Development of a Convenient and Versatile S_NAr-Decarboxylation Protocol for the Construction of $C(sp^2)$-$C(sp^3)$ Bonds

Alexander Burtea[1], Jacob DeForest[1], Neil Baldwin[2], Carolyn Leverett[2], and Gary M. Gallego[1]

[1] Pfizer La Jolla Laboratories, 10770 Science Center Drive, San Diego, CA 92121. [2] Pfizer Medicine Design, 445 Eastern Point Rd, Groton, CT 06340.

Supporting Information Table of Contents

I. General Experimental Details

All commercially obtained reagents were used as received. Anhydrous toluene was purchased from EMD Millipore and used received. LiHMDS was purchased as a 1 M solution in THF from Sigma-Aldrich and used as received. DABCO was purchased from Sigma-Aldrich and used as received. Reaction temperatures were controlled using an IKA mag temperature modulator and reactions were heated using an IKA RCT basic stir plate equipped with aluminum heating blocks. Thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F254) and visualized using UV light. Preparative silica-gel column chromatography was performed using Isco systems in conjunction with pre-packed cartridges. 1H NMR spectra were recorded on Bruker spectrometers (at 400 MHz) and are reported relative to the residual solvent signal. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Bruker spectrometers (at 101 MHz) and are reported relative to the residual solvent signal. Data for proton-carbon decoupled ^{13}C NMR spectra are reported in terms of chemical shift and, when necessary, multiplicity, and coupling constant (Hz) and integration. Rotamers were reported as a mixture of rotamers. High resolution mass spectra were obtained using an Agilent 6230 Accurate Mass TOF LC/MS. Accurate masses are reported for the molecular ion $[M+H]^{+}$ or a suitable ion fragment. Compound numbers used in the experimental section correspond to those employed in the main paper.

II. General Experimental Procedures

General Procedure 1 (GP1): *Used if ester is highly susceptible to Claisen condensation.*

A flask containing aryl halide (1 equiv) was evacuated with vacuum and backfilled with nitrogen gas (3x) before the addition of LiHMDS (2 equiv, 1 M in THF) followed by the dropwise addition of ester (2 equiv, 1 M in PhMe). The reaction mixture was allowed to stir at room temperature for 1 h before adding DABCO (10-15 equiv) and stirring at 85-100 °C until the reaction was deemed complete by LCMS (typically 16-94 h). The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride and extracted with EtOAc (3x). The combined organic layers were dried with sodium sulfate, filtered, concentrated, and purified using flash column chromatography to afford the title compound.

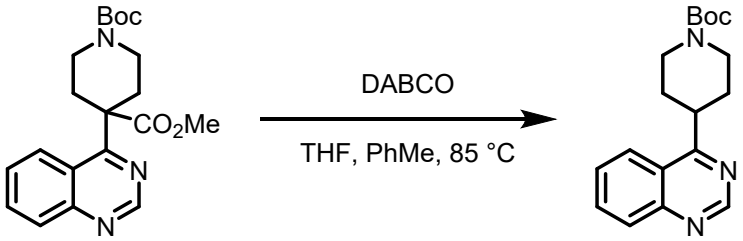
General Procedure 2 (GP2): *Used as most convenient protocol.*

A flask containing aryl halide (1 equiv) was evacuated with vacuum and backfilled with nitrogen gas (3x) before the addition of PhMe (0.5 M) followed by LiHMDS (2 equiv, 1 M in THF). After stirring until the mixture was fully dissolved, the ester (2 equiv) was added. The reaction mixture was allowed to stir at room temperature for 1 h before adding DABCO (10-15 equiv) and stirring at 85-100 °C until the reaction was deemed complete by LCMS (typically 16-94 h). The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride and extracted with EtOAc (3x). The combined organic layers were dried with sodium sulfate, filtered, concentrated, and purified using flash column chromatography to afford the title compound.

