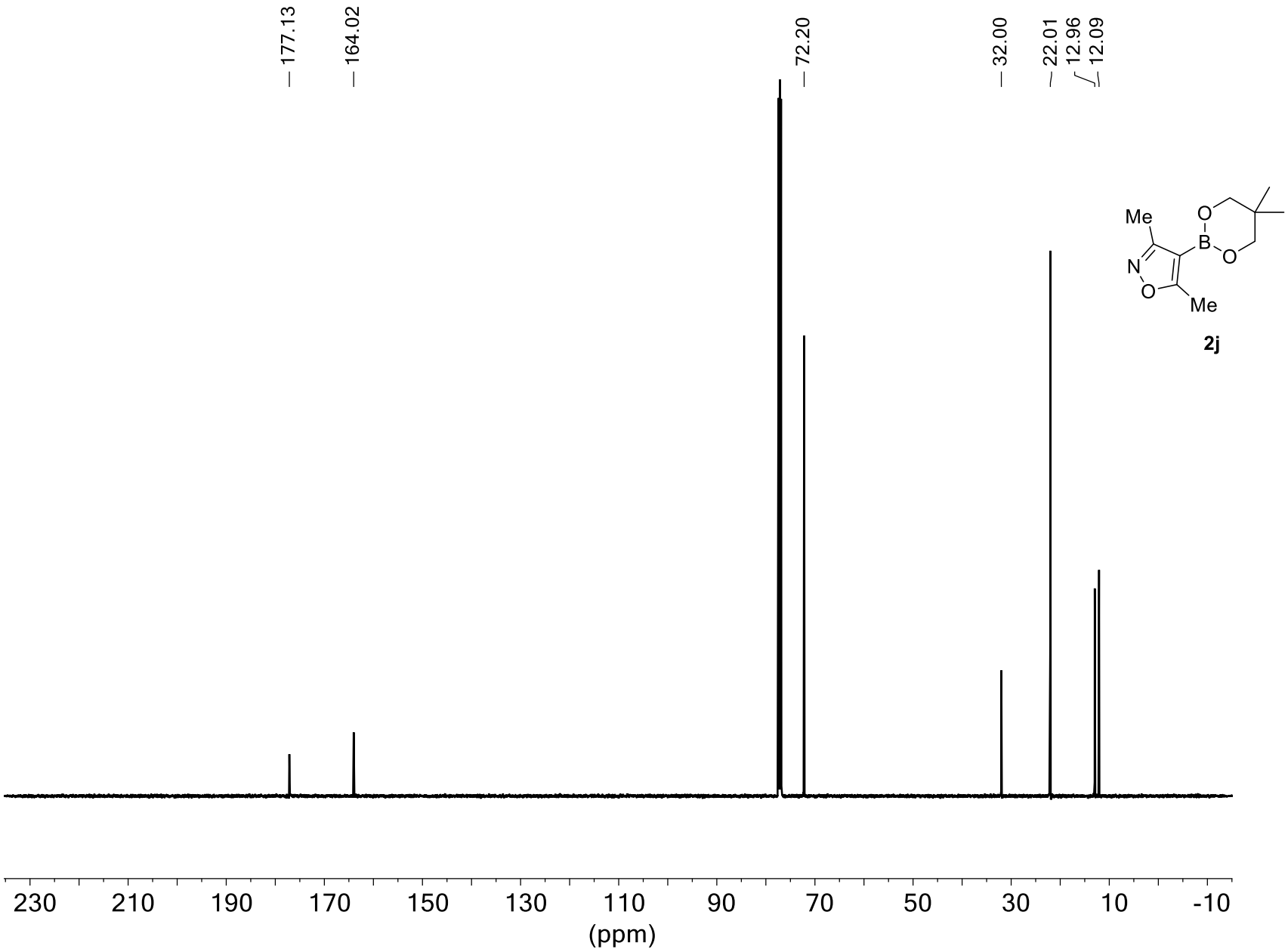
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
(ppm)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32.00
22.01
12.96
12.09
Me
O
B
O
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O
Me
2j
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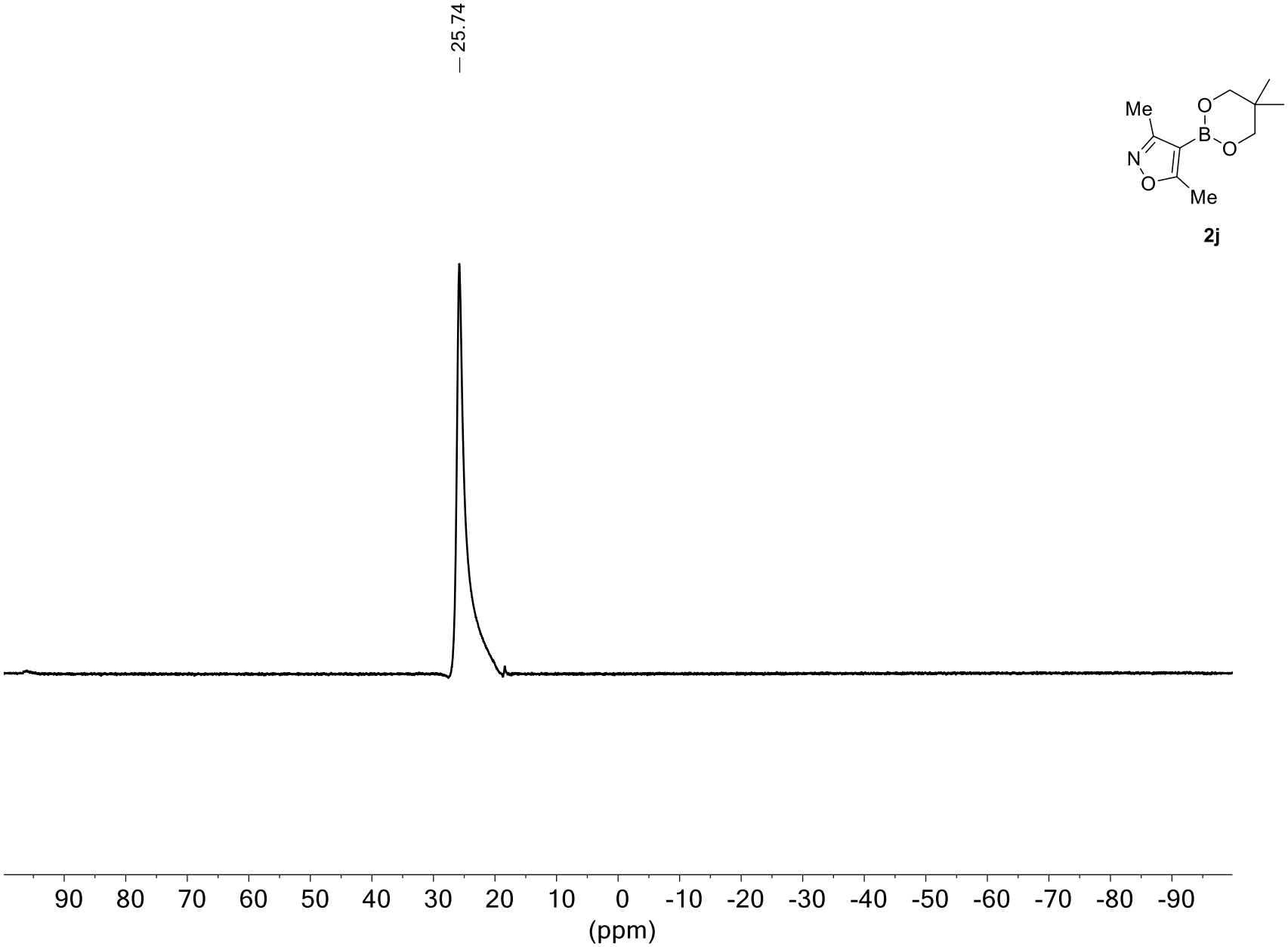
170
150
130
110
90
70
50
30
10
-10
(ppm)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Me
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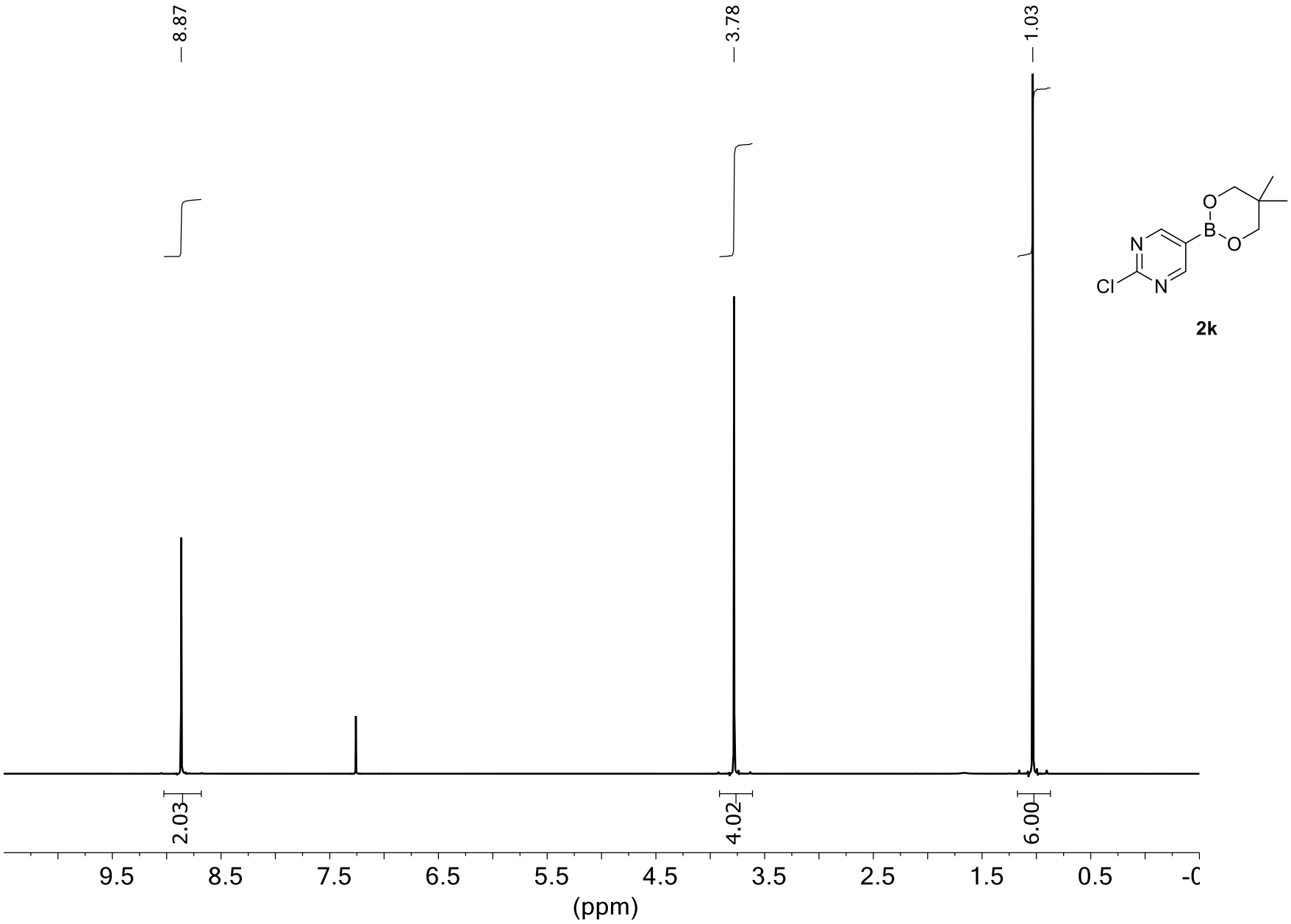
(ppm)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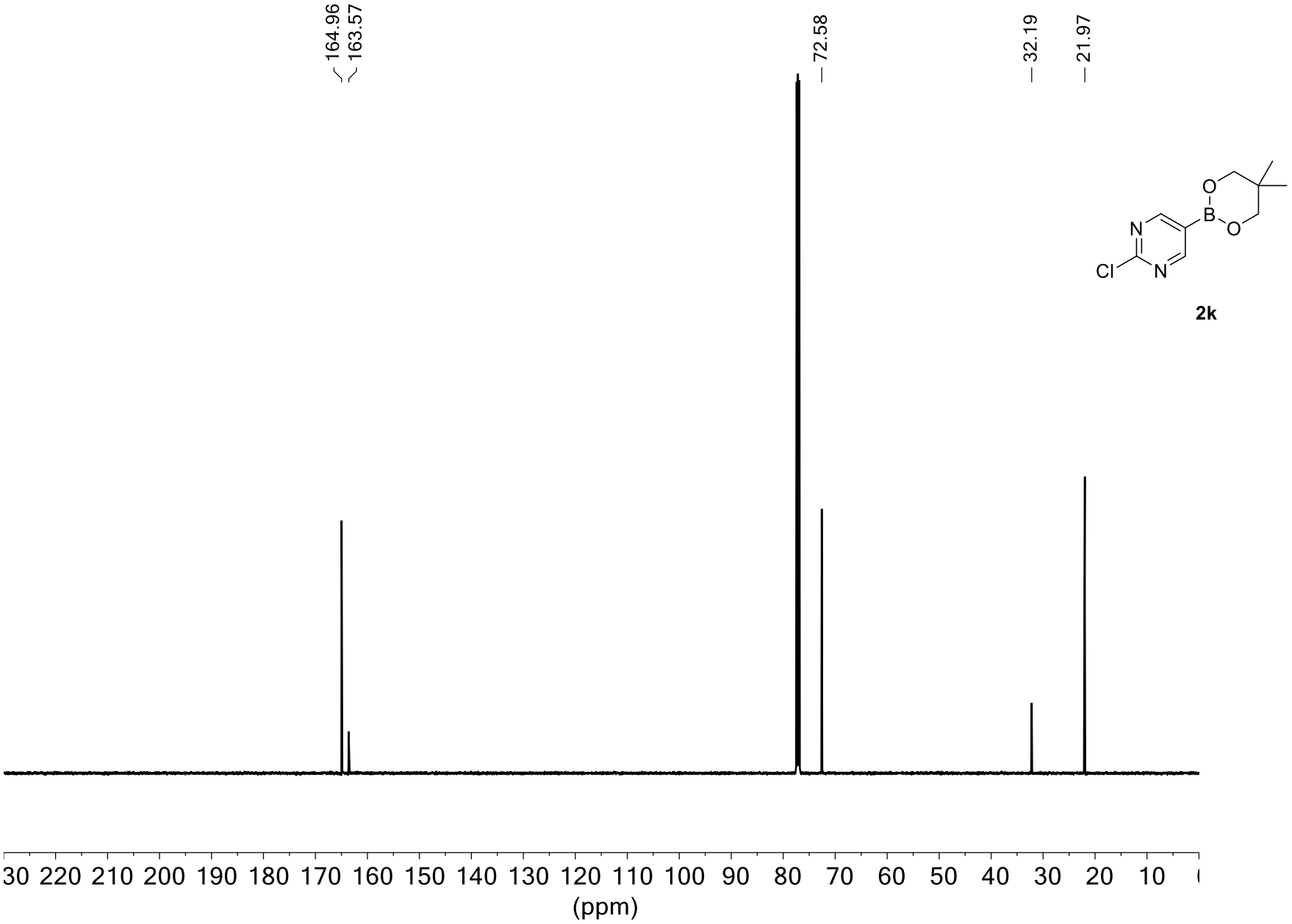
1.03
2.03
4.02
6.00
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
(ppm)
O
B
O
N
Cl
N
2k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163.57
72.58
32.19
21.97
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B
O
N
Cl
N
2k
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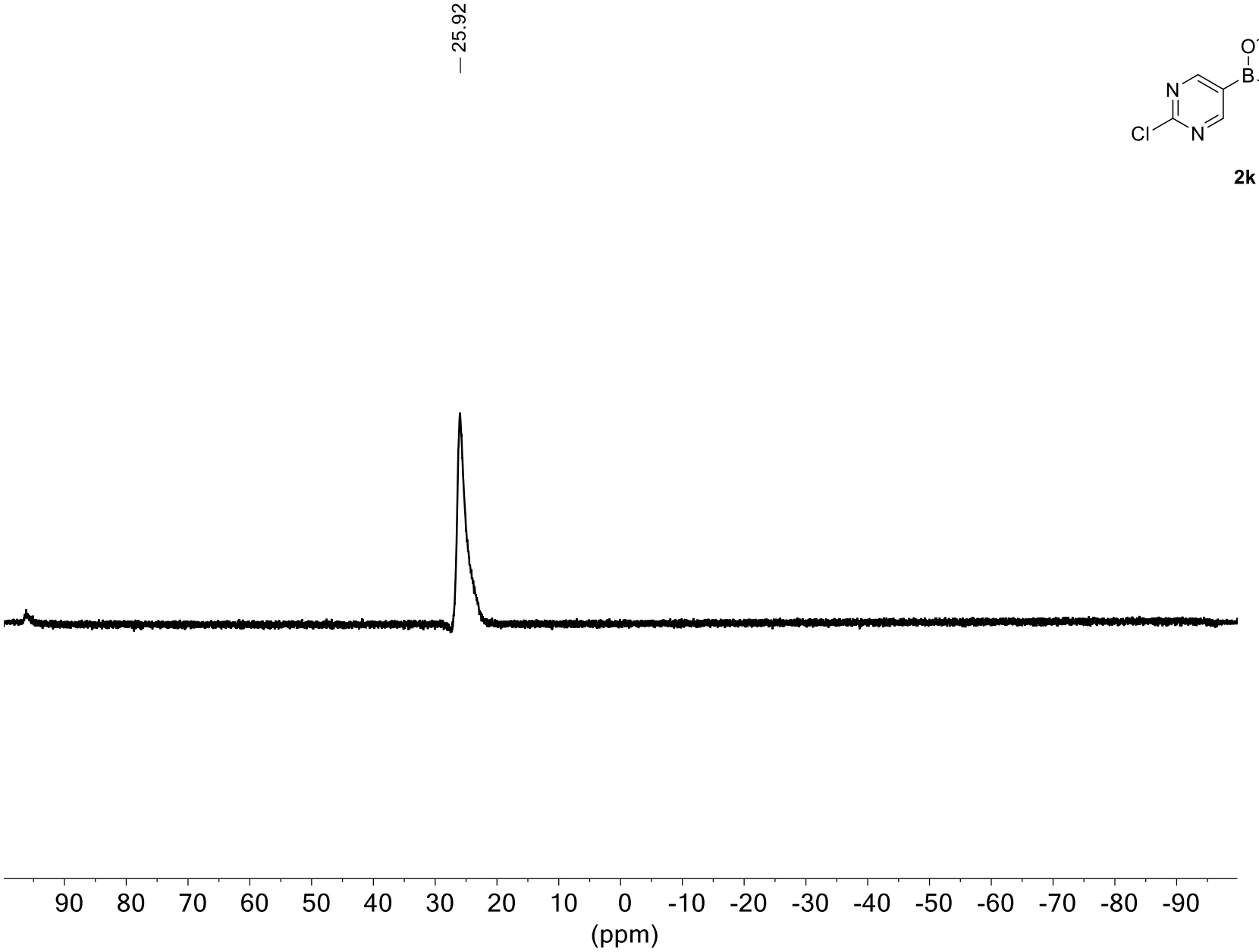
(ppm)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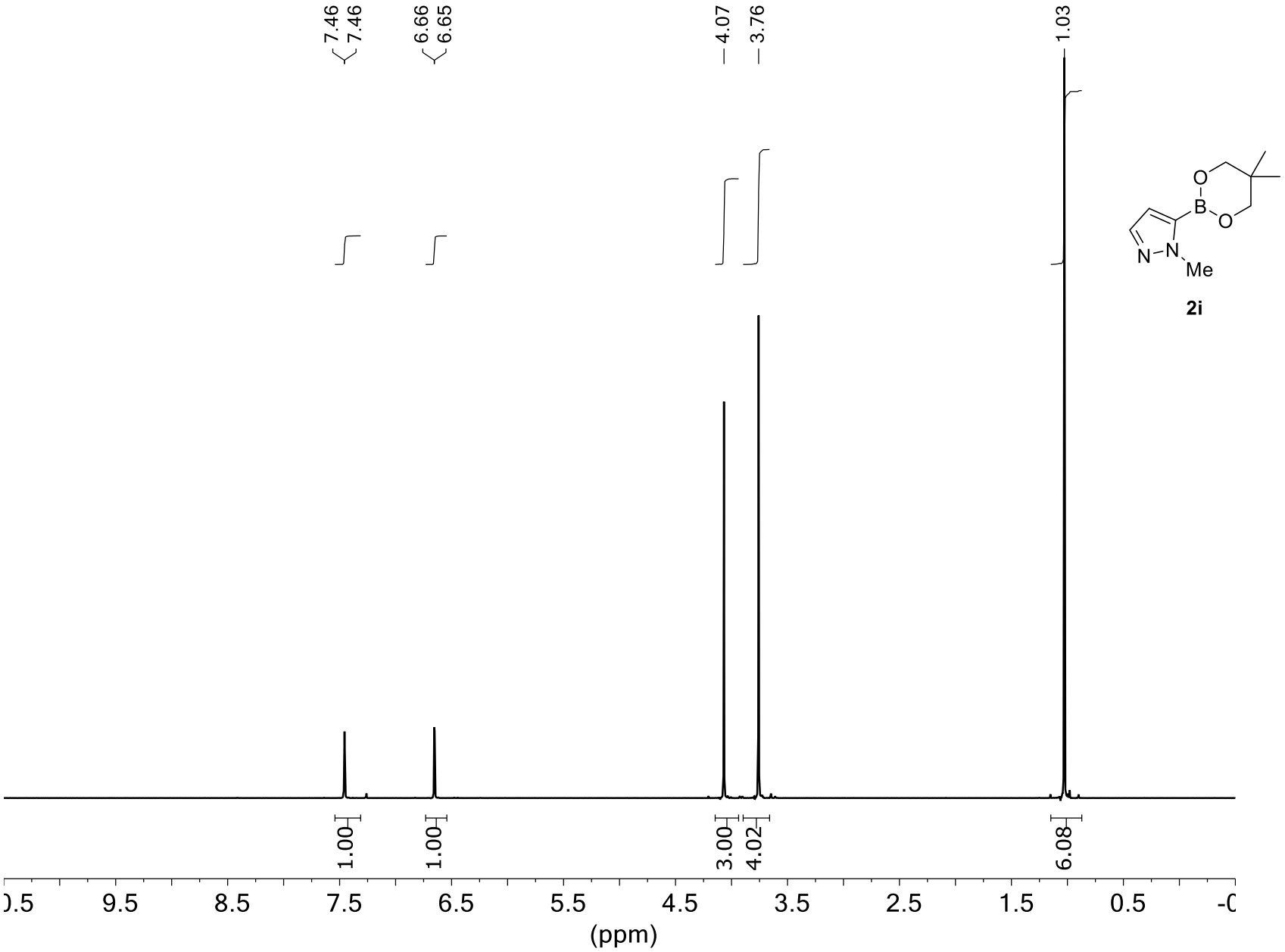
(ppm)