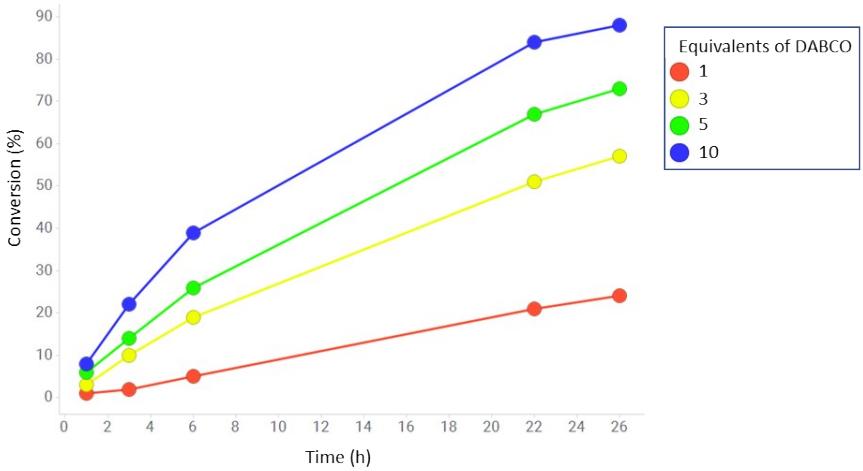
General Procedure 3 (GP3): *Used if aryl chloride is base sensitive.*

To a nitrogen purged flask containing LiHMDS (2 equiv, 1 M in THF) was added ester (2 equiv, 1 M in PhMe) dropwise. After stirring for 30 min, aryl halide (1 equiv) was added in one portion. The reaction mixture was allowed to stir at room temperature for 1 h before adding DABCO (10-15 equiv) and stirring at 85-100 °C until the reaction was deemed complete by LCMS (typically 16-94 h). The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride and extracted with EtOAc (3x). The combined organic layers were dried with sodium sulfate, filtered, concentrated, and purified using flash column chromatography to afford the title compound.

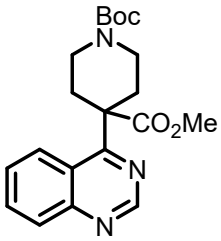
III. Decarboxylation Study of Isolated Ester Intermediate



To four separate vials was added ester **S1** (74.3 mg, 0.200 mmol), THF (0.400 mL), and PhMe (0.400 mL). To each vial was then added either 22.4 mg (1 equiv), 67.3 mg (3 equiv), 112 mg (5 equiv), or 224 mg (10 equiv) of DABCO and the vials were sealed and heated to 85 °C. Aliquots of each reaction were taken at 1 h, 3 h, 6 h, 22 h, and 26 h for LCMS analysis. Percent conversion for each timepoint was calculated by integration of the HPLC UV spectrum at 254 nM.



IV. Characterization of Compounds



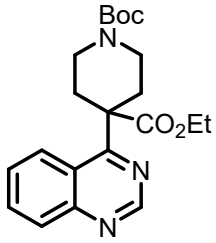
1-(*tert*-butyl) 4-methyl 4-(quinazolin-4-yl)piperidine-1,4-dicarboxylate (4):

A flask containing 4-chloroquinazoline (300 mg, 1.82 mmol, 1 equiv) was evacuated with vacuum and backfilled with nitrogen gas (3x) before the addition of PhMe (3.65 mL, 0.5 M) followed by LiHMDS (3.65 mL, 3.65 mmol, 2 equiv, 1 M in THF). After stirring until the mixture was fully dissolved, 1-(*tert*-butyl) 4-methyl piperidine-1,4-dicarboxylate (887 mg, 3.65 mmol, 2 equiv) was added. The reaction mixture was allowed to stir at room temperature for 1 h before the addition of saturated aqueous ammonium chloride and extraction with EtOAc (3x). The combined organic layers were dried with sodium sulfate, filtered, concentrated, and purified using flash column chromatography to afford title compound **4** (616 mg, 91%) as a clear oil.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{26}N_3O_4$ 372.1918; Found 372.1920.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.12 – 8.01 (m, 2H), 7.86 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.58 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 3.72 – 3.62 (m, 4H), 3.60 (s, 3H), 2.45 (t, *J* = 5.9 Hz, 4H), 1.46 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 169.1, 154.9, 153.9, 151.0, 133.3, 130.2, 128.0, 124.0, 123.3, 79.7, 52.9, 52.2, 33.4, 28.6.



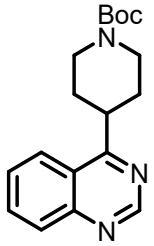
1-(*tert*-butyl) 4-ethyl 4-(quinazolin-4-yl)piperidine-1,4-dicarboxylate (5):

Following **GP1**, using aryl chloride (50.0 mg, 0.304 mmol, 1 equiv), ester (156 mg, 0.608 mmol, 2 equiv), PhMe (0.608 mL), LiHMDS (0.608 mL [1 M in THF], 0.608 mmol, 2 equiv), and DABCO (341 mg, 3.04 mmol, 10 equiv) stirring at 100 °C for 24 h, purified by flash column chromatography (0-100% EtOAc:heptane) to afford title compound **5** (51 mg, 44% yield) as a pale yellow oil.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{21}H_{27}N_3O_4$ 385.2007; Found 385.2002

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.97 – 7.88 (m, 1H), 7.68 (t, *J* = 7.7 Hz, 1H), 4.33 (br s, 2H), 3.71 (td, *J* = 11.3, 5.5 Hz, 1H), 2.97 (t, *J* = 12.9 Hz, 2H), 2.04 (m, 2H), 1.92 (app d, *J* = 13.4 Hz, 2H), 1.65 (m, 3H), 1.40-1.57 (m, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 169.2, 154.7, 153.7, 150.6, 133.2, 129.9, 127.7, 124.1, 123.1, 79.5, 61.6, 52.0, 33.3, 28.4, 13.8.



***tert*-butyl 4-(quinazolin-4-yl)piperidine-1-carboxylate (6):**

Following **GP2**, using aryl chloride (50.0 mg, 0.304 mmol, 1 equiv), ester (131 mg, 0.608 mmol, 2 equiv), PhMe (0.608 mL), LiHMDS (0.608 mL [1 M in THF], 0.608 mmol, 2 equiv), and DABCO (341 mg, 3.04 mmol, 10 equiv) stirring at 85 °C for 26 h, purified by flash column chromatography (0-30% EtOAc:heptane) to afford title compound **6** (75 mg, 79% yield) as a clear oil.

Gram Scale Reaction:

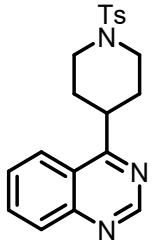
Following **GP2**, using aryl chloride (1.00 g, 6.08 mmol, 1 equiv), ester (2.96 g, 12.2 mmol, 2 equiv), PhMe (12.2 mL), LiHMDS (12.2 mL [1 M in THF], 12.2 mmol, 2 equiv), and DABCO (10.2 g, 91.1 mmol, 15 equiv) stirring at 85 °C for 24 h, purified by flash column chromatography (0-30% EtOAc:heptane) to afford title compound **6** (1.46 g, 77% yield) as an off-white solid.

R_f = 0.49 (50% EtOAc/Heptanes)

HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{18}H_{23}N_3O_2Na$ 336.1683; Found 336.1698.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.17 (d, J = 8.3 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.92 – 7.87 (m, 1H), 7.69 – 7.63 (m, 1H), 4.40 – 4.26 (m, 2H), 3.76 – 3.63 (m, 1H), 2.96 (t, J = 12.9 Hz, 2H), 2.09 – 1.87 (m, 4H), 1.48 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 154.9, 154.5, 149.9, 133.9, 129.4, 128.0, 123.9, 123.3, 79.8, 44.0, 39.7, 31.0, 28.6.

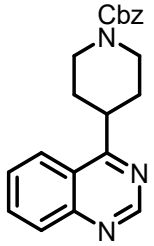


4-(1-tosylpiperidin-4-yl)quinazoline (10):
Following **GP1**, using aryl chloride (50.0 mg, 0.304 mmol, 1 equiv), ester (181 mg, 0.608 mmol, 2 equiv), PhMe (0.608 mL), LiHMDS (0.608 mL [1 M in THF], 0.608 mmol, 2 equiv), and DABCO (511 mg, 4.56 mmol, 15 equiv) stirring at 100 °C for 20 h, purified by flash column chromatography (0-100% EtOAc:heptane) to afford title compound **10** (77 mg, 69% yield) as a white solid.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{22}N_3O_2S$ 368.1427; Found 368.1428.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.03 (dd, *J* = 14.5, 8.4 Hz, 2H), 7.86 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.59 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.01 – 3.92 (m, 2H), 3.46 (tt, *J* = 11.5, 3.6 Hz, 1H), 2.55 (td, *J* = 12.0, 2.6 Hz, 2H), 2.46 (s, 3H), 2.27 – 2.15 (m, 2H), 2.04 – 1.92 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 154.4, 149.7, 143.7, 133.9, 133.4, 129.8, 129.3, 128.0, 127.9, 123.7, 123.1, 46.3, 38.8, 30.4, 21.7.