O
B
O
N
Cl
N

2k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6.65
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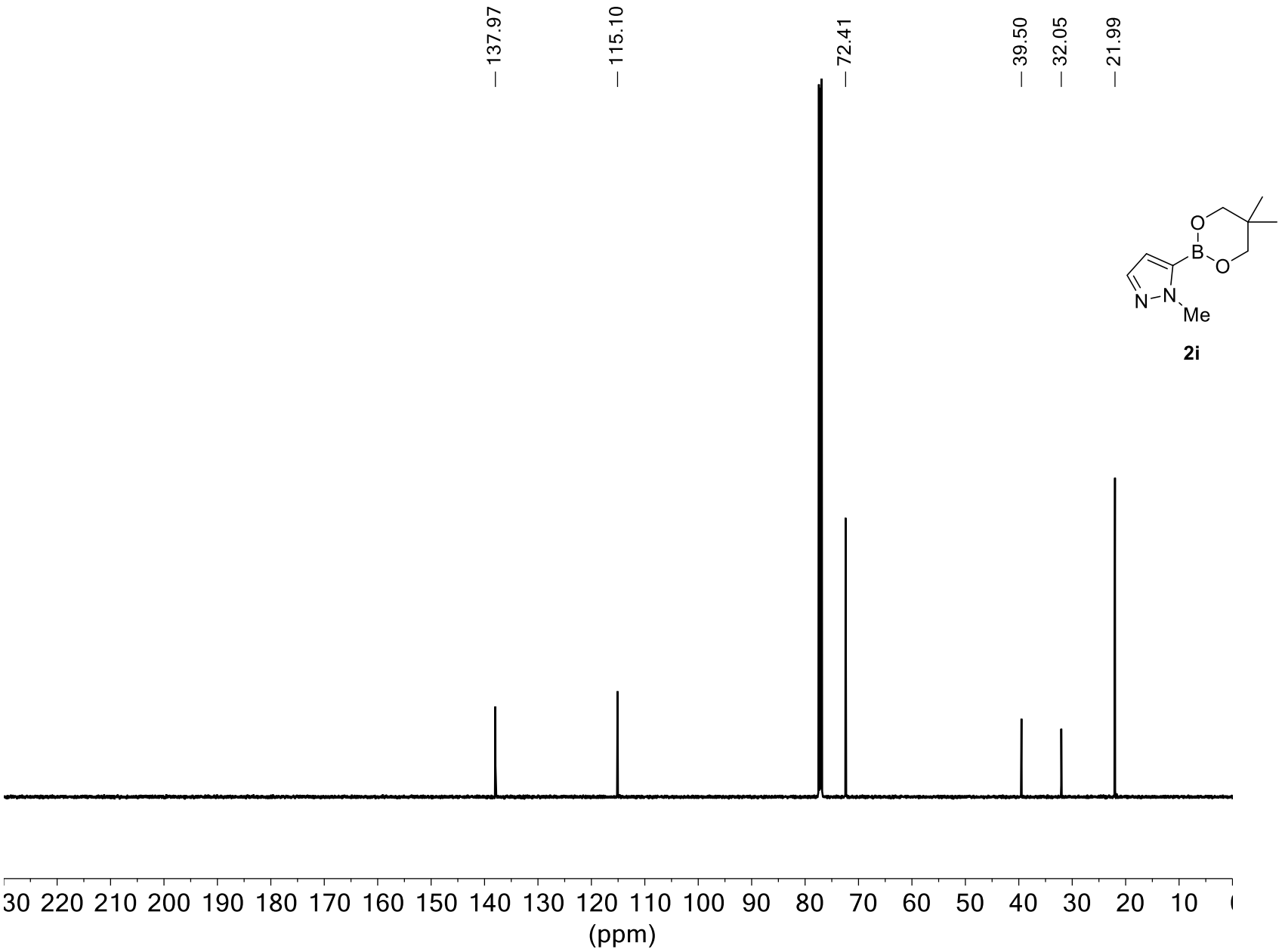
3.76
1.03
O
B
O
N
N
Me
2i
1.00
1.00
3.00
4.02
6.08
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
(ppm)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B
O
N
N
Me
2i
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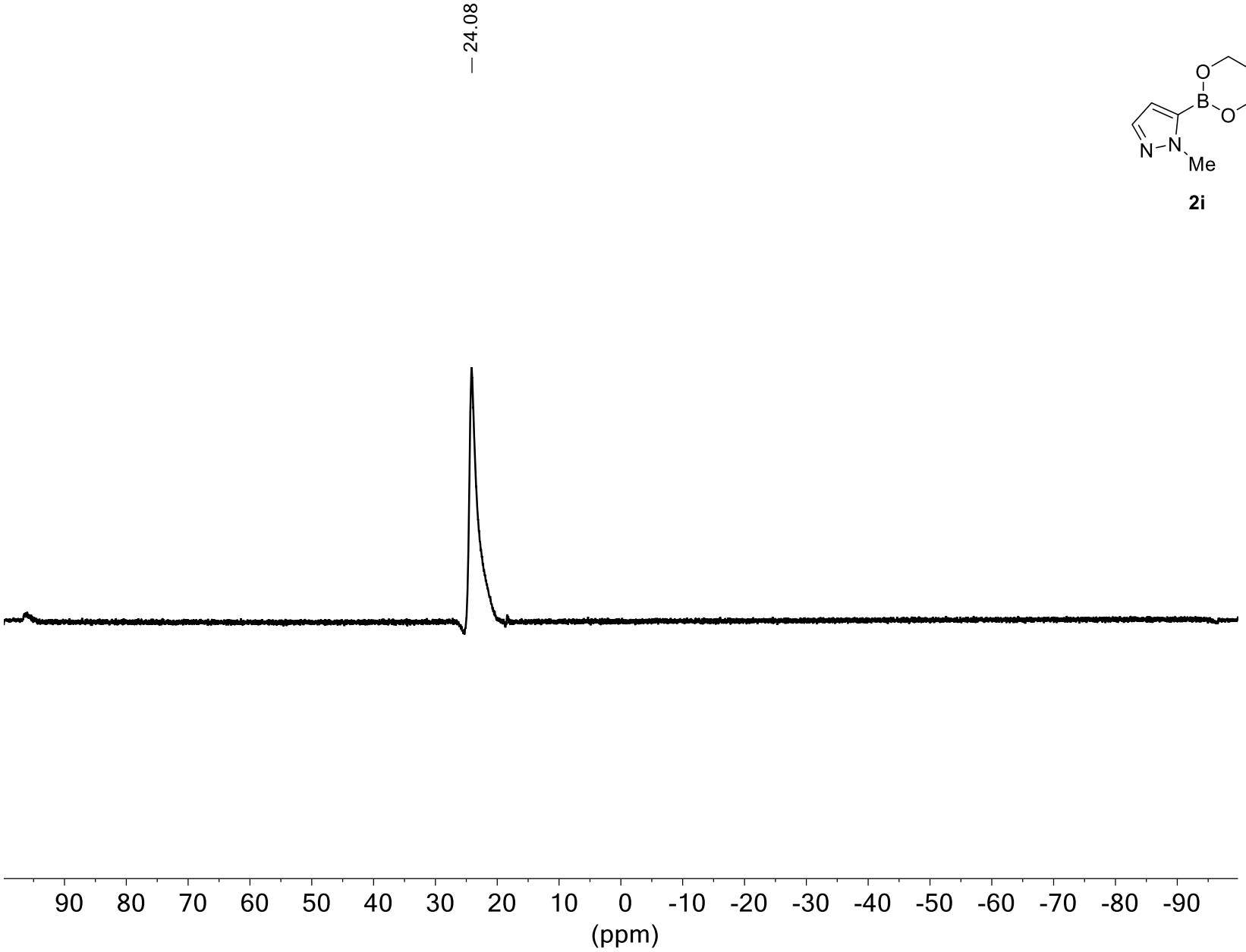
(ppm)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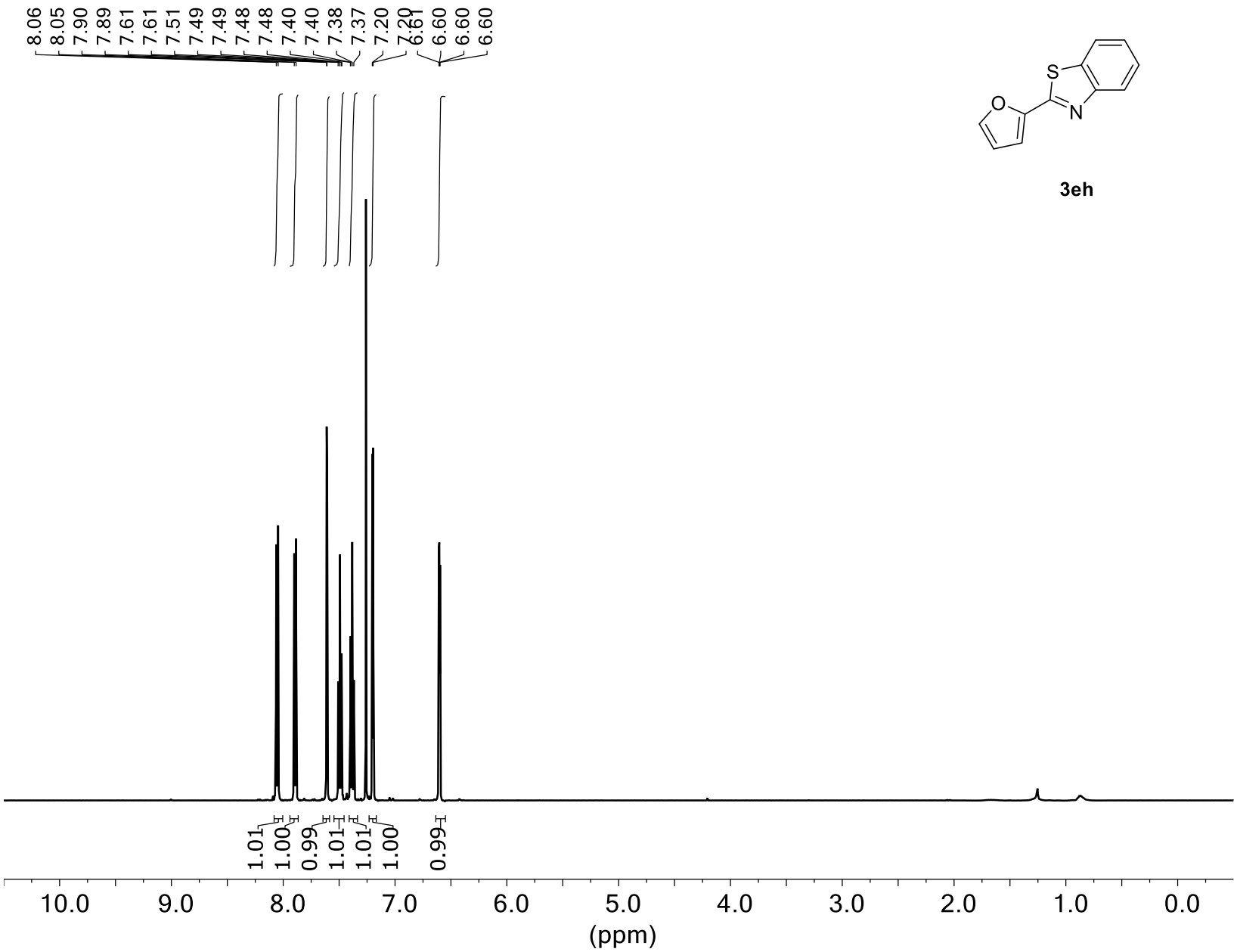
2i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7.40
7.38
7.37
7.20
7.20
6.61
6.60
6.60
6.60
S
O
N
3eh
1.01
1.00
0.99
1.01
1.01
1.00
0.99
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3.0
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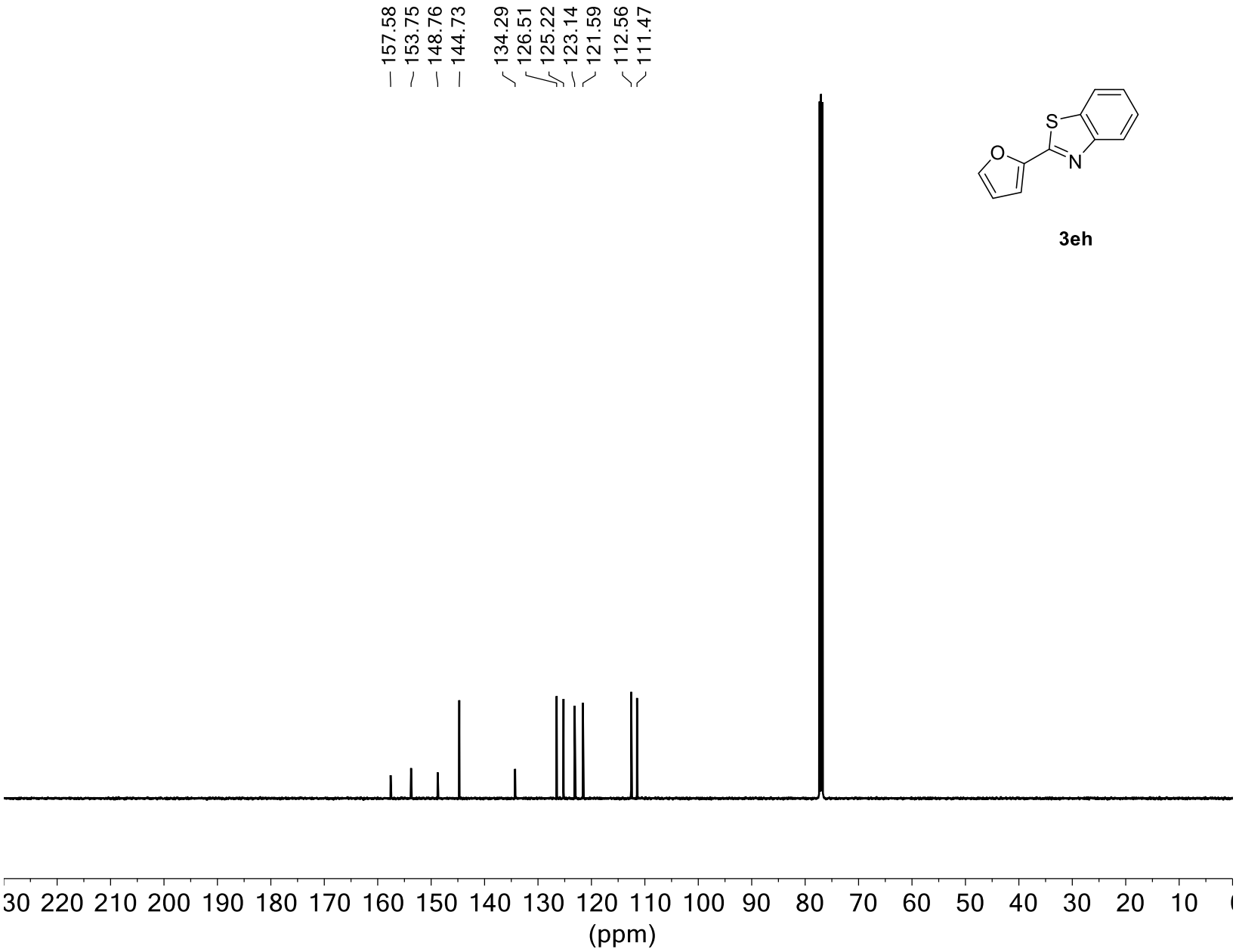
1.0
0.0
(ppm)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126.51
125.22
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111.47
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N
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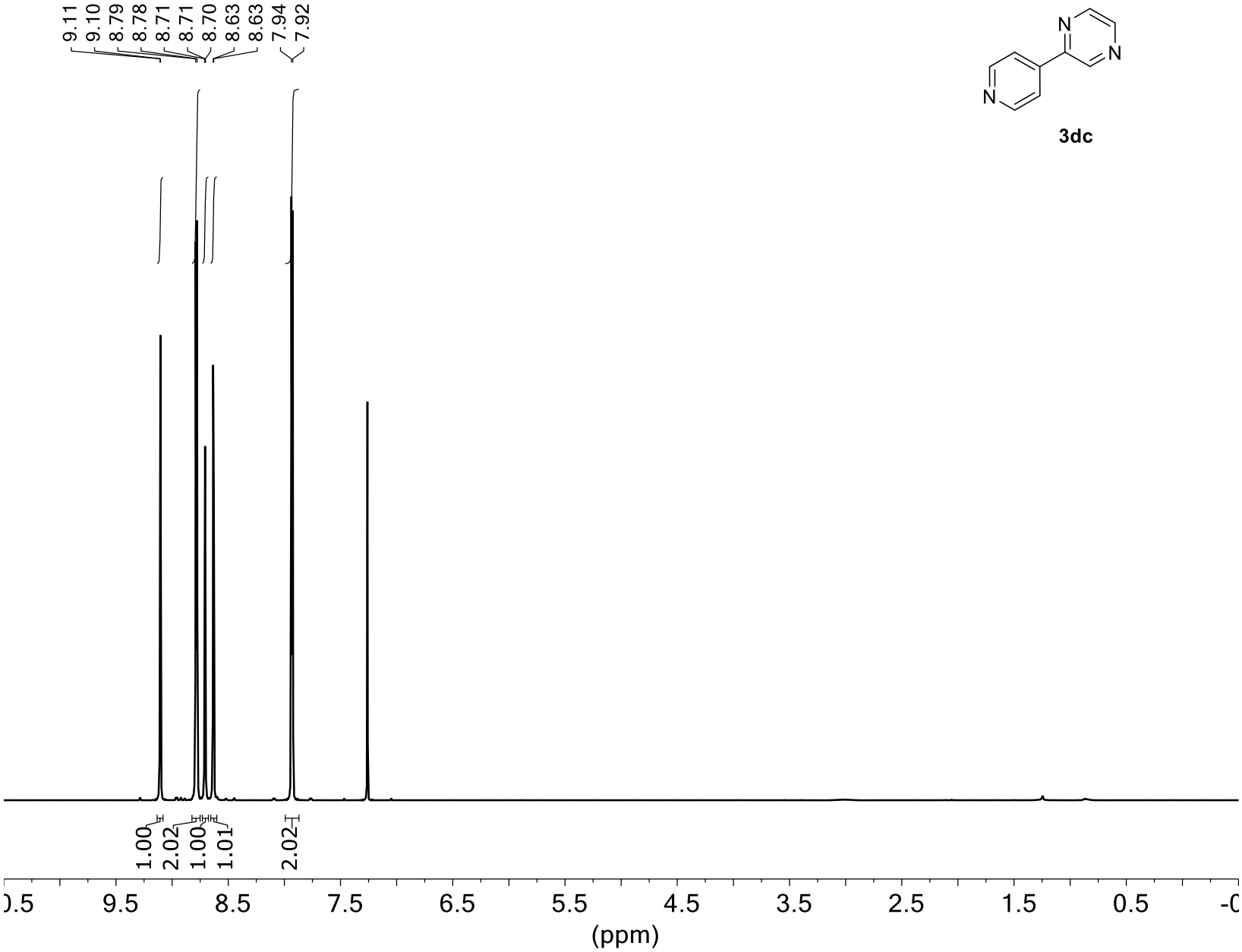
(ppm)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N
N
3dc
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2.02
1.00
1.01
2.02