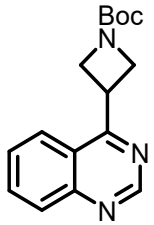
benzyl 4-(quinazolin-4-yl)piperidine-1-carboxylate (11):
Following **GP2**, using aryl chloride (50.0 mg, 0.306 mmol, 1 equiv), ester (168 mg, 0.608 mmol, 2 equiv), PhMe (0.608 mL), LiHMDS (0.608 mL [1 M in THF], 0.608 mmol, 2 equiv), and DABCO (511 mg, 4.56 mmol, 15 equiv) stirring at 85 °C for 19 h, purified by flash column chromatography (0-100% EtOAc:heptane) to afford title compound **11** (72 mg, 68% yield) as a clear oil.

R_f = 0.32 (1:1 heptanes/EtOAc)

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{21}H_{22}N_3O_2$ 348.1707; Found 348.1700.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.16 (d, J = 8.5 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.94 – 7.85 (m, 1H), 7.70 – 7.62 (m, 1H), 7.41 – 7.29 (m, 5H), 5.17 (s, 2H), 4.41 (s, 2H), 3.73 (tt, J = 11.3, 3.9 Hz, 1H), 3.06 (t, J = 13.2 Hz, 2H), 2.16 – 1.83 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 155.4, 154.8, 150.3, 137.0, 133.7, 129.7, 128.6, 128.1, 128.0, 127.8, 123.8, 123.2, 67.3, 44.2, 39.4, 30.9.



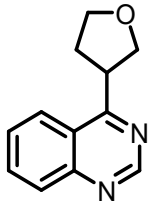
***tert*-butyl 3-(quinazolin-4-yl)azetidine-1-carboxylate (12):**
Following **GP2**, using aryl chloride (50.0 mg, 0.304 mmol, 1 equiv), ester (131 mg, 0.608 mmol, 2 equiv), PhMe (0.608 mL), LiHMDS (0.608 mL [1 M in THF], 0.608 mmol, 2 equiv), and DABCO (341 mg, 3.04 mmol, 10 equiv) stirring at 85 °C for 17 h, purified by flash column chromatography (0-50% EtOAc:heptane) to afford title compound **12** (66 mg, 76% yield) as a white solid.

R_f = 0.47 (1:1 Heptanes:EtOAc)

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{20}N_3O_2$ 286.1550; Found 286.1553.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.91 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.85 (dd, J = 8.4, 0.7 Hz, 1H), 7.65 (ddd, J = 8.3, 6.9, 1.2 Hz, 1H), 4.61 – 4.53 (m, 1H), 4.51 – 4.40 (m, 4H), 1.46 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 156.7, 154.8, 150.2, 134.1, 129.7, 128.3, 123.9, 123.5, 80.0, 53.5, 32.1, 28.7.

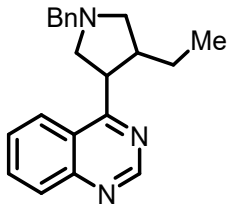


4-(tetrahydrofuran-3-yl)quinazoline (13):
Following **GP2**, using aryl chloride (50.0 mg, 0.304 mmol, 1 equiv), ester (79.1 mg, 0.608 mmol, 2 equiv), PhMe (0.608 mL), LiHMDS (0.608 mL [1 M in THF], 0.608 mmol, 2 equiv), and DABCO (511 mg, 4.56 mmol, 15 equiv) stirring at 85 °C for 26 h, purified by flash column chromatography (0-100% EtOAc:heptane) to afford title compound **13** (24 mg, 39% yield) as a clear oil.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{12}H_{13}N_2O$ 201.1022; Found 201.1024.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.89 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.66 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 4.39 – 4.24 (m, 2H), 4.16 – 4.09 (m, 2H), 4.06 – 3.99 (m, 1H), 2.58 – 2.37 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 154.5, 149.9, 133.8, 129.3, 128.0, 124.2, 124.1, 72.8, 69.0, 42.3, 32.5.

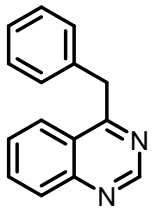


4-(1-benzyl-4-ethylpyrrolidin-3-yl)quinazoline (14):
Following **GP1**, using aryl chloride (50.0 mg, 0.304 mmol, 1 equiv), ester (150 mg, 0.608 mmol, 2 equiv), PhMe (0.608 mL), LiHMDS (0.608 mL [1 M in THF], 0.608 mmol, 2 equiv), and DABCO (511 mg, 4.56 mmol, 15 equiv) stirring at 100 °C for 21 h, purified by flash column chromatography (0-100% EtOAc:heptane) to afford title compound **14** (37 mg, 38% yield) as a yellow oil as a single diastereomer (Note: the relative stereochemistry was not elucidated.)

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{21}H_{24}N_3$ 318.1965; Found 318.1964.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.30 (d, *J* = 8.6 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.82 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.57 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.36 (d, *J* = 7.4 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 2H), 7.22 – 7.17 (m, 1H), 3.93 (q, *J* = 8.0 Hz, 1H), 3.81 (d, *J* = 12.9 Hz, 1H), 3.69 (d, *J* = 13.0 Hz, 1H), 3.25 – 3.13 (m, 1H), 3.11 – 3.02 (m, 1H), 2.95 – 2.78 (m, 2H), 2.68 (s, 1H), 1.50 (p, *J* = 7.3 Hz, 2H), 0.74 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 150.5, 133.7, 129.4, 129.2, 128.6, 127.8, 127.5, 124.8, 124.2, 60.7, 60.3, 59.8, 48.2, 46.4, 27.7, 12.8.



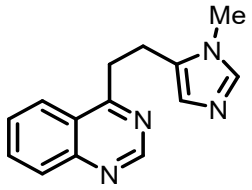
4-benzylquinazoline (15):
Following **GP2**, using aryl chloride (100 mg, 0.608 mmol, 1 equiv), ester (182 mg, 1.22 mmol, 2 equiv), PhMe (1.22 mL), LiHMDS (203 mg, 1.22 mmol, 2 equiv), and DABCO (1.02 g, 9.11 mmol, 15 equiv) stirring at 85 °C for 52 h, purified by flash column chromatography (0-100% EtOAc:heptane) to afford title compound **15** (90 mg, 67% yield) as a light yellow oil.

R_f = 0.49 (1:1 EtOAc/heptanes)

HRMS (ESI-TOF) m/z: [M+H]+ calcd for $C_{15}H_{13}N_2$ 221.1073; Found 221.1084.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.20 – 8.14 (m, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.89 – 7.82 (m, 1H), 7.64 – 7.55 (m, 1H), 7.33 – 7.25 (m, 4H), 7.24 – 7.19 (m, 1H), 4.64 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 154.8, 150.5, 137.8, 133.8, 129.3, 129.0, 128.9, 127.9, 127.0, 125.3, 124.2, 41.4.

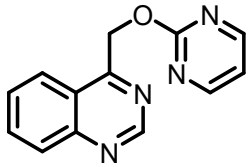


4-(2-(1-methyl-1H-imidazol-5-yl)ethyl)quinazoline (16):
Following **GP1** except no work-up was performed and the reaction mixture was directly purified, using aryl chloride (50.0 mg, 0.304 mmol, 1 equiv), ester (124 mg, 0.608 mmol, 2 equiv), PhMe (0.608 mL), LiHMDS (0.608 mL [1 M in THF], 0.608 mmol, 2 equiv), and DABCO (511 mg, 4.56 mmol, 15 equiv) stirring at 100 °C for 24 h, purified by flash column chromatography (0-20% DCM:MeOH) to afford title compound **16** (42 mg, 58% yield) as a clear oil.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{14}H_{15}N_4$ 239.1291; Found 239.1292.

^{1}H NMR (400 MHz, CD_3OD) δ 9.14 (s, 1H), 8.29 (dt, *J* = 8.6, 1.2 Hz, 1H), 8.03 – 7.96 (m, 2H), 7.75 (ddd, *J* = 8.3, 5.7, 2.5 Hz, 1H), 7.50 (s, 1H), 6.69 (d, *J* = 1.0 Hz, 1H), 3.72 – 3.66 (m, 2H), 3.65 (s, 3H), 3.23 (ddd, *J* = 8.6, 6.4, 1.1 Hz, 2H).