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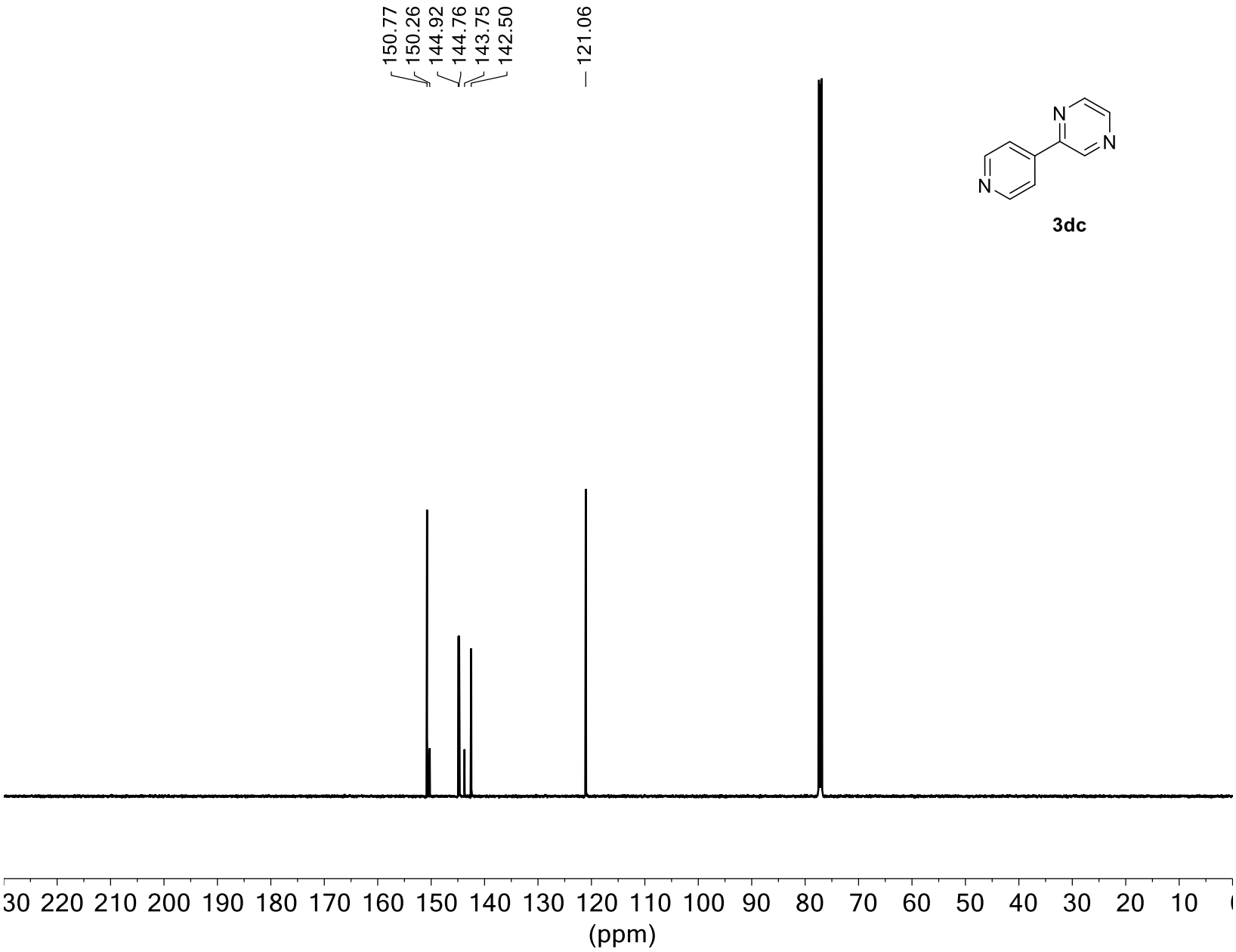
(ppm)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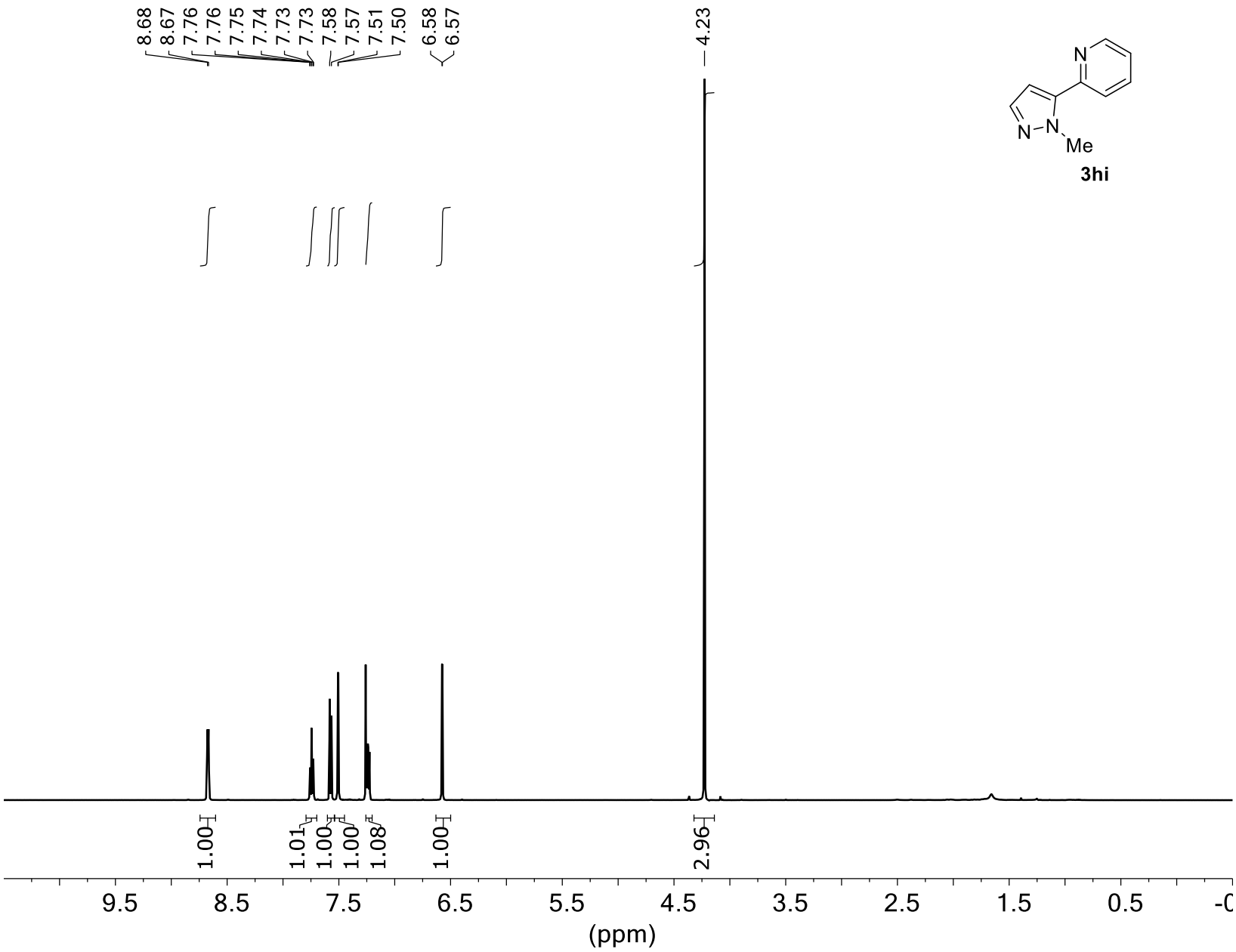
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6.57
4.23
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1.08
1.00
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1.5
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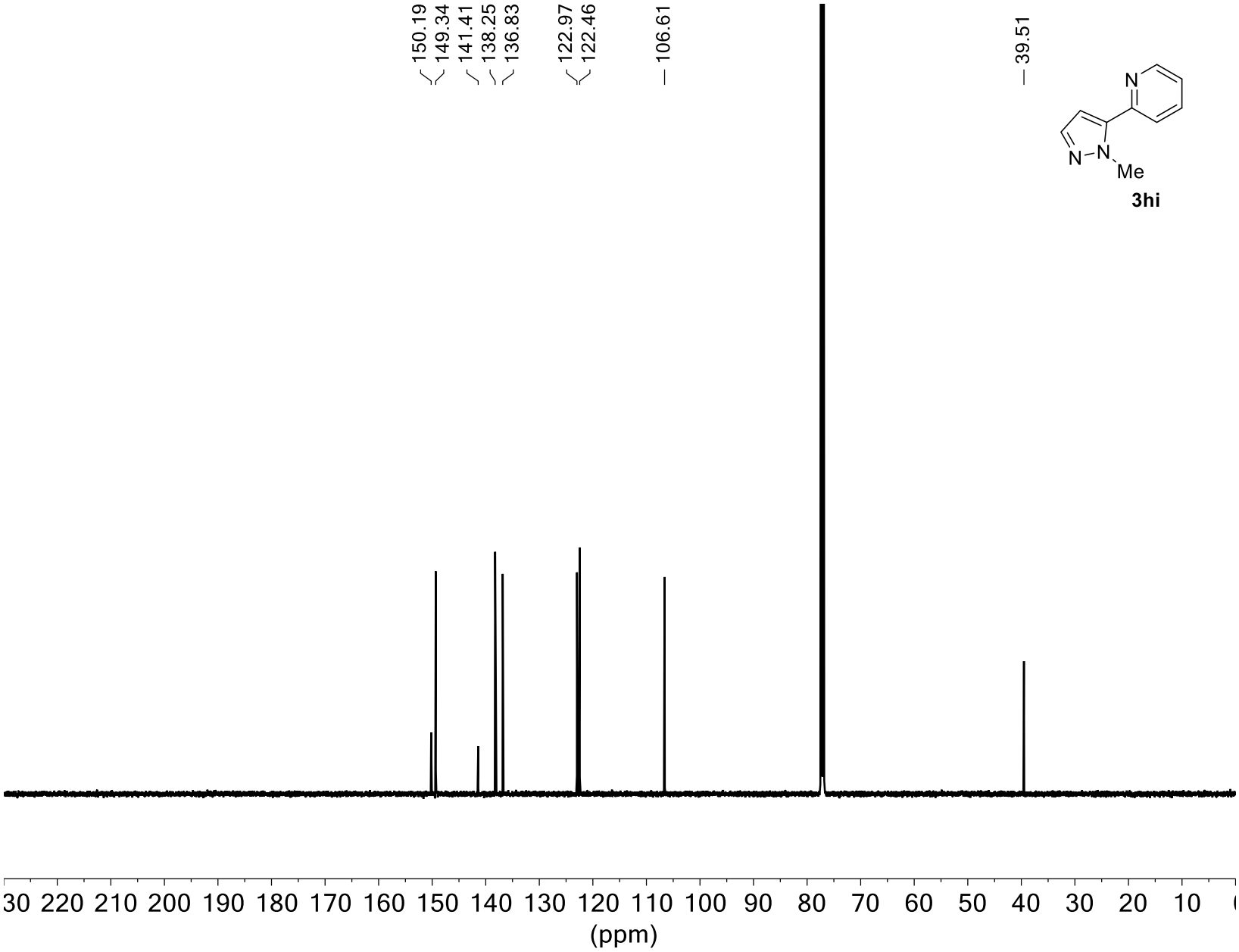
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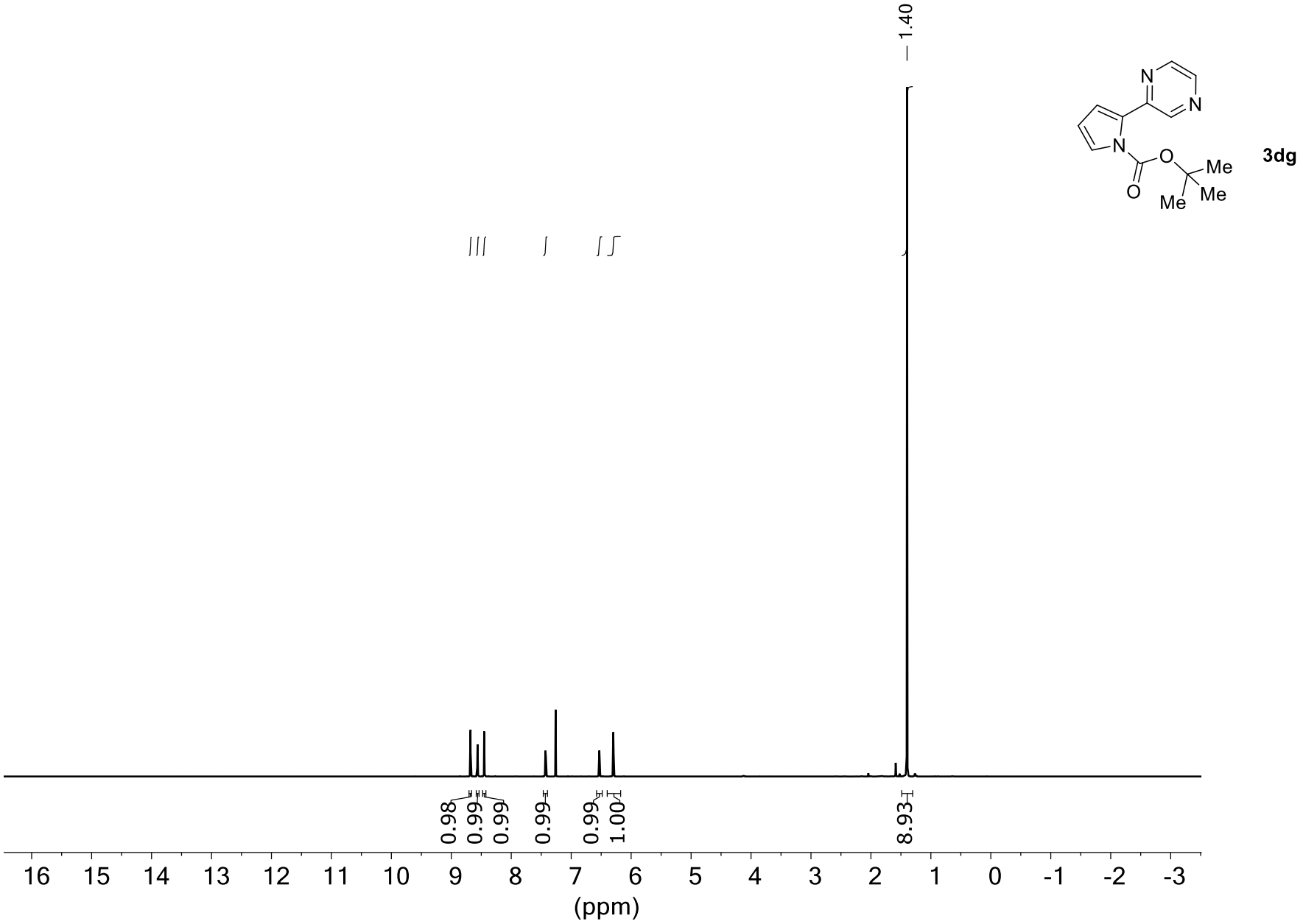
(ppm)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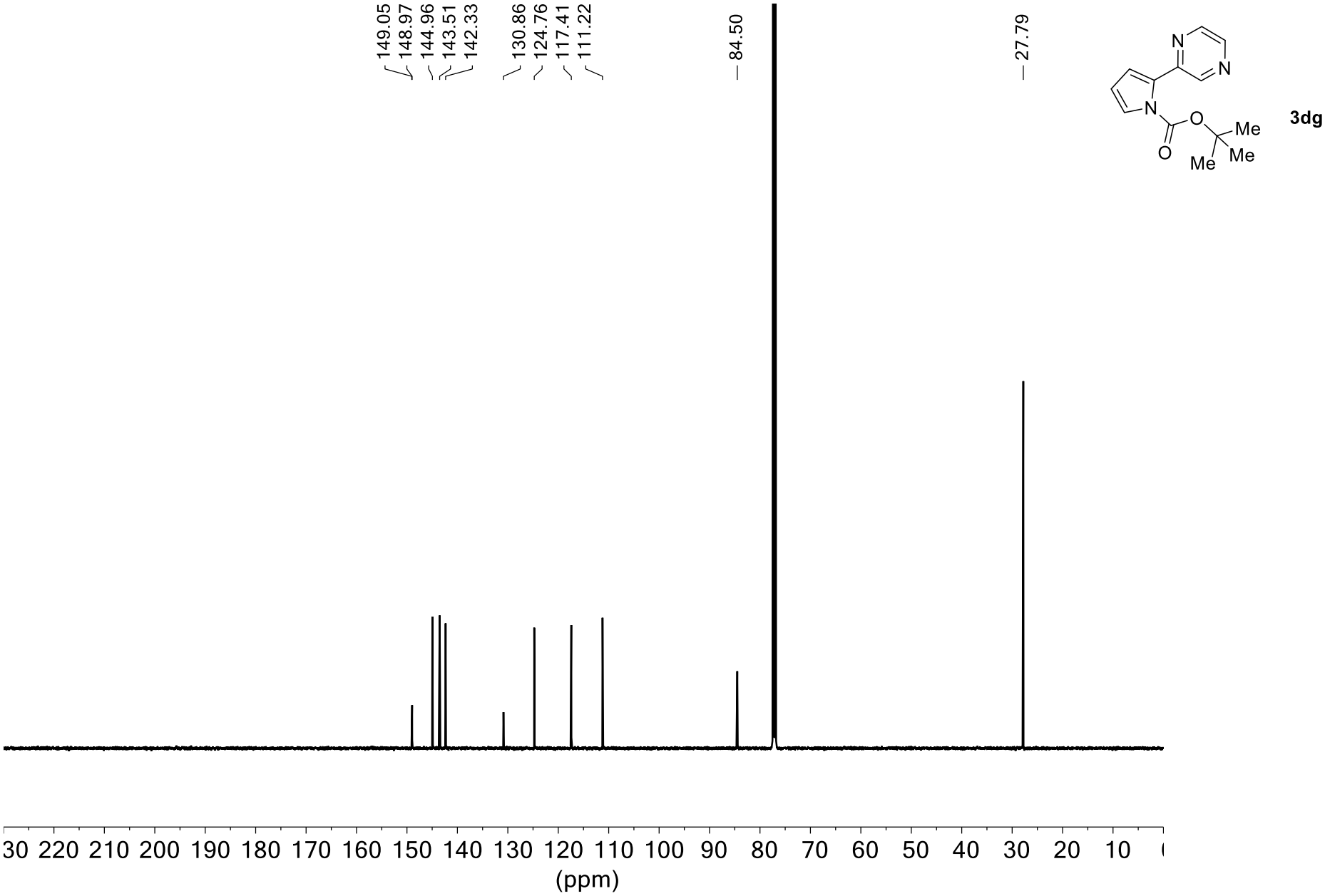
(ppm)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O
O
Me
Me
Me
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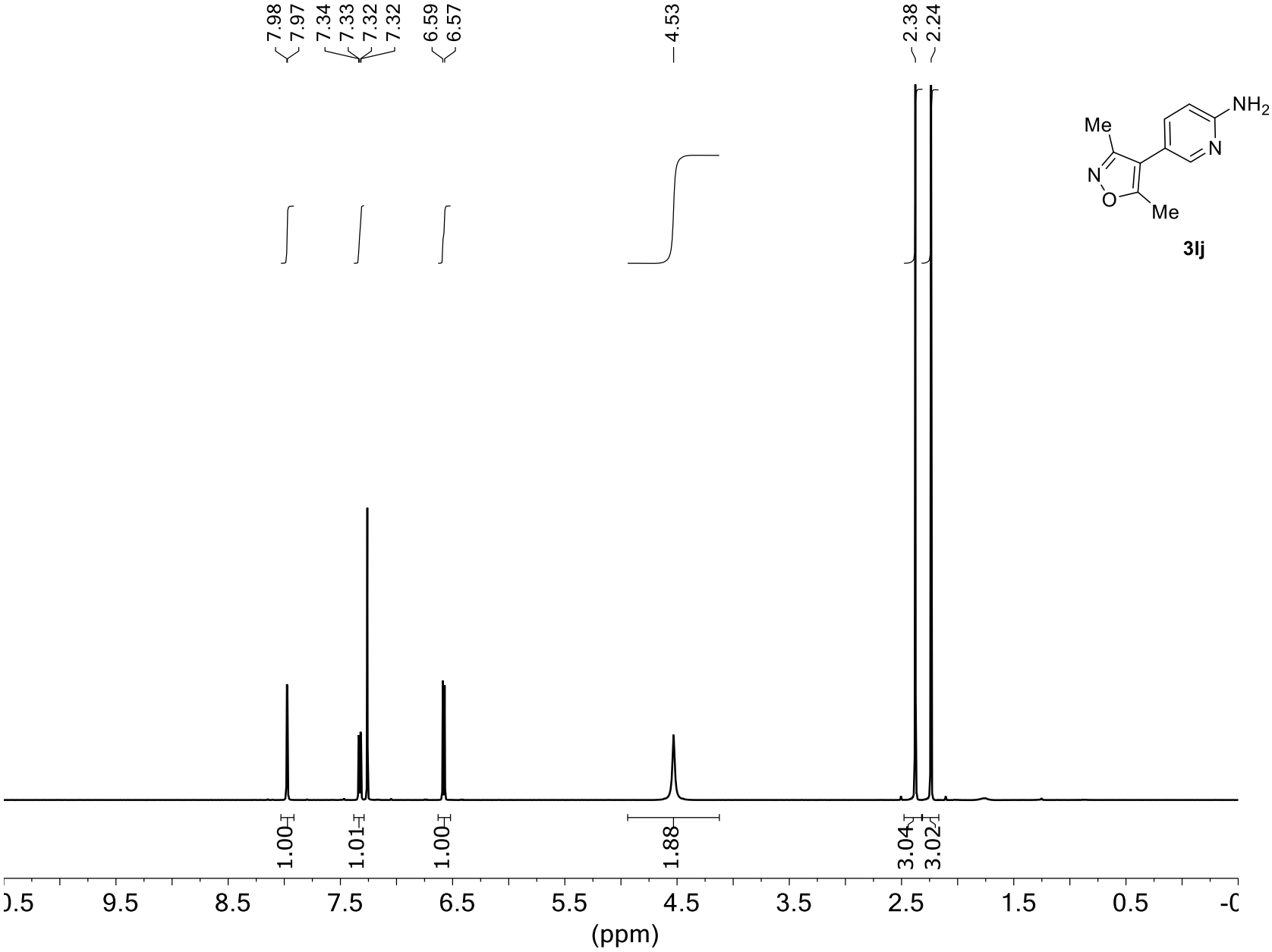
(ppm)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6.57
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O
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1.00
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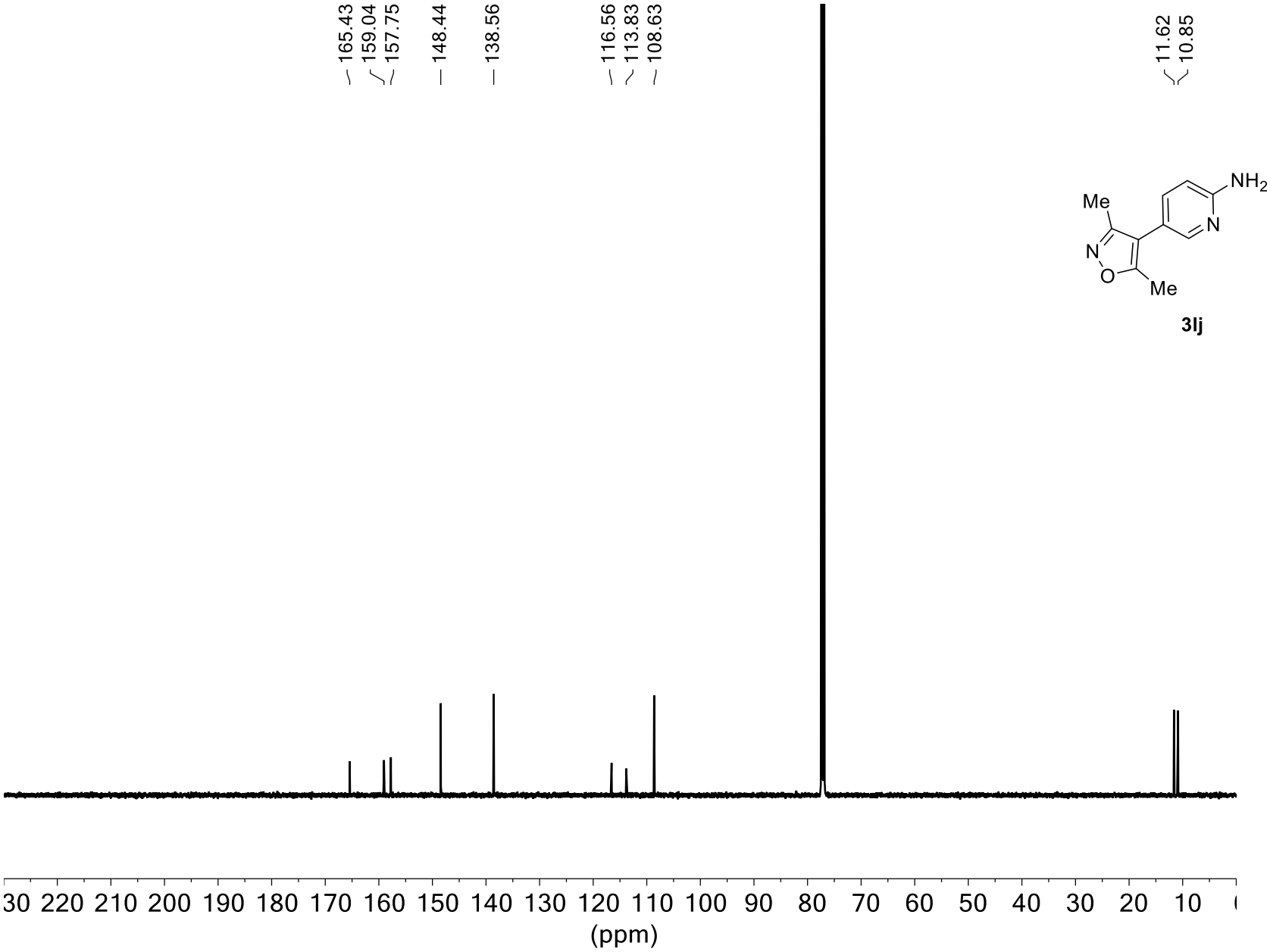
3.02
(ppm)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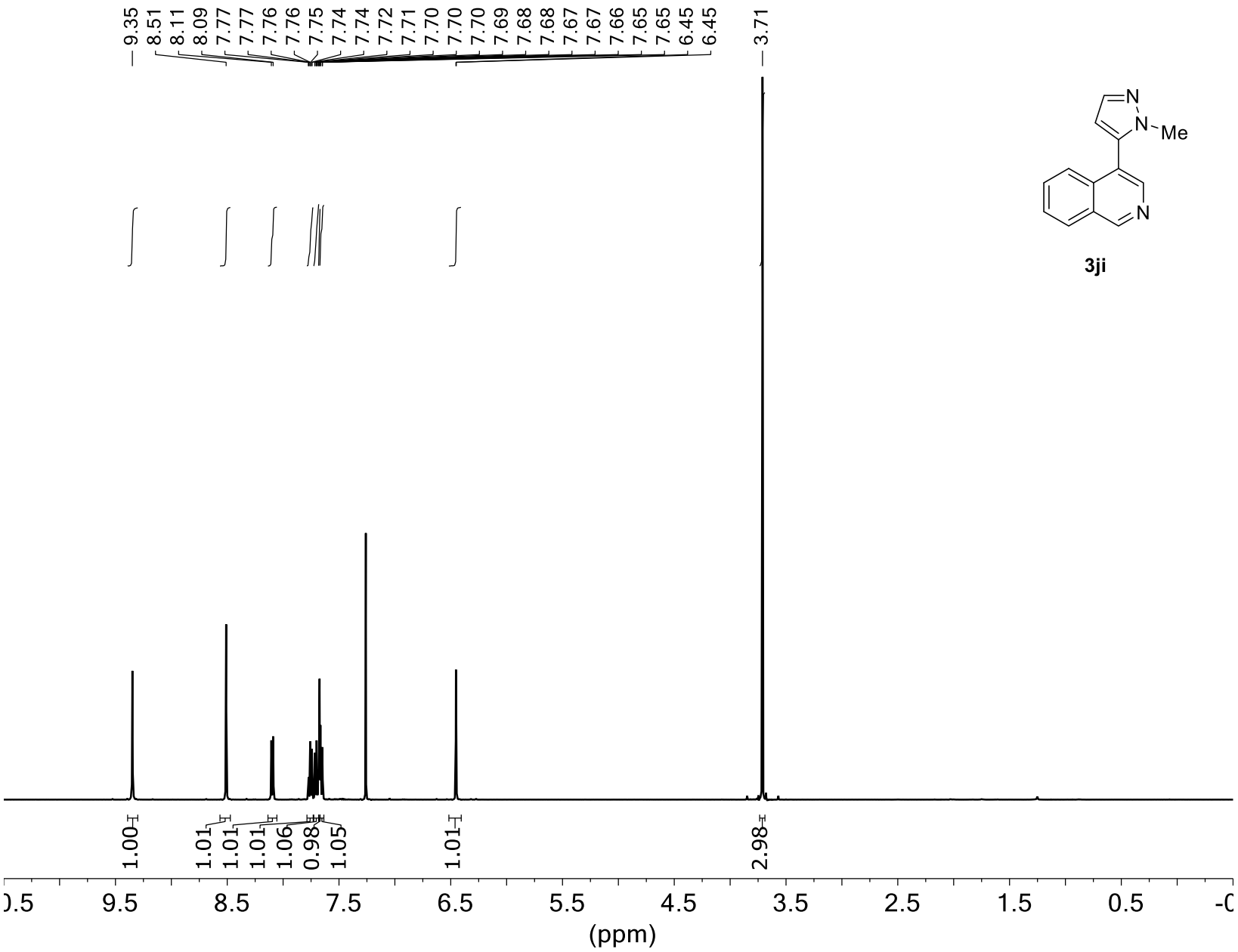
(ppm)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7.74
7.74
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7.70
7.69
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7.68
7.67
7.67
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7.65
6.45
6.45
3.71
N
N
Me
N
3ji
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1.01
1.01
1.01
1.06
0.98
1.05
1.01
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4.5
3.5
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1.5
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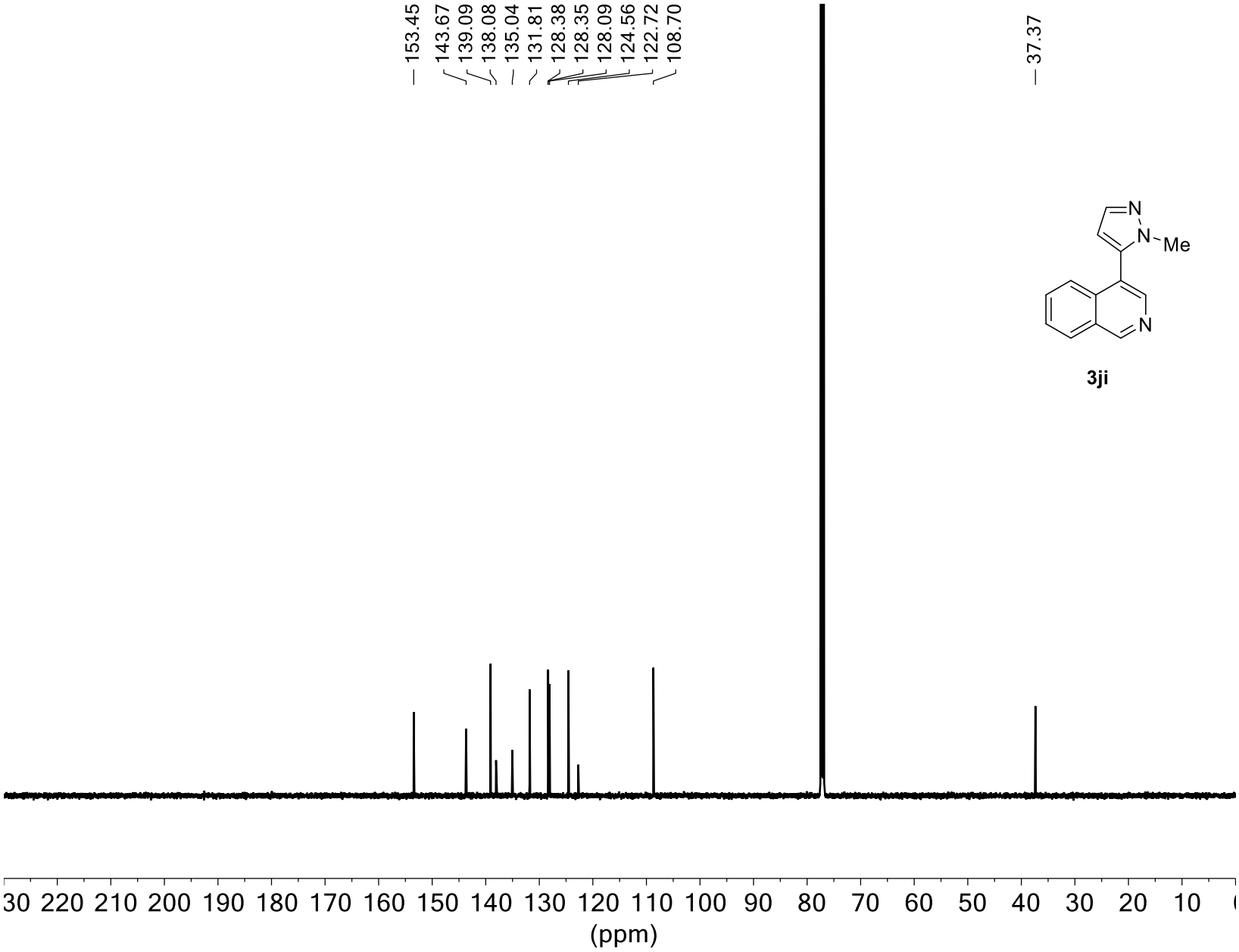
(ppm)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128.35
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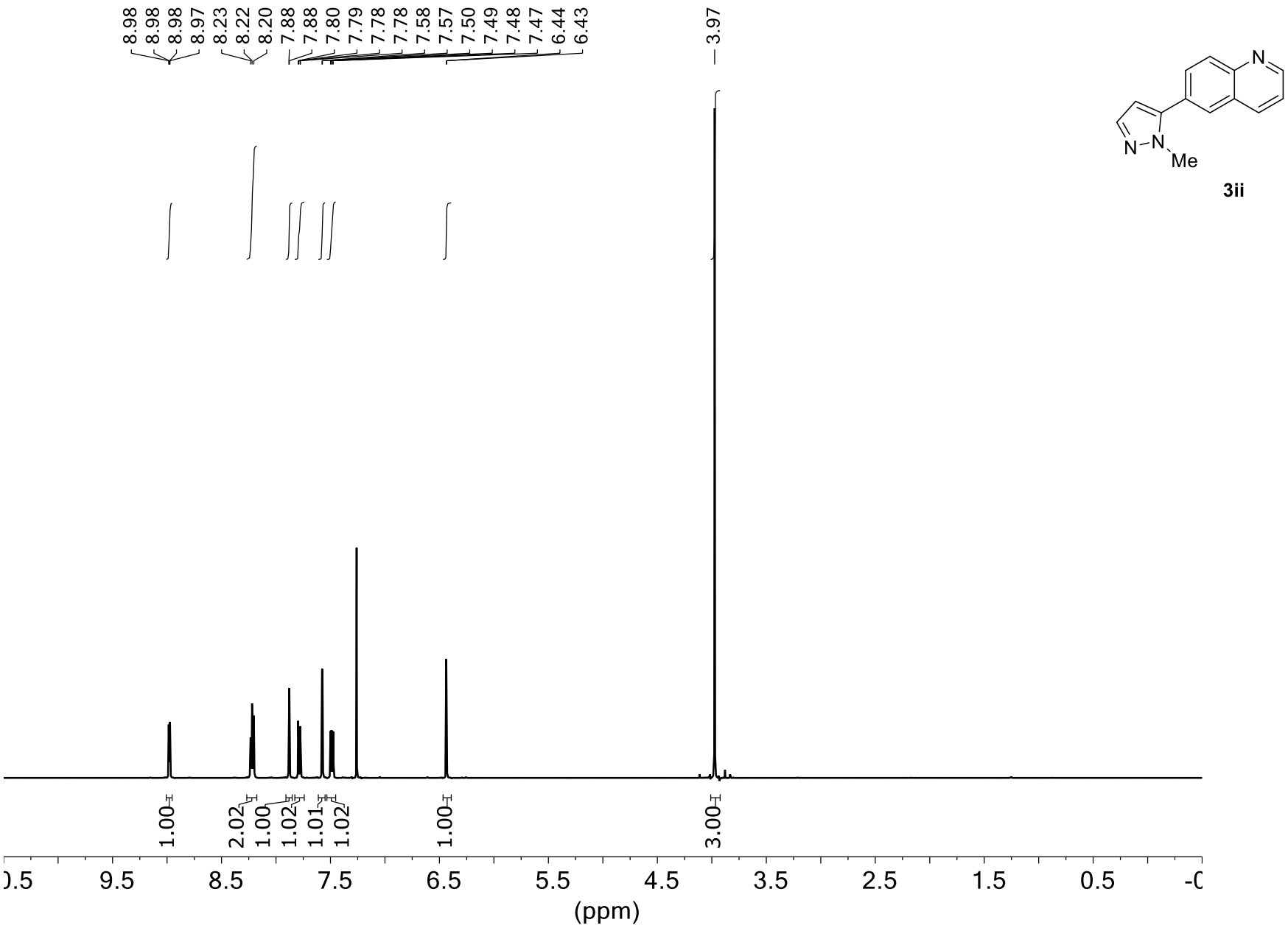
124.56
122.72
108.70
37.37
N
N
Me
N
3ji
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)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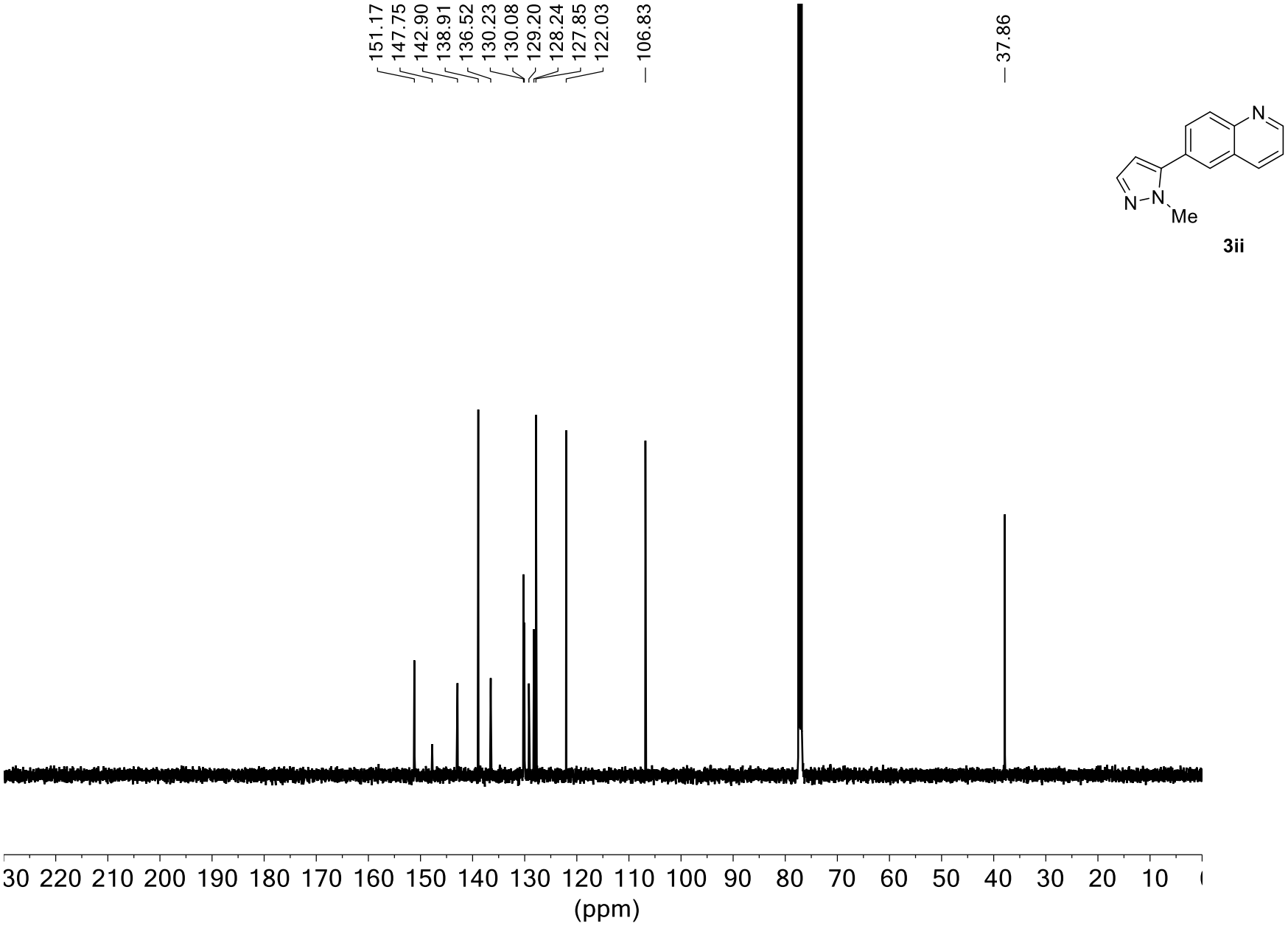
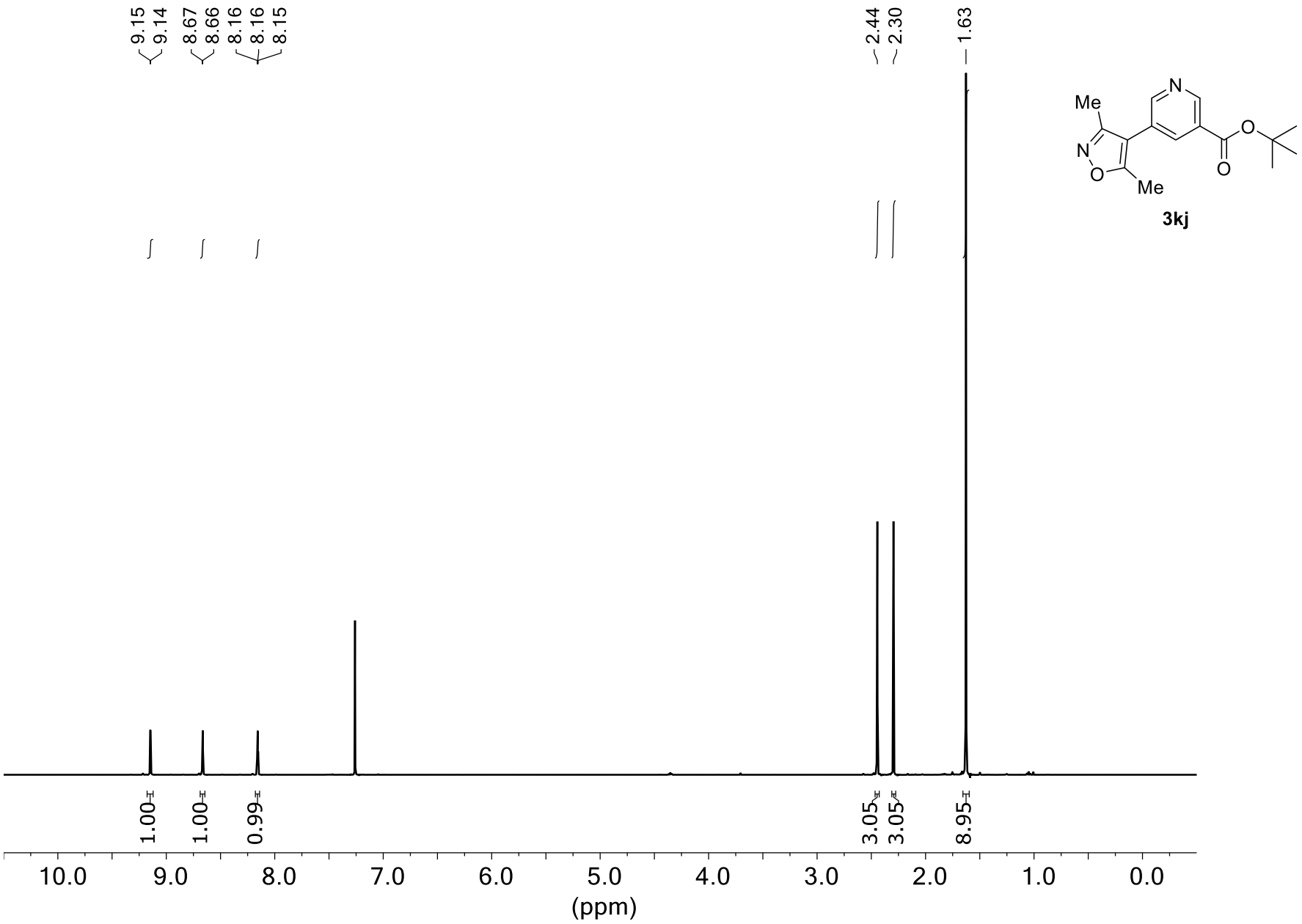
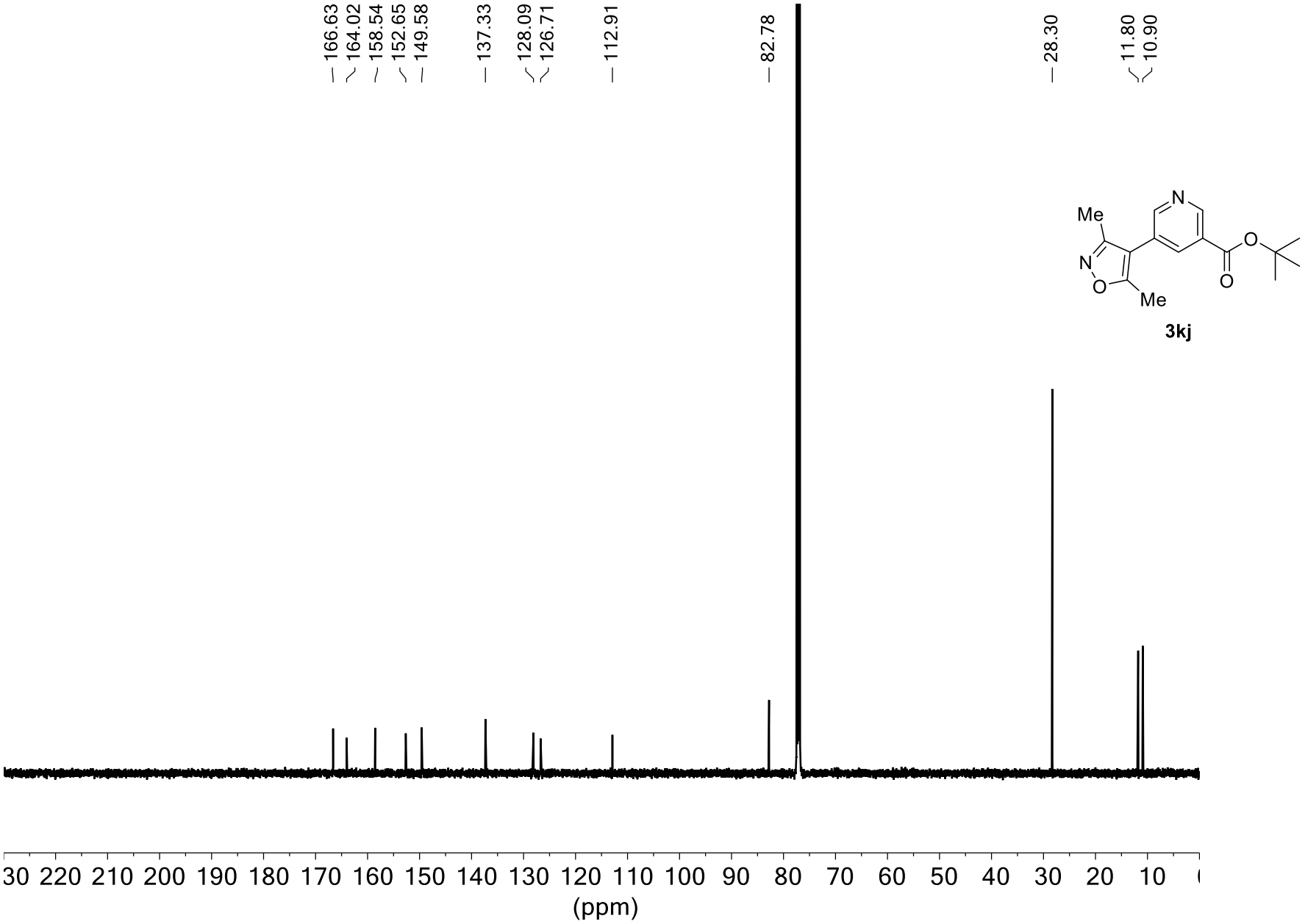
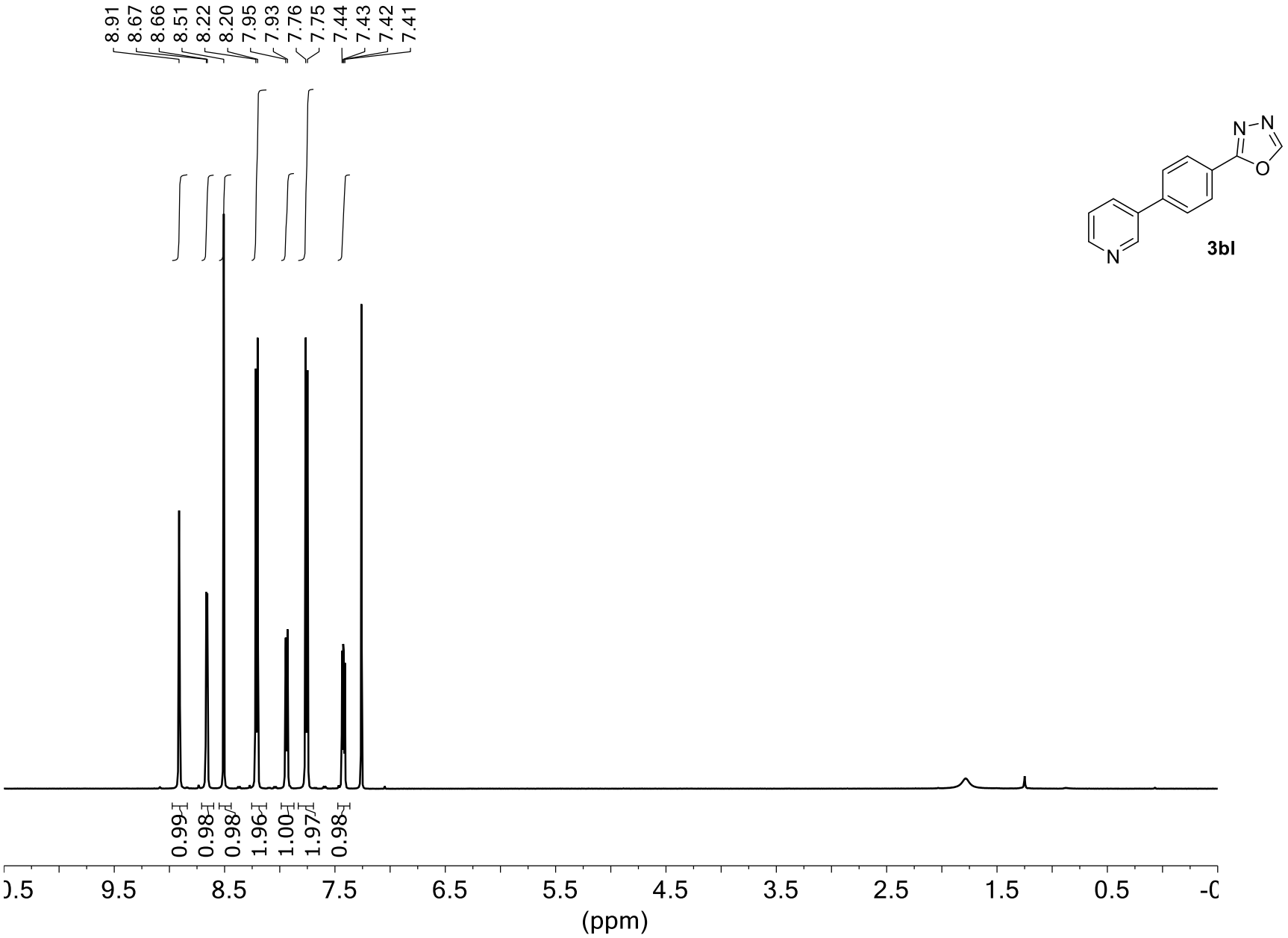
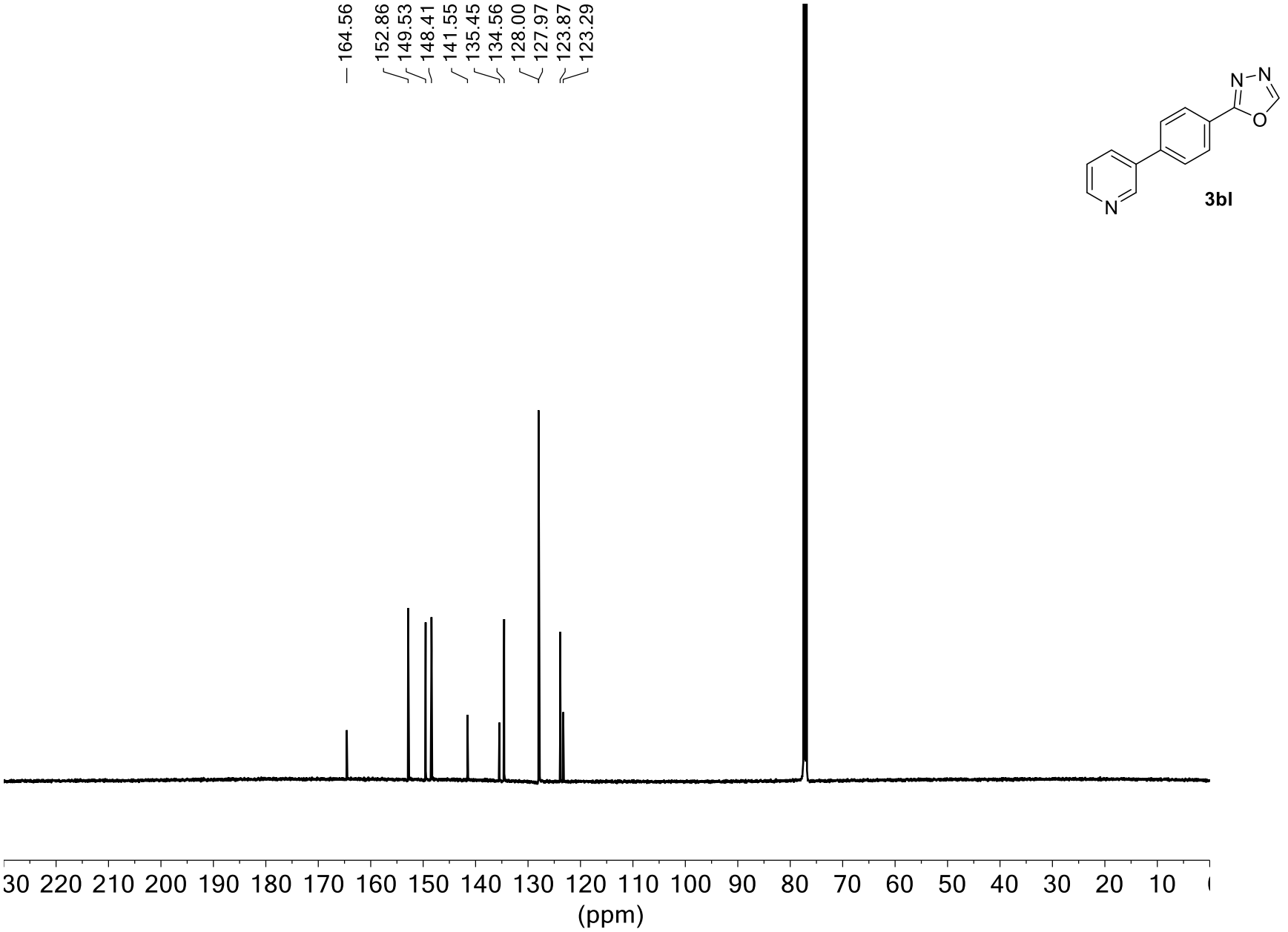
8.98
8.98
8.97
8.23
8.22
8.20
7.88
7.88
7.80
7.79
7.78
7.78
7.58
7.57
7.50
7.49
7.48
7.47
6.44
6.43
3.97
N
N
N
Me
3ii
1.00
2.02
1.00
1.02
1.01
1.02
1.00
3.00
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
(ppm)