^{13}C NMR (101 MHz, CD_3OD) δ 172.1, 155.1, 150.6, 138.9, 135.6, 132.8, 129.5, 129.2, 126.3, 126.1, 125.3, 33.7, 31.6, 22.9.

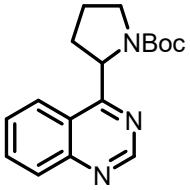


4-((pyrimidin-2-yloxy)methyl)quinazoline (17):
Following **GP2** except no work-up was performed and the reaction mixture was directly purified, using aryl chloride (50.0 mg, 0.304 mmol, 1 equiv), ester (102 mg, 0.608 mmol, 2 equiv), PhMe (0.608 mL), LiHMDS (0.608 mL [1 M in THF], 0.608 mmol, 2 equiv), and DABCO (511 mg, 4.56 mmol, 15 equiv) stirring at 100 °C for 24 h, purified by flash column chromatography (3% MeOH in DCM) to afford title compound **17** (23 mg, 31% yield) as a clear oil.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{11}N_4O$ 239.0927; Found 239.0927.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.52 (d, *J* = 4.8 Hz, 2H), 8.31 (dt, *J* = 8.4, 1.1 Hz, 1H), 8.08 (dt, *J* = 8.5, 1.0 Hz, 1H), 7.92 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.68 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 6.97 (t, *J* = 4.8 Hz, 1H), 6.05 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 164.7, 159.6, 154.7, 150.5, 134.0, 129.4, 128.2, 124.7, 123.4, 115.8, 67.7.



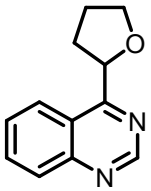
***tert*-butyl 2-(quinazolin-4-yl)pyrrolidine-1-carboxylate (18):**

Following **GP2**, using aryl chloride (50.0 mg, 0.304 mmol, 1 equiv), ester (139 mg, 0.608 mmol, 2 equiv), PhMe (0.608 mL), LiHMDS (0.608 mL [1 M in THF], 0.608 mmol, 2 equiv), and DABCO (511 mg, 4.56 mmol, 15 equiv) stirring at 100 °C for 48 h, purified by flash column chromatography (0-100% EtOAc:heptane) to afford title compound **18** (74 mg, 82% yield) as a waxy solid which was reported as a 2:1 mixture of rotamers.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{22}N_3O_2$ 300.1707; Found 300.1709.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (d, *J* = 14.1 Hz, 1H), 8.43 (d, *J* = 8.4 Hz, 1H), 8.06 – 7.98 (m, 2H), 7.81 – 7.72 (m, 1H), 5.71 (dd, *J* = 8.2, 4.6 Hz, 1H), 3.64 (ddd, *J* = 10.2, 7.7, 6.1 Hz, 1H), 3.54 (dt, *J* = 10.4, 6.7 Hz, 1H), 2.58 – 2.50 (m, 2H), 2.09 – 1.76 (m, 3H), 1.36 (s, 3H), 0.82 (s, 6H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 172.13, 171.24, 154.17, 154.10, 153.37, 152.80, 149.40, 149.37, 134.02, 133.96, 128.44, 127.82, 124.50, 124.33, 121.94, 121.92, 78.46, 77.87, 57.52, 57.49, 46.91, 46.83, 33.26, 32.24, 28.10, 27.44, 23.67, 23.25.



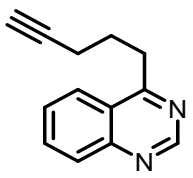
4-(tetrahydrofuran-2-yl)quinazoline (19):

Following **GP2**, using aryl chloride (50.0 mg, 0.304 mmol, 1 equiv), ester (79.1 mg, 0.608 mmol, 2 equiv), PhMe (0.608 mL), LiHMDS (0.608 mL [1 M in THF], 0.608 mmol, 2 equiv), and DABCO (511 mg, 4.56 mmol, 15 equiv) stirring at 100 °C for 67 h, purified by flash column chromatography (0-100% EtOAc:heptane) to afford title compound **19** (21 mg, 35% yield) as a clear oil.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{12}H_{13}N_2O$ 201.1022; Found 201.1022.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.31 (d, *J* = 7.9 Hz, 0H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.89 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.65 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 5.69 (t, *J* = 7.1 Hz, 1H), 4.20 (dt, *J* = 8.2, 6.7 Hz, 1H), 4.12 – 4.02 (m, 1H), 2.52 – 2.37 (m, 3H), 2.22 – 2.04 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 154.6, 150.6, 133.7, 129.3, 127.7, 125.1, 123.2, 78.7, 69.5, 31.4, 26.2.