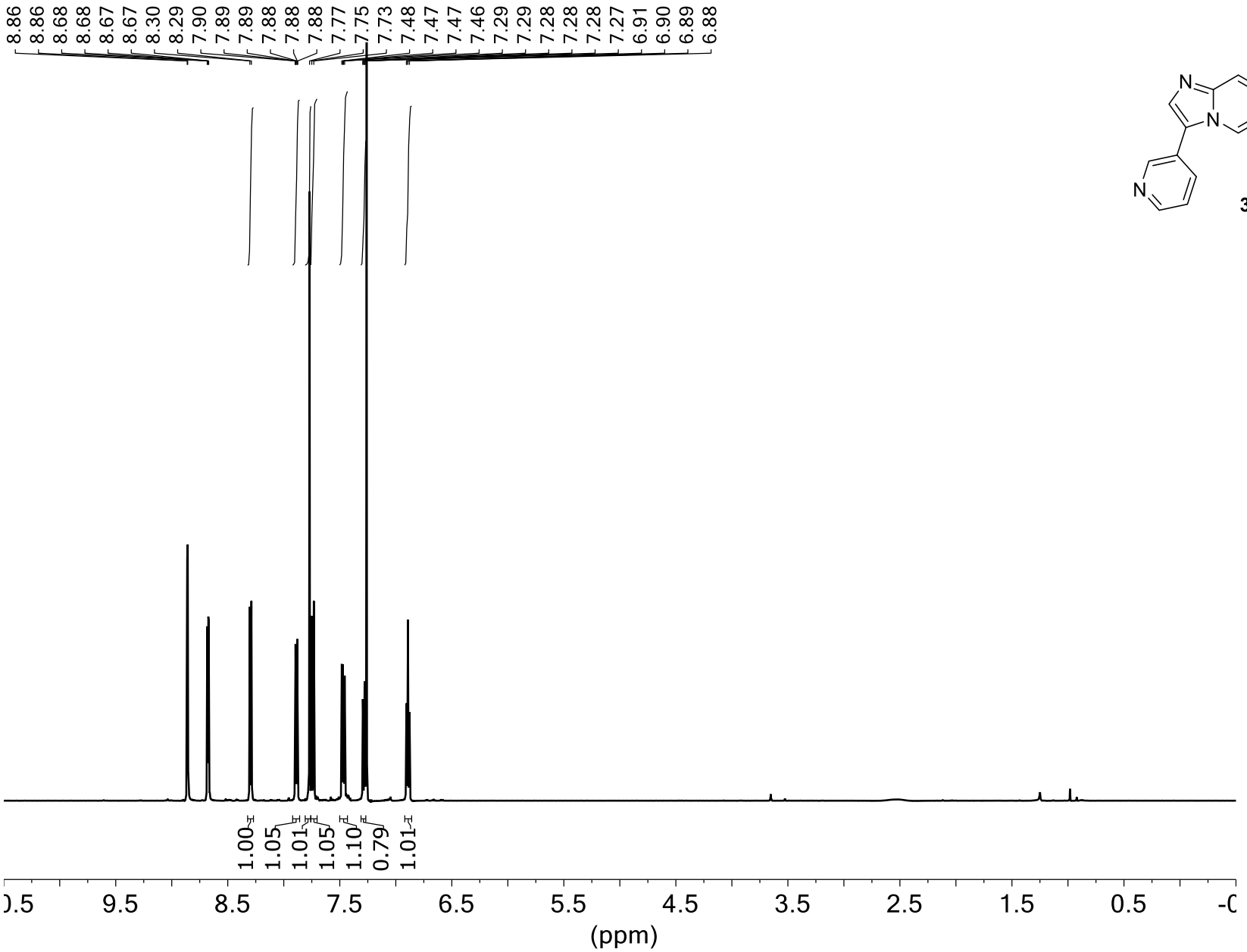

151.17
147.75
142.90
138.91
136.52
130.23
130.08
129.20
128.24
127.85
122.03
106.83
37.86
N
N
N
Me
3ii
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)


9.15
9.14
8.67
8.66
8.16
8.16
8.15
2.44
2.30
1.63
Me
N
O
Me
N
O
O
3kj
1.00
1.00
0.99
3.05
3.05
8.95
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

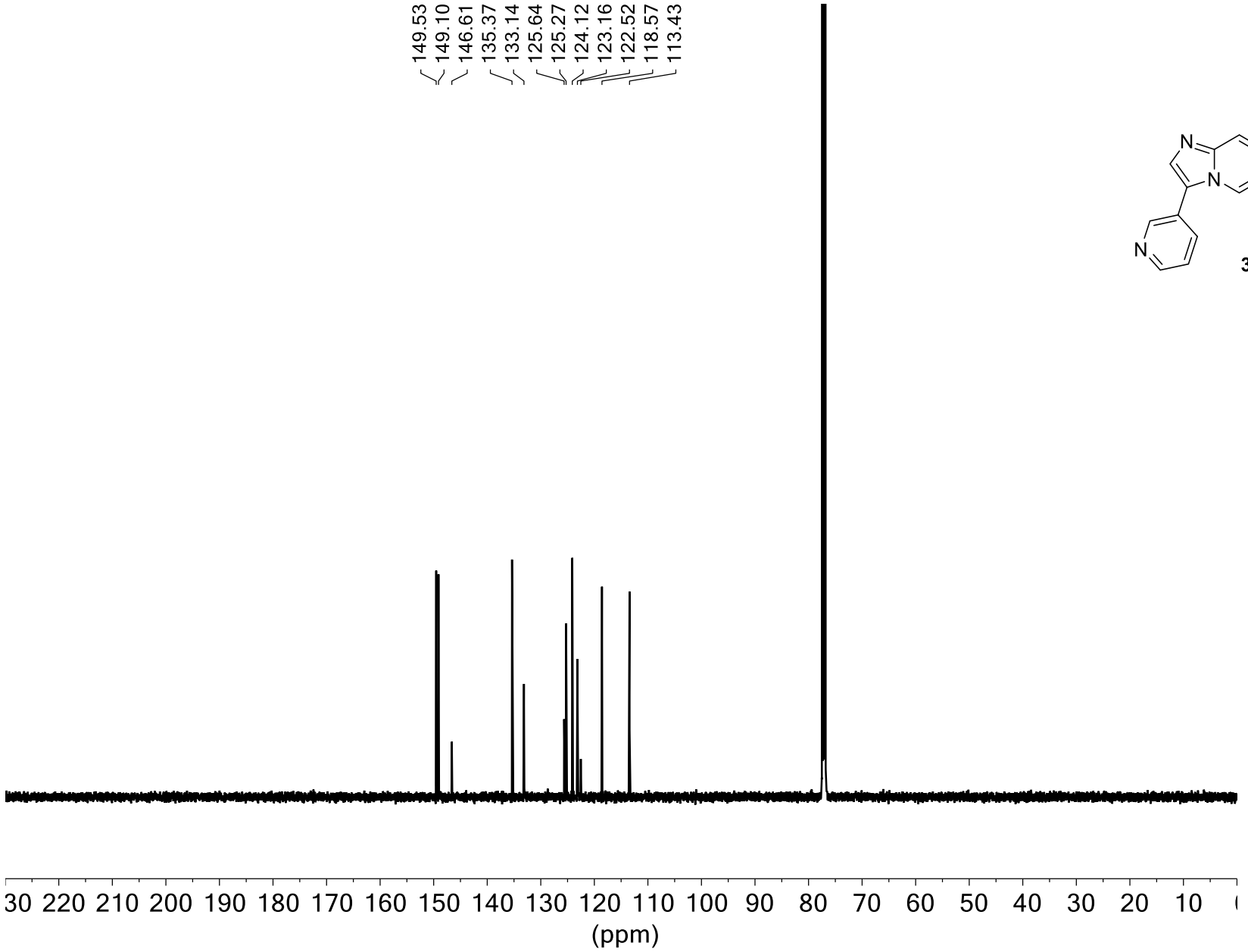

166.63
164.02
158.54
152.65
149.58
137.33
128.09
126.71
112.91
82.78
28.30
11.80
10.90
Me
N
O
Me
N
O
O
3kj
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

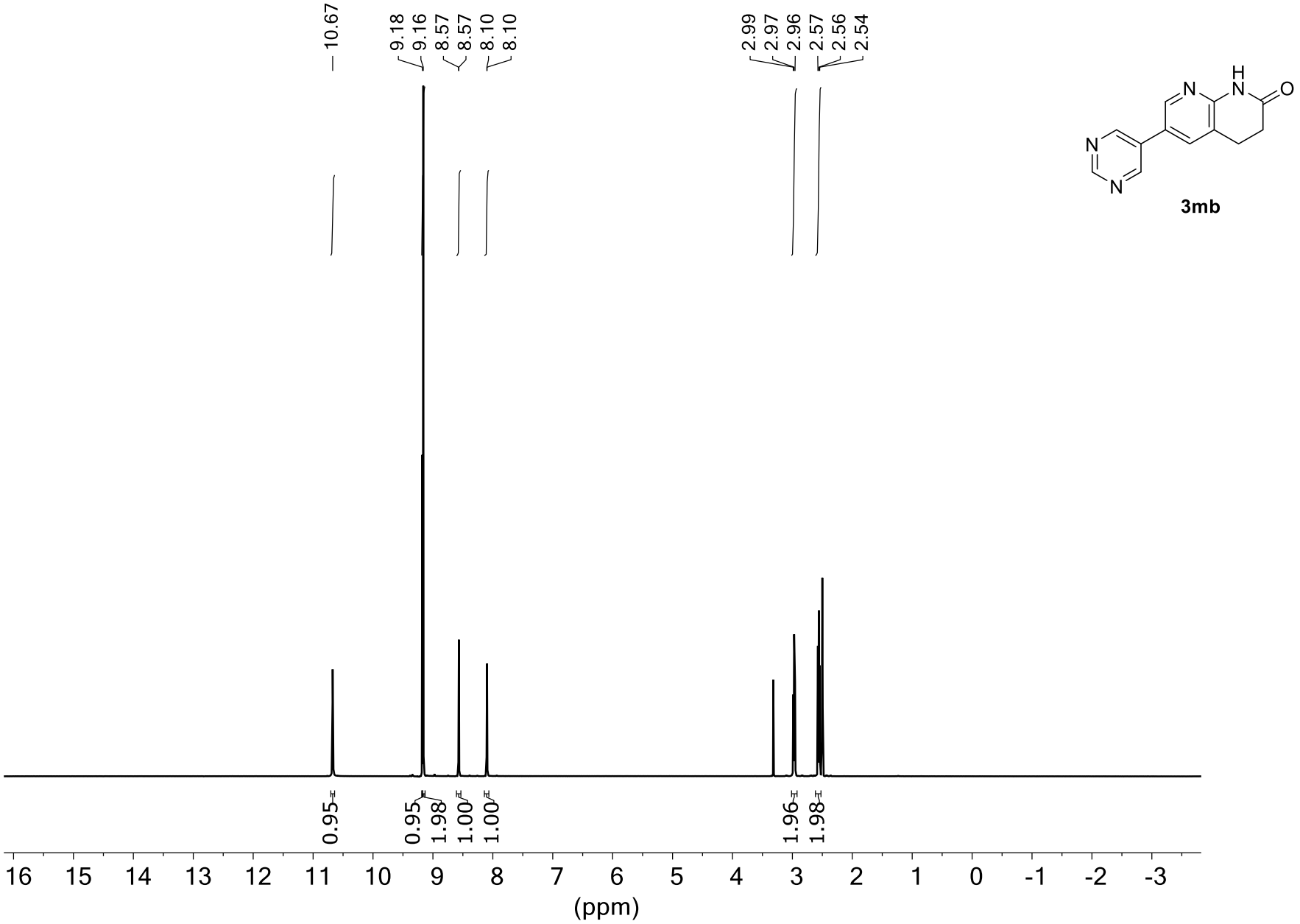

8.91
8.67
8.66
8.51
8.22
8.20
7.95
7.93
7.76
7.75
7.44
7.43
7.42
7.41
0.99
0.98
0.98
1.96
1.00
1.97
0.98
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
(ppm)
N
N
O
N
3bl

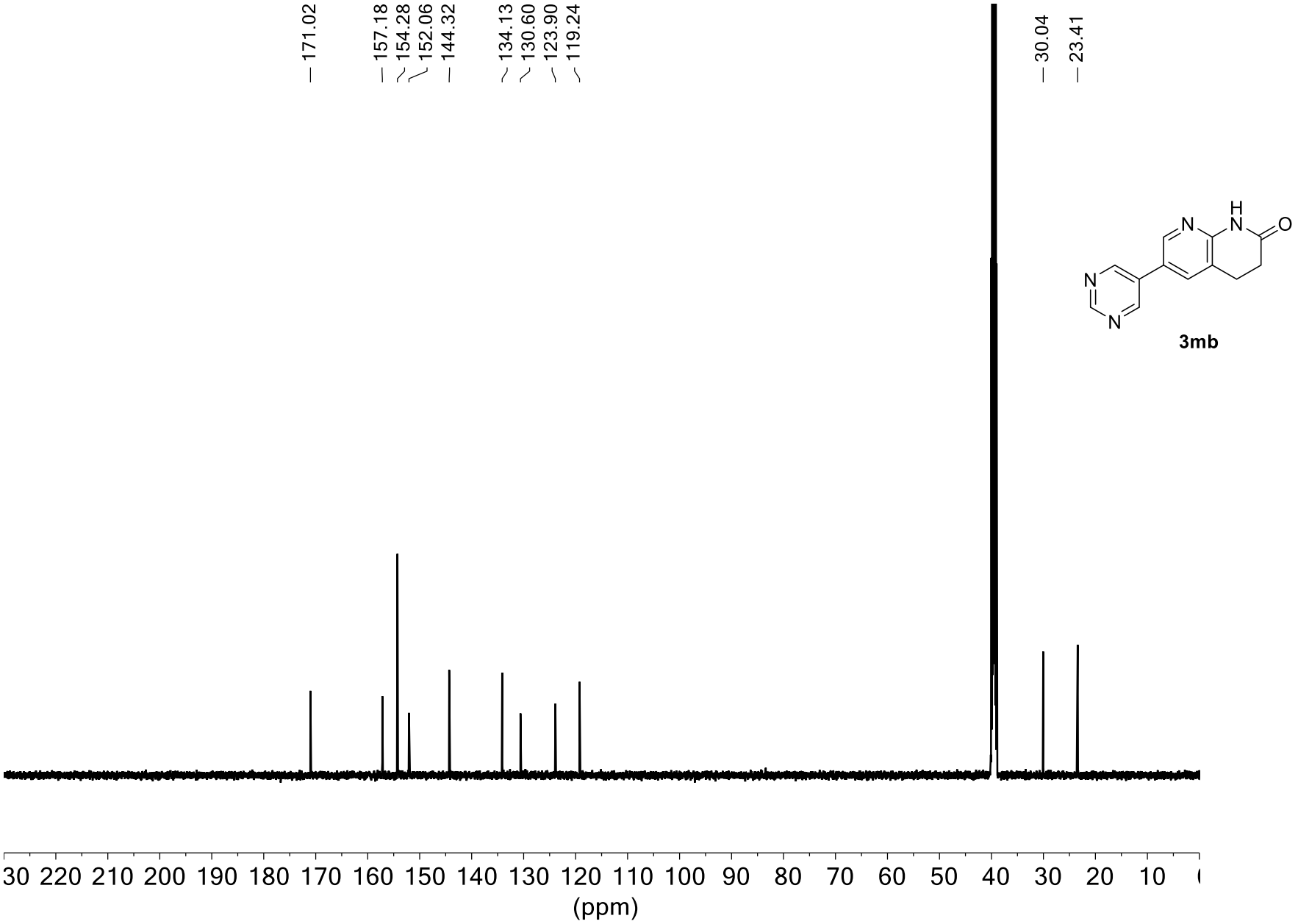

164.56
152.86
149.53
148.41
141.55
135.45
134.56
128.00
127.97
123.87
123.29
N
N
O
N
3bl
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

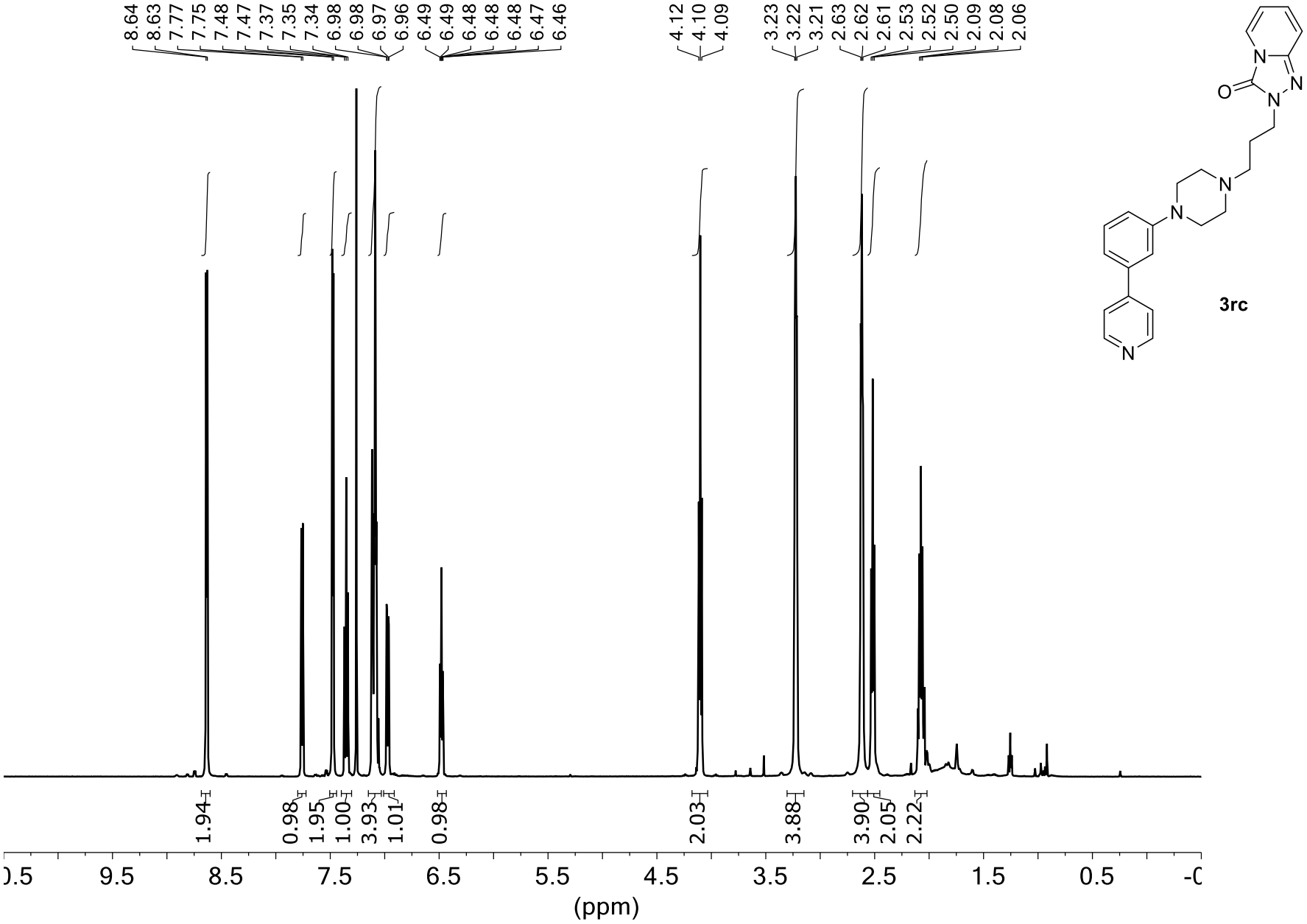

8.86
8.86
8.68
8.68
8.67
8.67
8.30
8.29
7.90
7.89
7.89
7.88
7.88
7.88
7.77
7.75
7.73
7.48
7.47
7.47
7.46
7.29
7.29
7.28
7.28
7.28
7.27
6.91
6.90
6.89
6.88
1.00
1.05
1.01
1.05
1.10
0.79
1.01
(ppm)

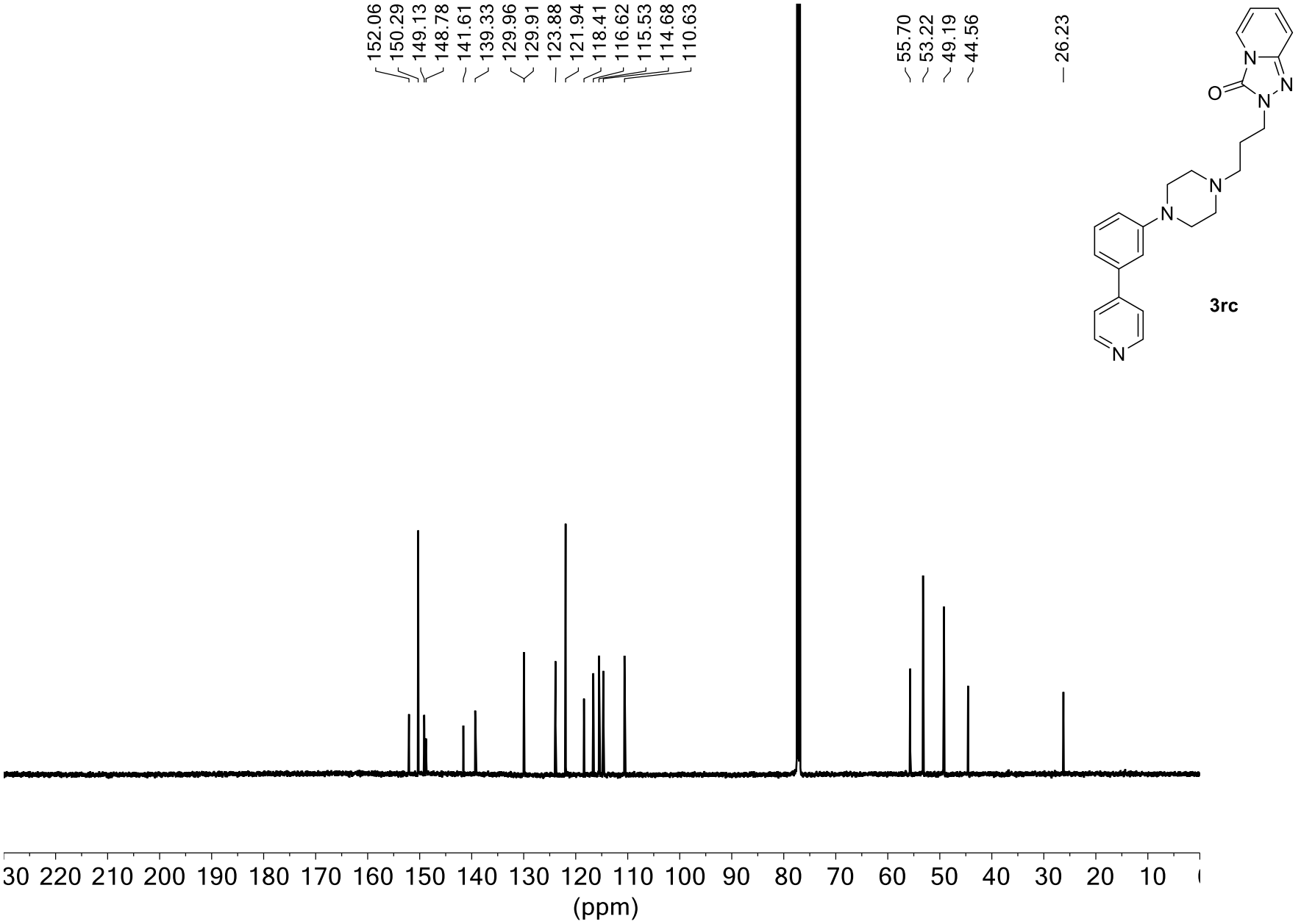
3pl

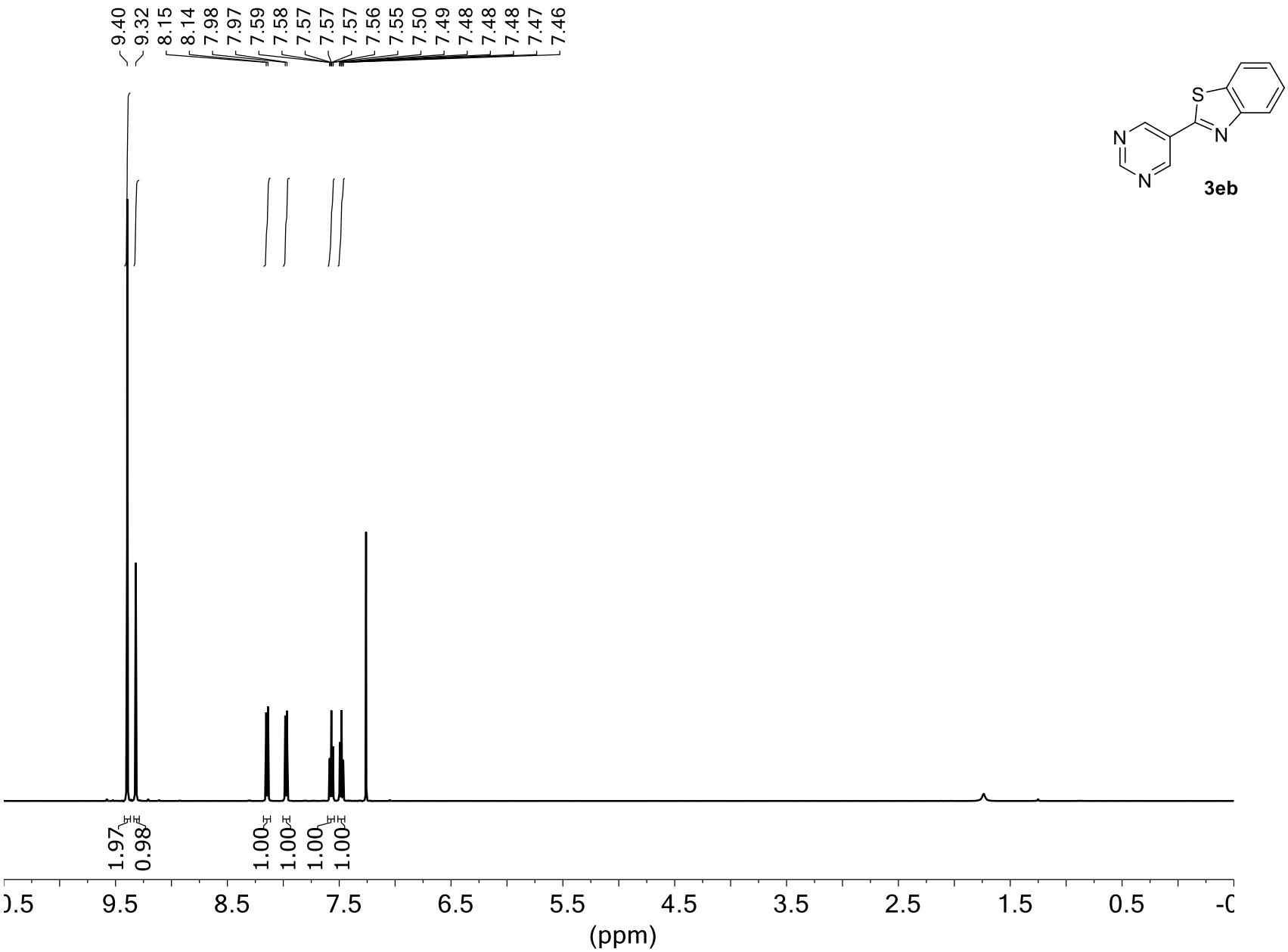

149.53
149.10
146.61
135.37
133.14
125.64
125.27
124.12
123.16
122.52
118.57
113.43
N
N
N
3pl
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

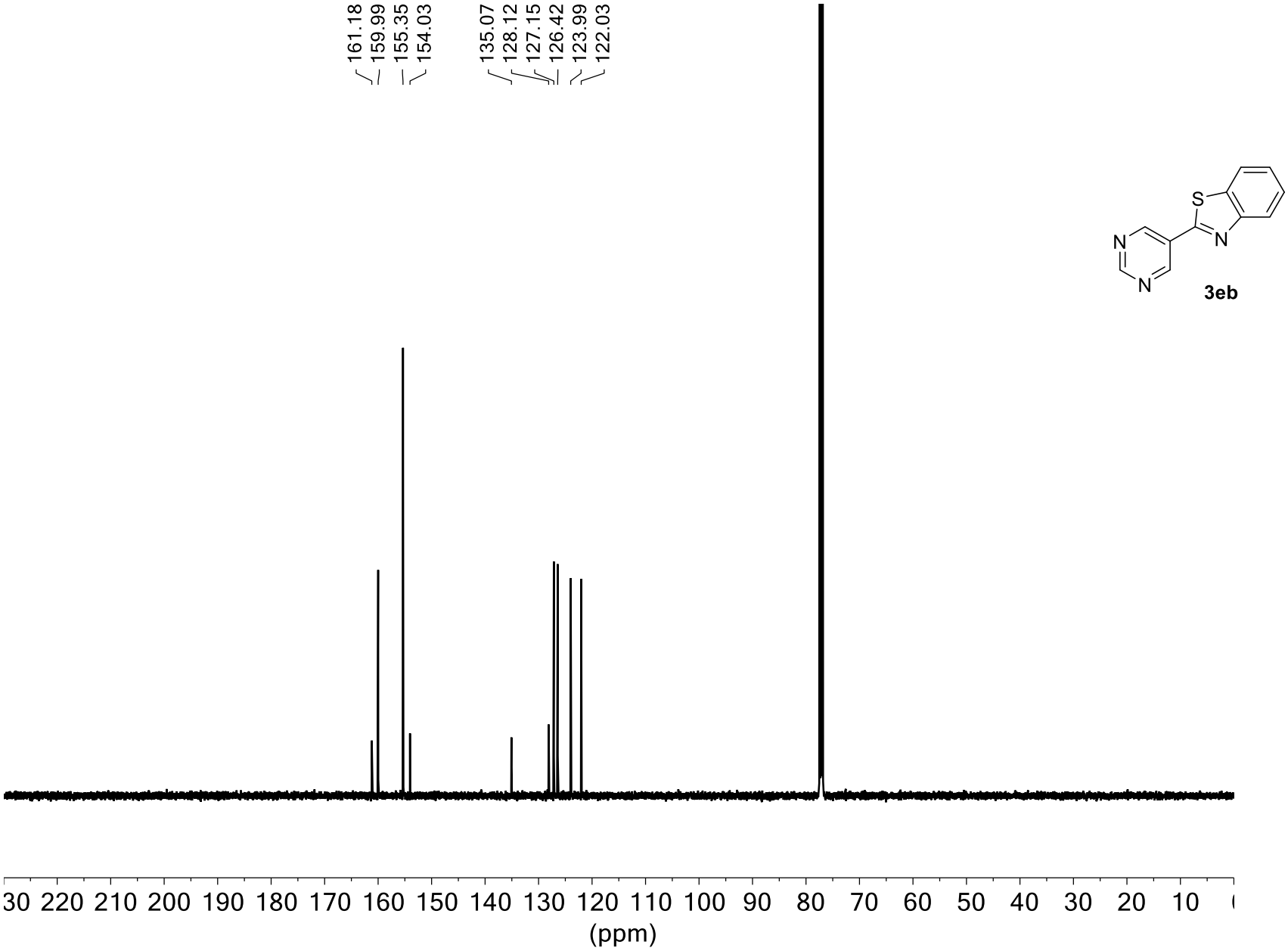

10.67
9.18
9.16
8.57
8.57
8.10
8.10
2.99
2.97
2.96
2.57
2.56
2.54
0.95
0.95
1.98
1.00
1.00
1.96
1.98
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
(ppm)
N
H
N
O
N
N
3mb

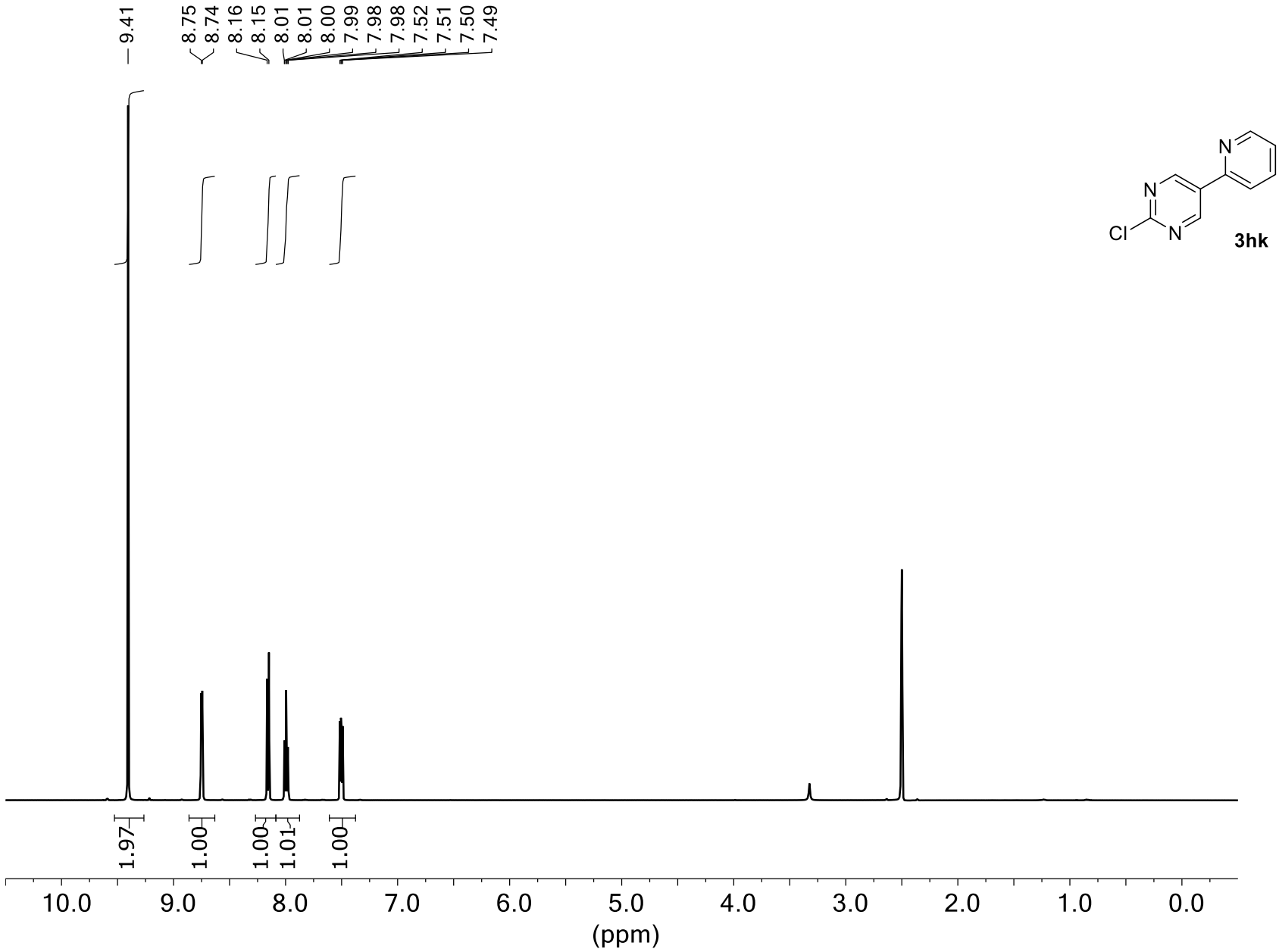

171.02
157.18
154.28
152.06
144.32
134.13
130.60
123.90
119.24
30.04
23.41
3mb
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

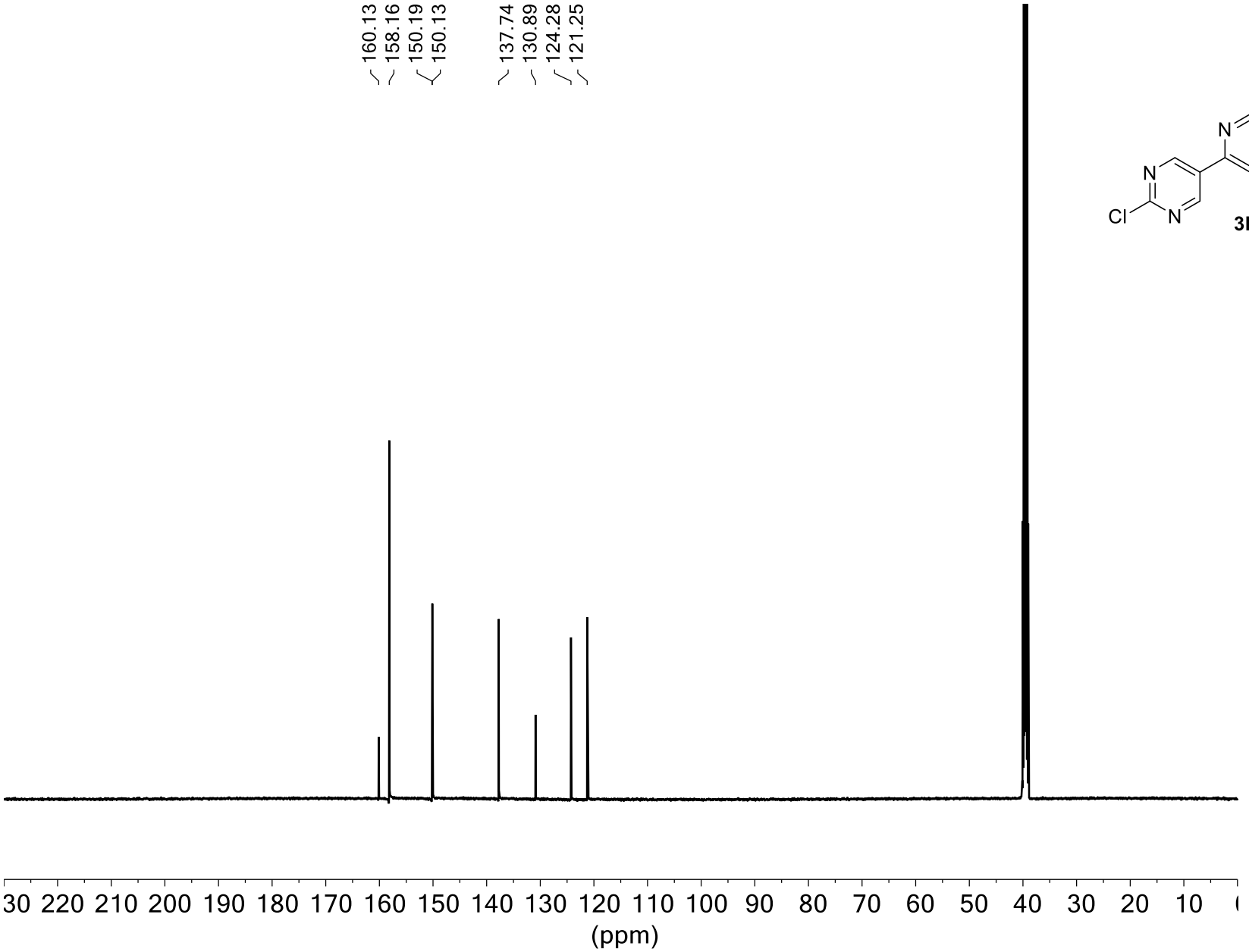

8.64
8.63
7.77
7.75
7.48
7.47
7.37
7.35
7.34
6.98
6.98
6.97
6.96
6.49
6.49
6.48
6.48
6.48
6.47
6.46
4.12
4.10
4.09
3.23
3.22
3.21
2.63
2.62
2.61
2.53
2.52
2.50
2.09
2.08
2.06
1.94
0.98
1.95
1.00
3.93
1.01
0.98
2.03
3.88
3.90
2.05
2.22
(ppm)
3rc