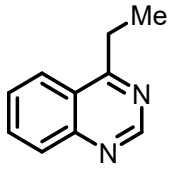


4-(pent-4-yn-1-yl)quinazoline (20):
Following **GP1**, using aryl chloride (50.0 mg, 0.304 mmol, 1 equiv), ester (76.6 mg, 0.608 mmol, 2 equiv), PhMe (0.608 mL), LiHMDS (1.22 mL [1 M in THF], 1.22 mmol, 4 equiv), and DABCO (511 mg, 4.56 mmol, 15 equiv) stirring at 100 °C for 46 h, purified by flash column chromatography (0-100% EtOAc:heptane) to afford title compound **20** (20 mg, 34% yield) as a yellow oil.

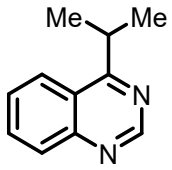
HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{13}N_2$ 197.1073; Found 197.1072.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.3 Hz, 1H), 7.91 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.67 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 3.49 – 3.39 (m, 2H), 2.39 (td, *J* = 6.8, 2.6 Hz, 2H), 2.21 – 2.09 (m, 2H), 2.03 (t, *J* = 2.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 154.0, 149.6, 134.2, 129.1, 128.1, 124.8, 124.1, 83.7, 69.5, 33.0, 27.1, 18.4.



4-ethylquinazoline (21):
Following **GP2**, using aryl chloride (85.1 mg, 0.304 mmol, 1 equiv), ester (53.5 mg, 0.608 mmol, 2 equiv), PhMe (0.608 mL), LiHMDS (0.608 mL [1 M in THF], 0.608 mmol, 2 equiv), and DABCO (511 mg, 4.56 mmol, 15 equiv) stirring at 85 °C for 94 h, purified by flash column chromatography (0-100% EtOAc:heptane) to afford title compound **21** (38 mg, 79% yield) as a clear oil. Spectral data is consistent with previously reported data (*Adv. Synth. Catal.* **2018**, *360*, 1938 – 1942).

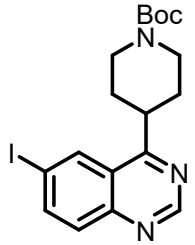


4-isopropylquinazoline (22):
Following **GP2**, using aryl chloride (50.0 mg, 0.304 mmol, 1 equiv), ester (69.6 µL, 0.608 mmol, 2 equiv), PhMe (0.608 mL), LiHMDS (0.608 mL [1 M in THF], 0.608 mmol, 2 equiv), and DABCO (511 mg, 4.56 mmol, 15 equiv) stirring at 100 °C for 44 h, purified by flash column chromatography (0-100% EtOAc:heptane) to afford title compound **22** (32 mg, 61% yield) as a clear oil.

HRMS (ESI-TOF) m/z: [M+H]+ calcd for $C_{11}H_{13}N_2$ 173.1073; Found 173.1073.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.85 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.61 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 3.92 (hept, *J* = 6.8 Hz, 1H), 1.43 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 154.8, 150.0, 133.5, 129.4, 127.6, 124.3, 123.3, 31.0, 21.8.



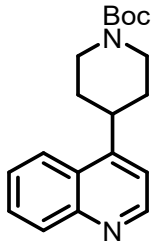
***tert*-butyl 4-(6-iodoquinazolin-4-yl)piperidine-1-carboxylate (23):**
Following **GP1**, using aryl chloride (87.1 mg, 0.300 mmol, 1 equiv), ester (146 mg, 0.600 mmol, 2 equiv), PhMe (0.600 mL), LiHMDS (0.600 mL [1 M in THF], 0.600 mmol, 2 equiv), and DABCO (505 mg, 4.50 mmol, 15 equiv) stirring at 100 °C for 26 h, purified by flash column chromatography (0-25% EtOAc:heptane) to afford title compound **23** (90 mg, 68% yield) as a clear oil.