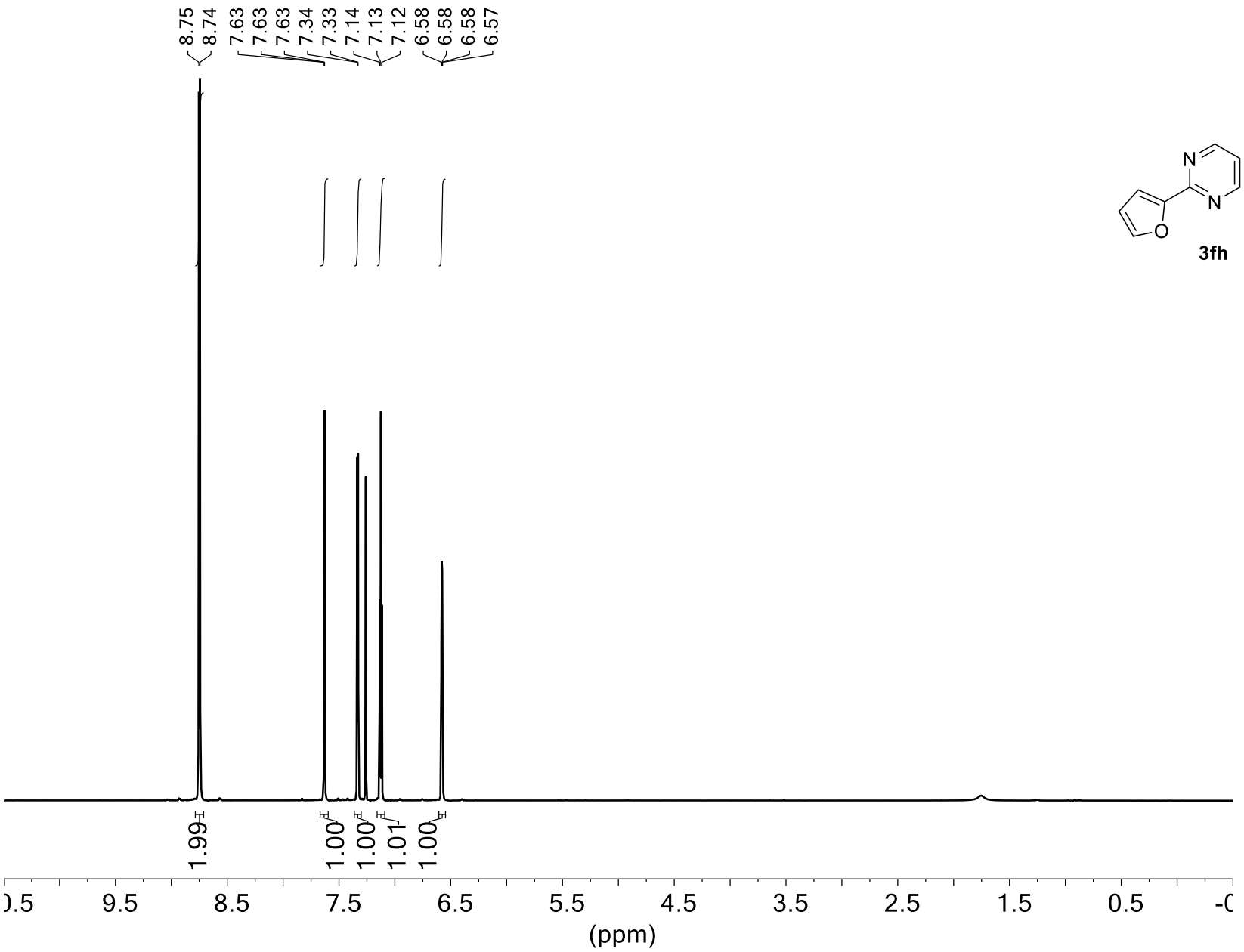

152.06
150.29
149.13
148.78
141.61
139.33
129.96
129.91
123.88
121.94
118.41
116.62
115.53
114.68
110.63
55.70
53.22
49.19
44.56
26.23
3rc
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

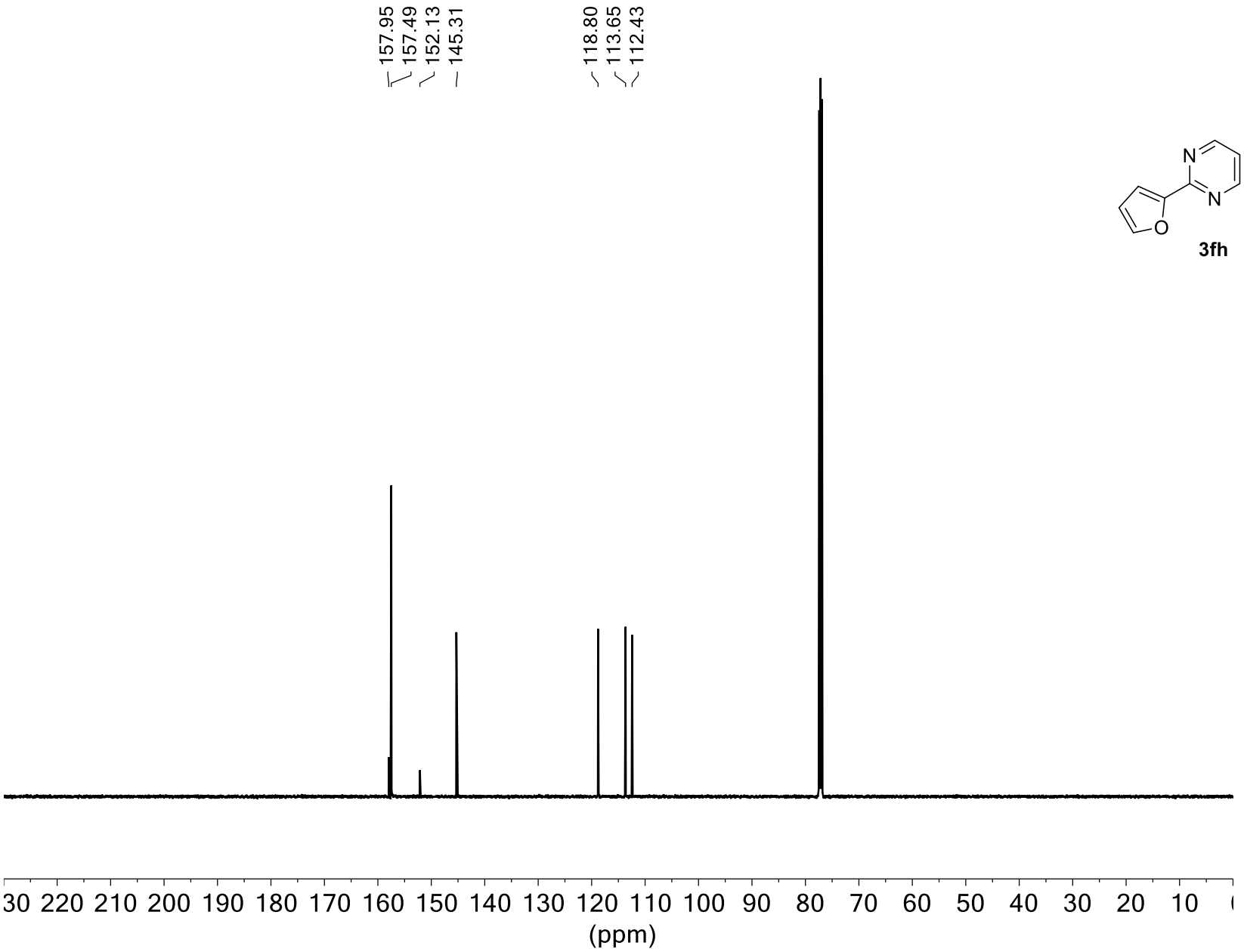

9.40
9.32
8.15
8.14
7.98
7.97
7.59
7.58
7.57
7.57
7.57
7.56
7.55
7.50
7.49
7.48
7.48
7.48
7.47
7.46
S
N
N
N
3eb
1.97
0.98
1.00
1.00
1.00
1.00
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
(ppm)

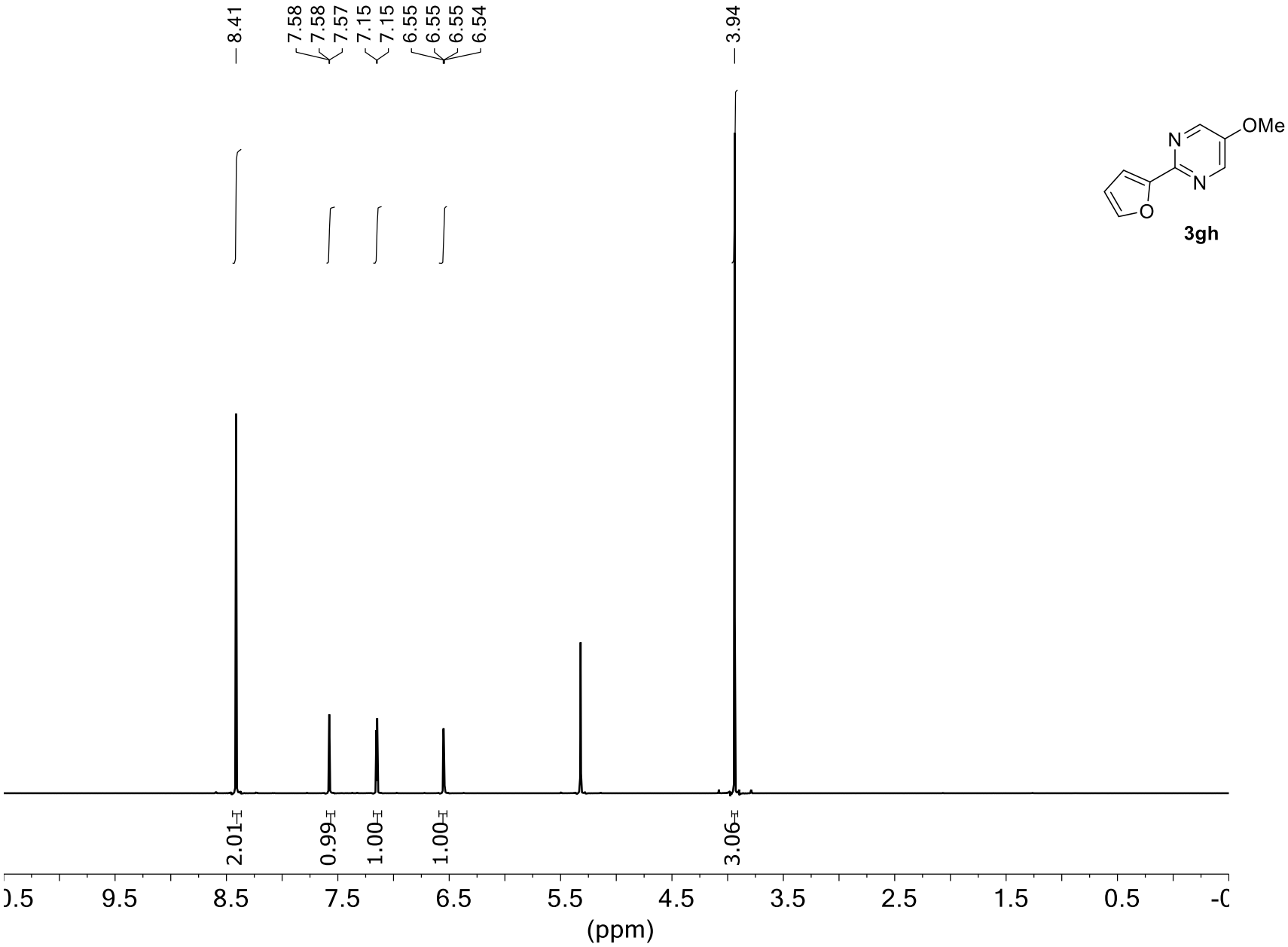

161.18
159.99
155.35
154.03
135.07
128.12
127.15
126.42
123.99
122.03
S
N
N
N
3eb
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

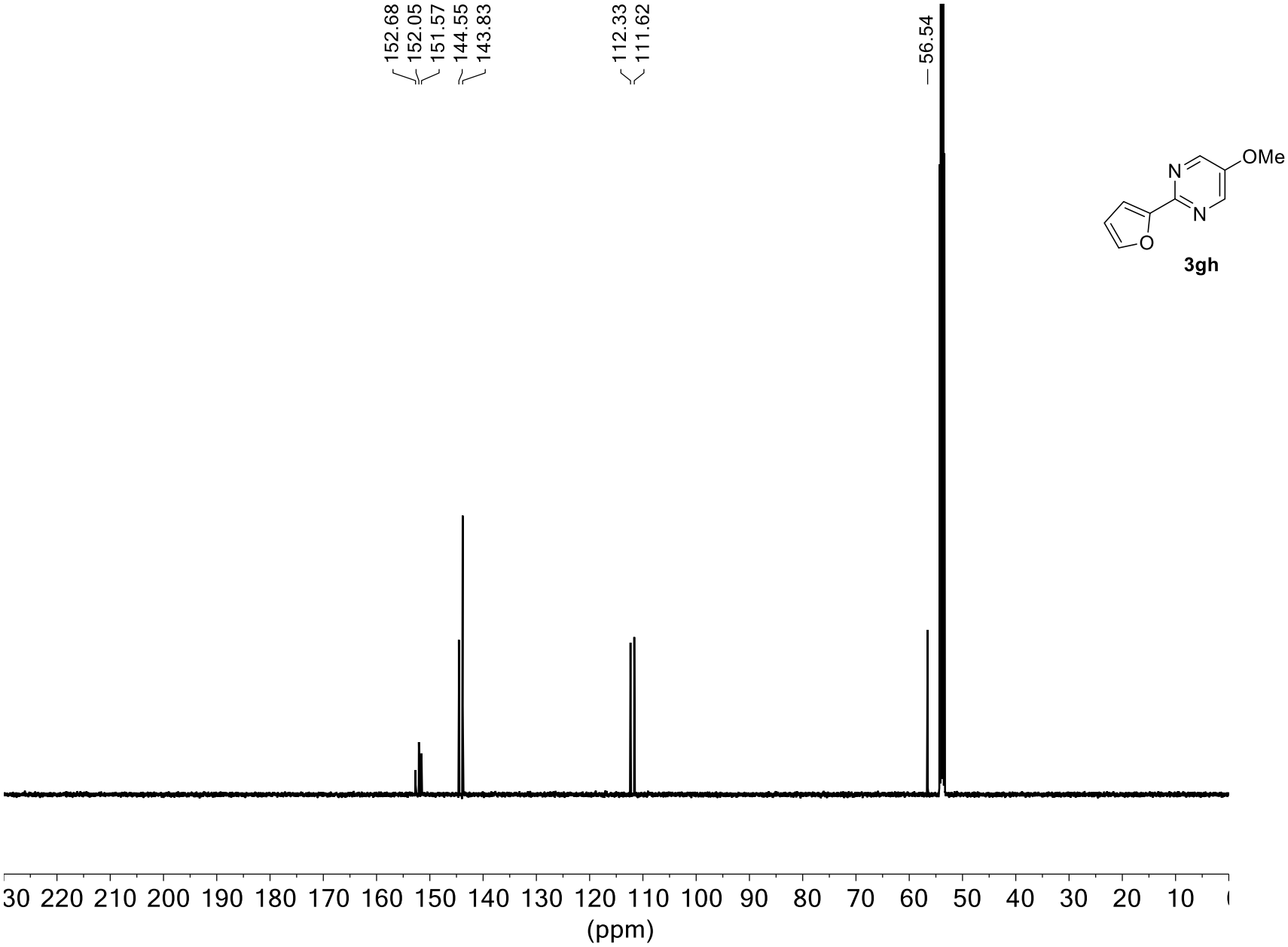

9.41
8.75
8.74
8.16
8.15
8.01
8.01
8.00
7.99
7.98
7.98
7.52
7.51
7.50
7.49
N
N
Cl
N
3hk
1.97
1.00
1.00
1.01
1.00
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

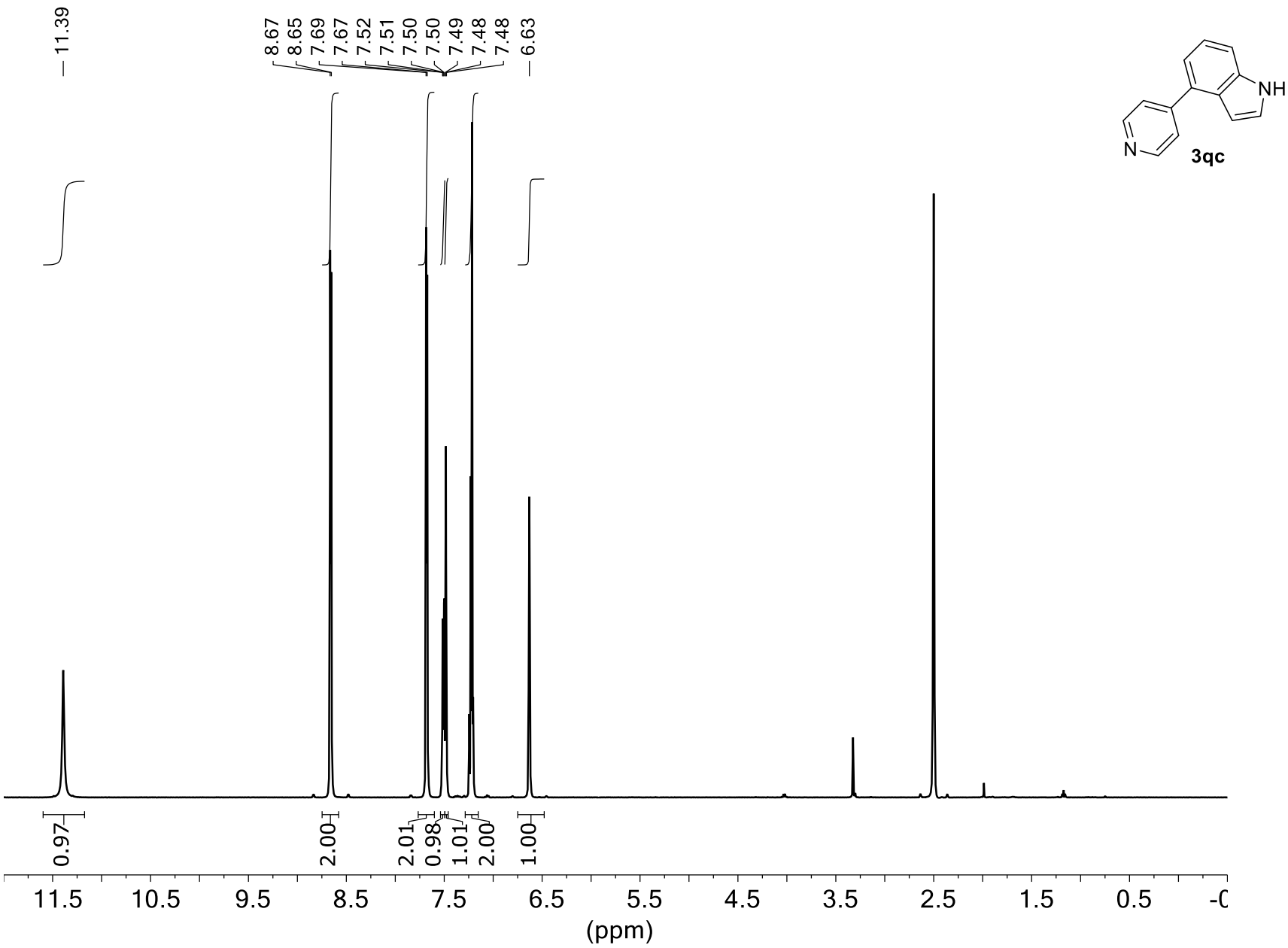

160.13
158.16
150.19
150.13
137.74
130.89
124.28
121.25
N
N
Cl
N
3hk
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

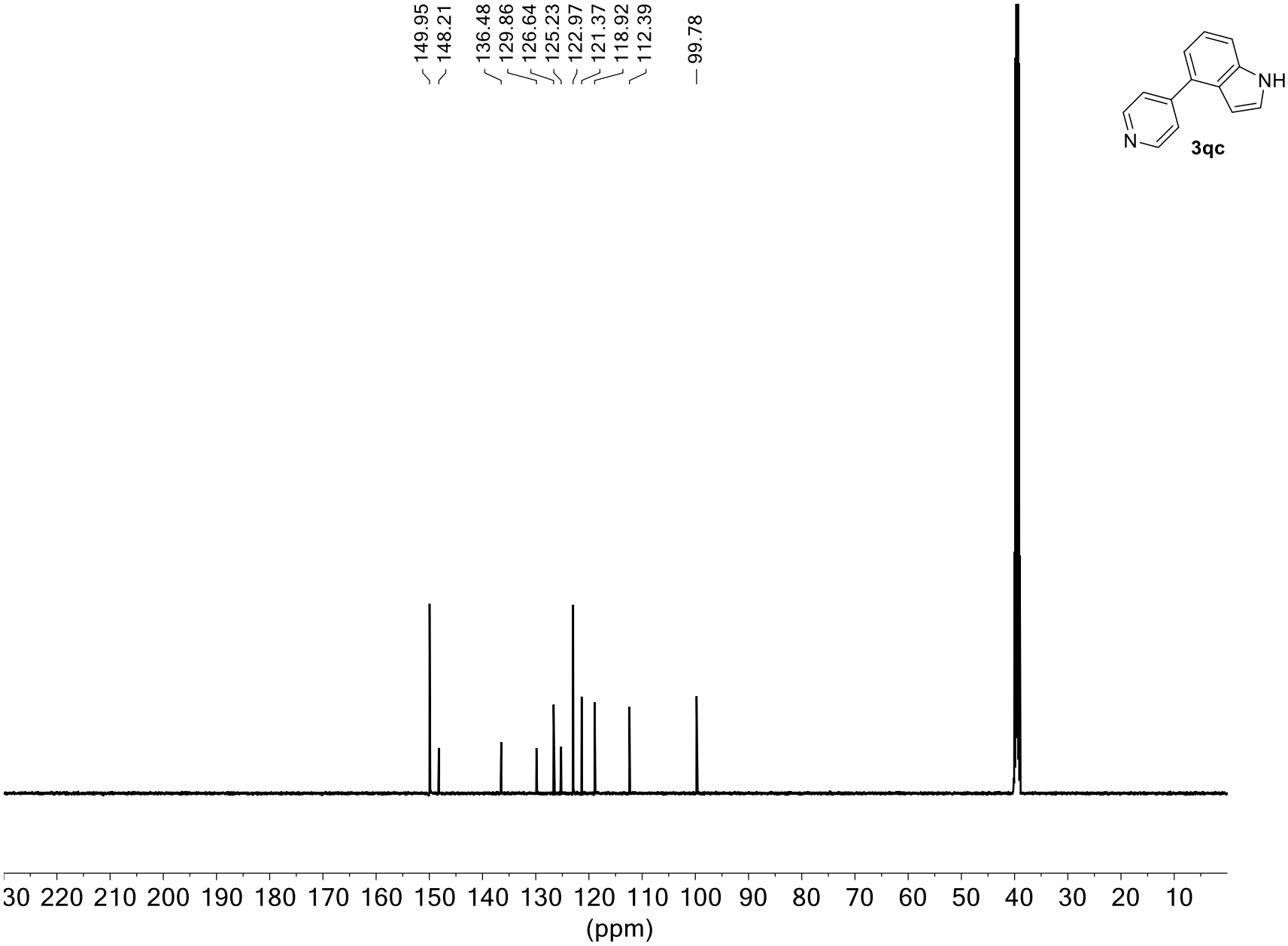

8.75
8.74
7.63
7.63
7.63
7.34
7.33
7.14
7.13
7.12
6.58
6.58
6.58
6.57
N
N
O
3fh
1.99
1.00
1.00
1.01
1.00
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
(ppm)

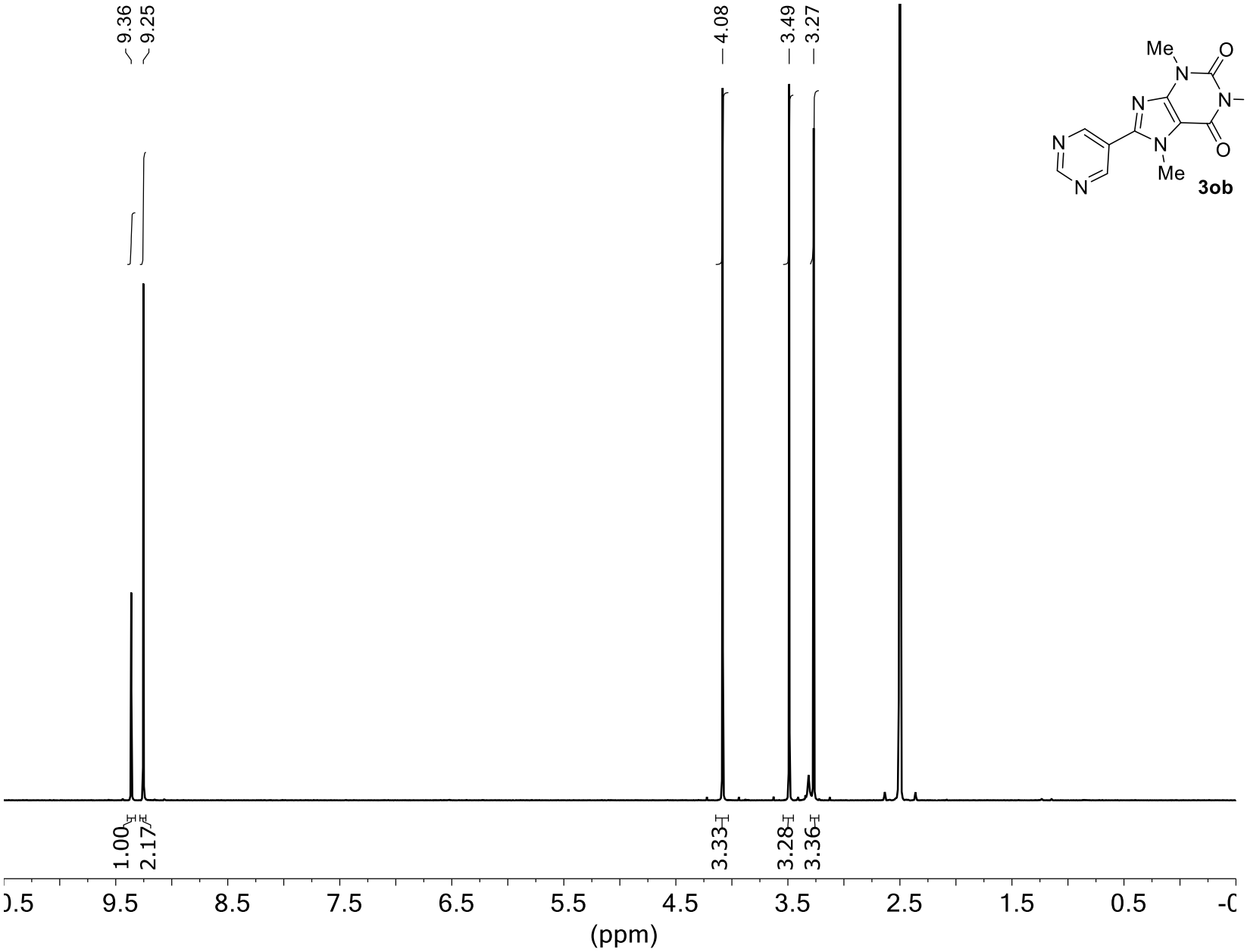

157.95
157.49
152.13
145.31
118.80
113.65
112.43
N
N
O
3fh
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

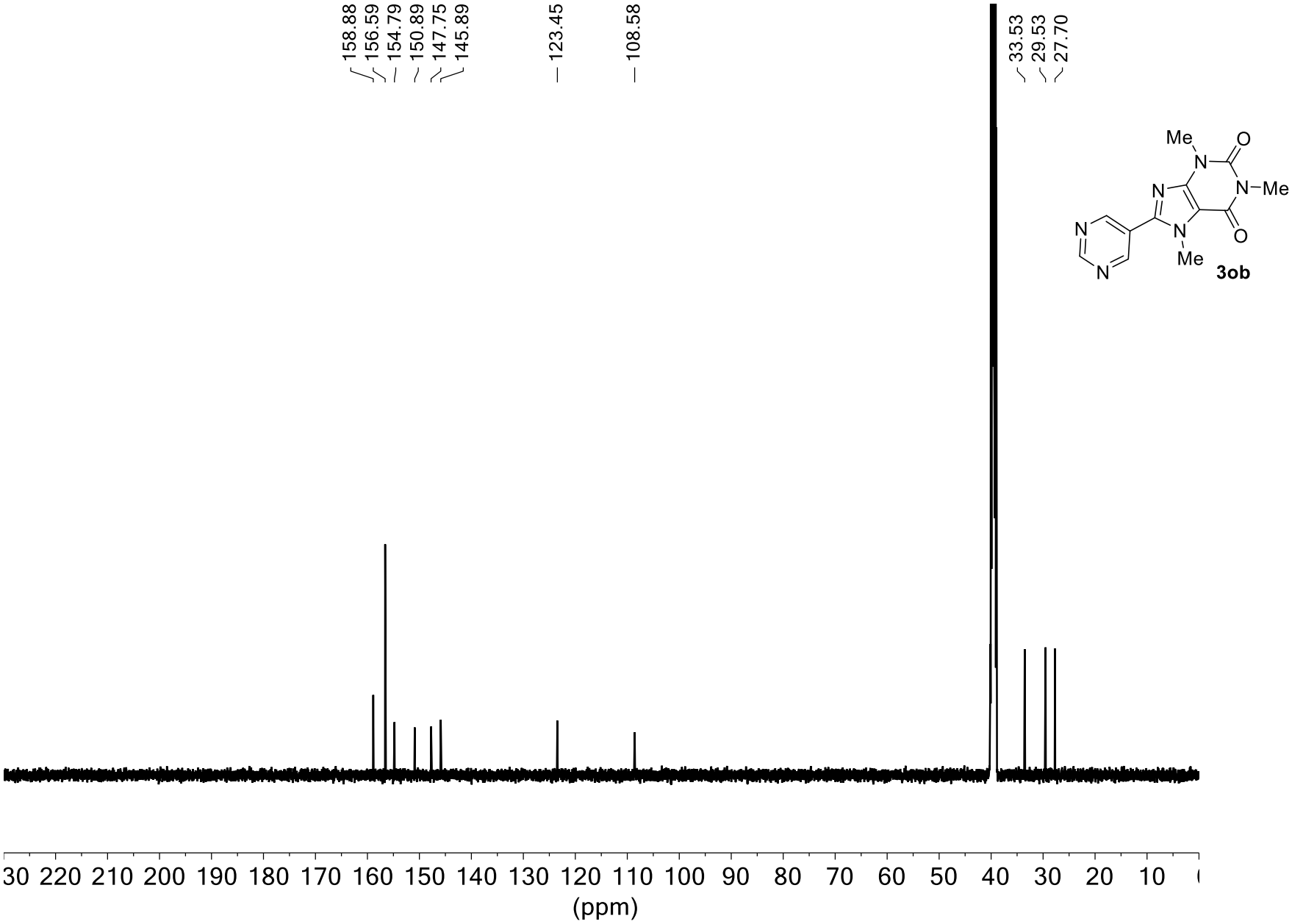

8.41
7.58
7.58
7.57
7.15
7.15
6.55
6.55
6.55
6.54
3.94
OMe
N
N
O
3gh
2.01
0.99
1.00
1.00
3.06
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
(ppm)

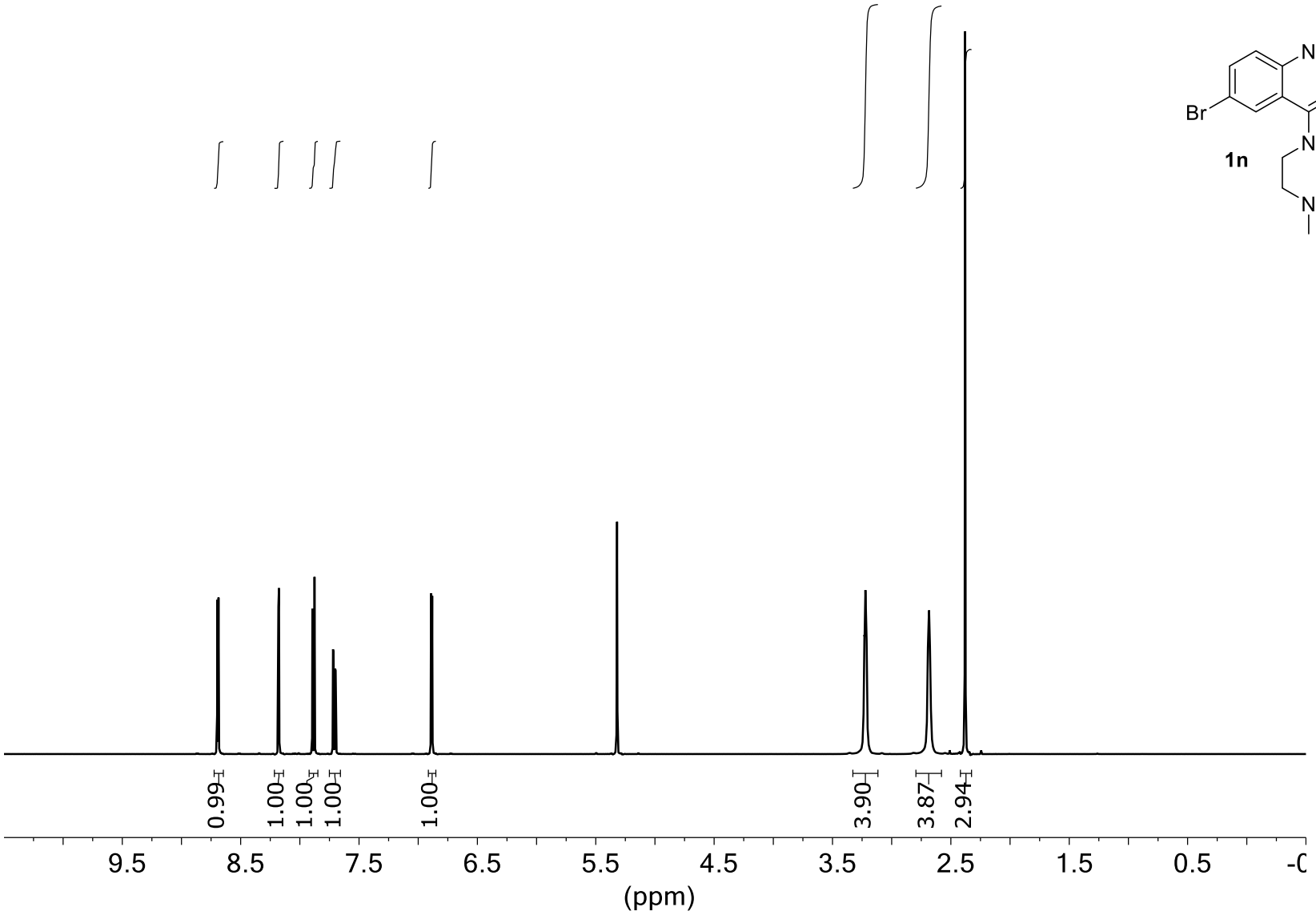

152.68
152.05
151.57
144.55
143.83
112.33
111.62
56.54
OMe
N
N
O
3gh
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

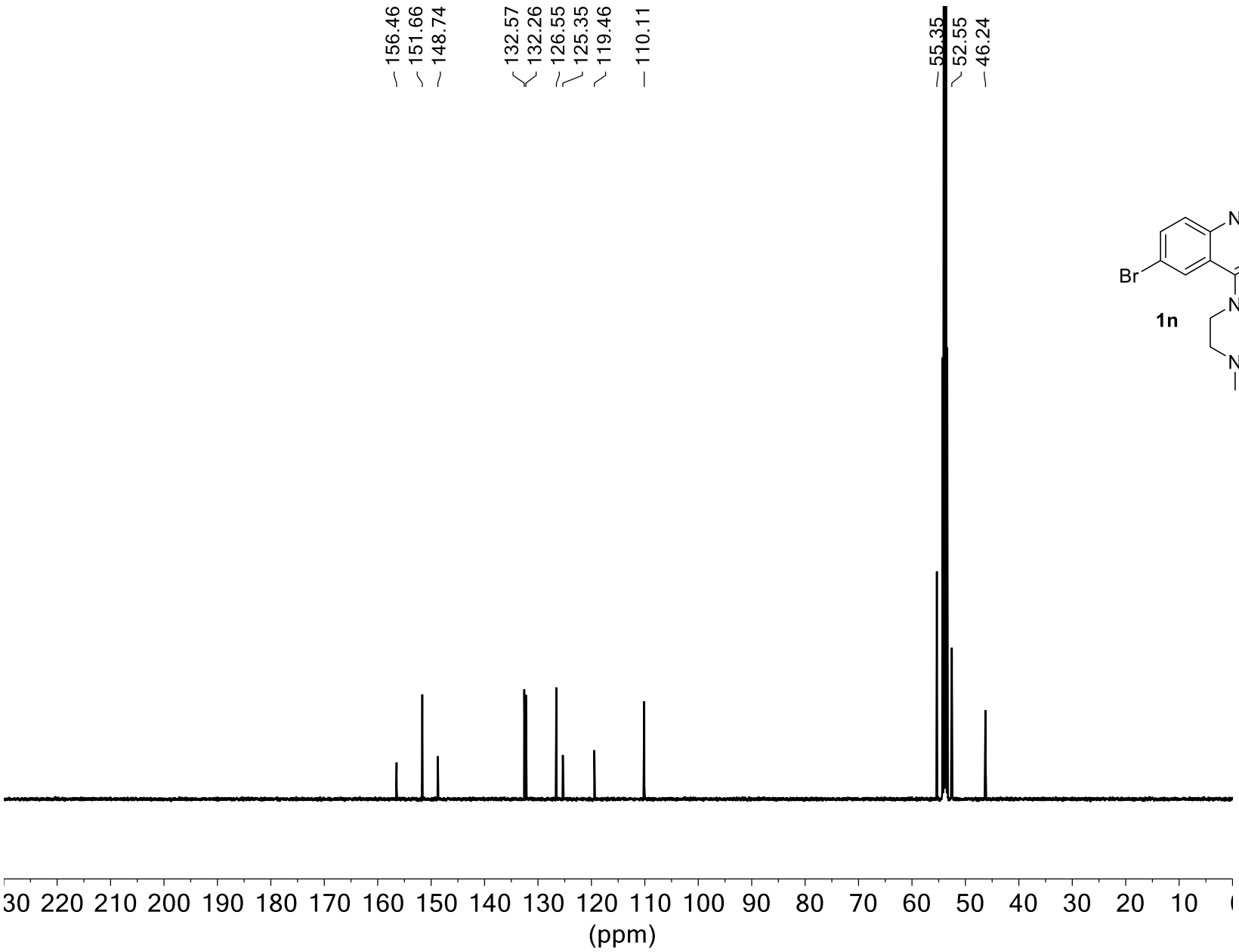

11.39
8.67
8.65
7.69
7.67
7.52
7.51
7.50
7.50
7.49
7.48
7.48
6.63
NH
N
3qc
0.97
2.00
2.01
0.98
1.01
2.00
1.00
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
(ppm)

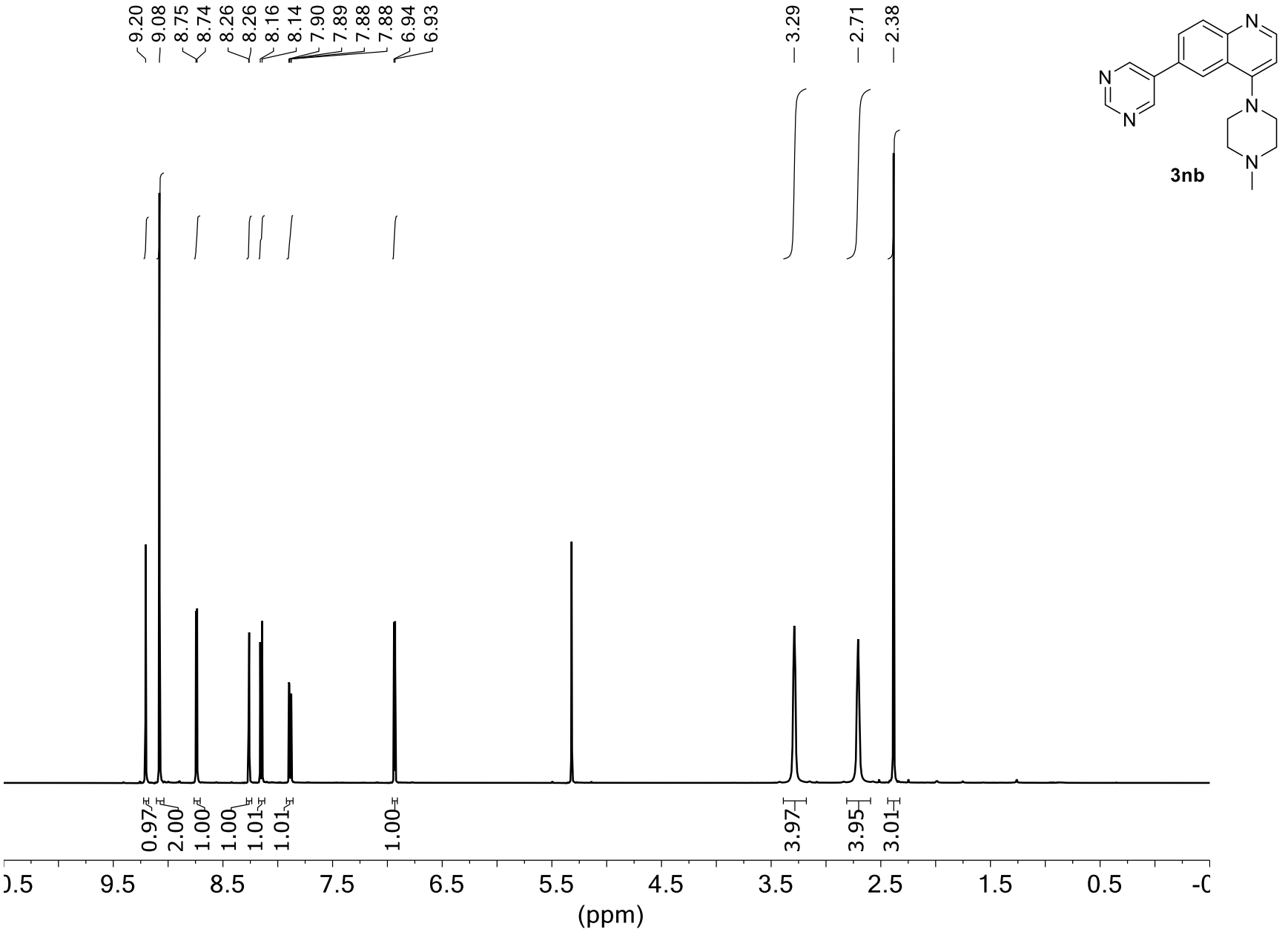

149.95
148.21
136.48
129.86
126.64
125.23
122.97
121.37
118.92
112.39
99.78
NH
N
3qc
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

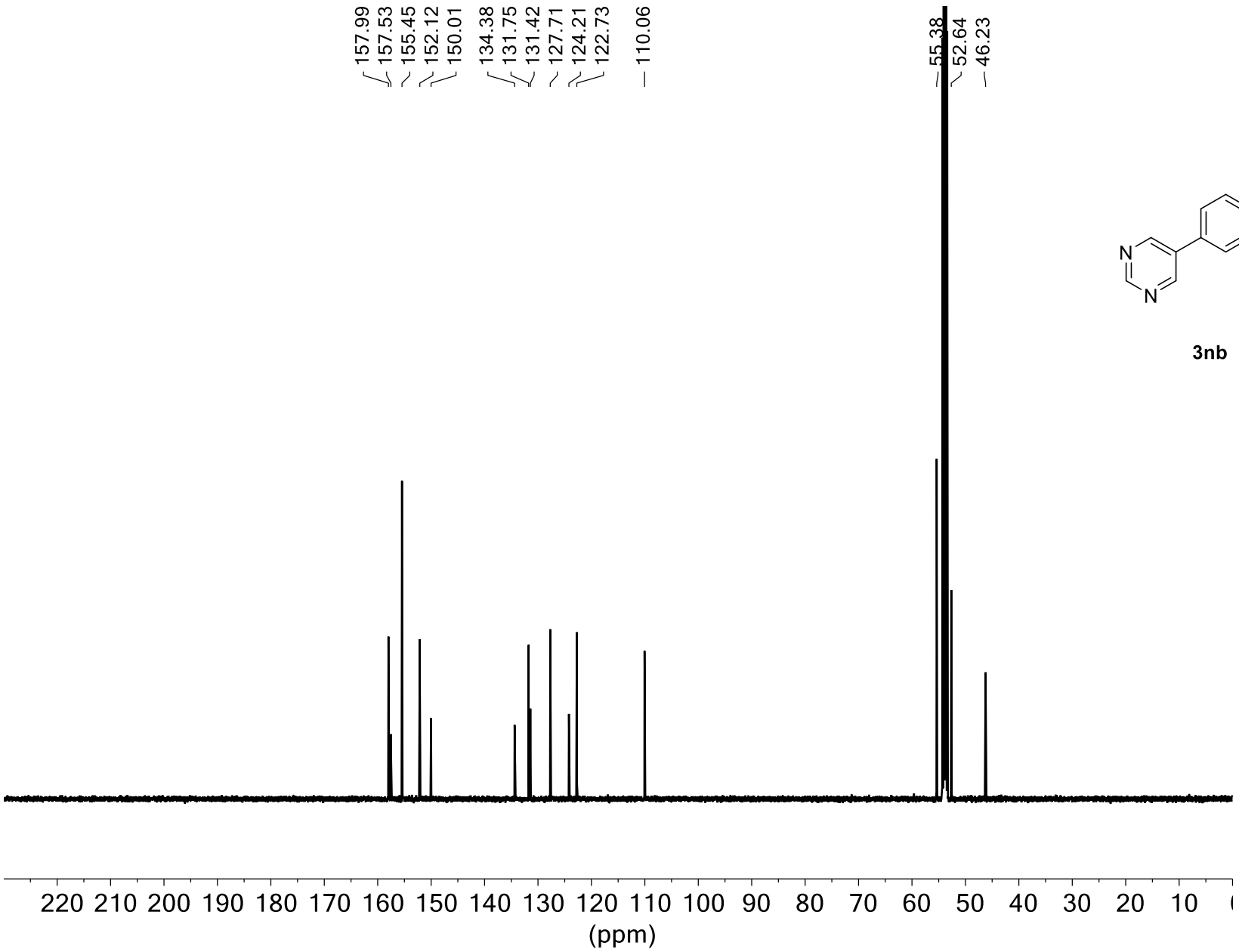

9.36
9.25
4.08
3.49
3.27
1.00
2.17
3.33
3.28
3.36
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
(ppm)
Me
N
O
N–Me
N
N
Me
O
N
N
3ob


158.88
156.59
154.79
150.89
147.75
145.89
123.45
108.58
33.53
29.53
27.70
Me
N
O
N
N–Me
N
N
O
Me
3ob
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)


Br
N
N
N
1n
0.99
1.00
1.00
1.00
1.00
3.90
3.87
2.94
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
(ppm)


156.46
151.66
148.74
132.57
132.26
126.55
125.35
119.46
110.11
55.35
52.55
46.24
Br
N
N
N
1n
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)


9.20
9.08
8.75
8.74
8.26
8.26
8.16
8.14
7.90
7.89
7.88
7.88
6.94
6.93
3.29
2.71
2.38
0.97
2.00
1.00
1.00
1.01
1.01
1.00
3.97
3.95
3.01
3nb
(ppm)


157.99
157.53
155.45
152.12
150.01
134.38
131.75
131.42
127.71
124.21
122.73
110.06
55.38
52.64
46.23
3nb
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)