$\mathbf{R_f}$ = 0.20 (3:1 Heptanes:EtOAc)

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{23}IN_3O_2$ 440.0830; found 440.0835.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.49 (d, *J* = 1.9 Hz, 1H), 8.09 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 4.30 (s, 2H), 3.64 – 3.52 (m, 1H), 2.96 (t, *J* = 13.1 Hz, 2H), 2.08 – 1.91 (m, 2H), 1.91 – 1.80 (m, 2H), 1.47 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 155.2, 154.9, 149.5, 142.3, 132.9, 131.5, 124.9, 93.1, 79.7, 44.0, 39.6, 31.1, 28.7.

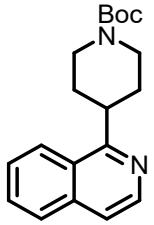


***tert*-butyl 4-(quinolin-4-yl)piperidine-1-carboxylate (24):**
Following **GP3** except the SNAr was allowed to stir at rt for 68 h followed by 60 °C for 24 h, using aryl chloride (50.0 mg, 0.306 mmol, 1 equiv), ester (149 mg, 0.612 mmol, 2 equiv), PhMe (0.612 mL), LiHMDS (0.612 mL [1 M in THF], 0.612 mmol, 2 equiv), and DABCO (515 mg, 4.59 mmol, 15 equiv) stirring at 100 °C for 24 h, purified by flash column chromatography (0-100% EtOAc:heptane) to afford title compound **24** (36 mg, 38% yield) as a clear oil.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{25}N_2O_2$ 313.1911; Found 313.1912.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 4.6 Hz, 1H), 8.17 – 8.12 (m, 1H), 8.09 (dt, *J* = 8.6, 0.9 Hz, 1H), 7.72 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H), 7.58 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H), 7.25 (s, 2H), 4.34 (d, *J* = 13.0 Hz, 2H), 3.49 (tt, *J* = 12.1, 3.3 Hz, 1H), 2.96 (t, *J* = 12.8 Hz, 2H), 2.03 – 1.95 (m, 2H), 1.75 (qd, *J* = 12.5, 4.3 Hz, 2H), 1.50 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 151.2, 150.6, 148.7, 130.8, 129.2, 126.8, 126.6, 122.7, 117.7, 79.9, 43.1, 37.4, 32.5, 28.6.



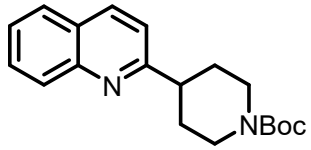
***tert*-butyl 4-(isoquinolin-1-yl)piperidine-1-carboxylate (25):**
Following **GP1** except the SNAr was allowed to stir for 4 h, using aryl chloride (50.0 mg, 0.306 mmol, 1 equiv), ester (149 mg, 0.611 mmol, 2 equiv), PhMe (0.611 mL), LiHMDS (0.611 mL [1 M in THF], 0.611 mmol, 2 equiv), and DABCO (514 mg, 4.59 mmol, 10 equiv) stirring at 85 °C for 90 h, purified by flash column chromatography (0-100% EtOAc:heptane) to afford title compound **25** (92 mg, 96% yield) as a clear oil.

$\mathbf{R_f}$ = 0.67 (60% EtOAc/Heptane)

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{25}N_2O_2$ 313.1911; Found 313.1918.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 5.7 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.67 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.61 (ddd, J = 8.3, 6.9, 1.4 Hz, 1H), 7.52 (d, J = 5.7 Hz, 1H), 4.33 (s, 2H), 3.77 – 3.64 (m, 1H), 2.97 (t, J = 12.9 Hz, 2H), 2.05 (s, 2H), 1.97 – 1.87 (m, 2H), 1.49 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 154.9, 141.9, 136.6, 129.9, 127.9, 127.3, 126.3, 124.4, 119.5, 79.5, 44.3, 39.9, 31.6, 28.7.

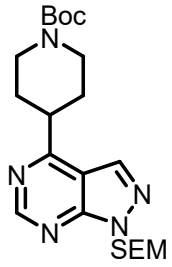


***tert*-butyl 4-(quinolin-2-yl)piperidine-1-carboxylate (26):**
Following **GP3** except the SNAr was allowed to stir at rt for 68 h followed by 60 °C for 3 h, using aryl chloride (50.0 mg, 0.306 mmol, 1 equiv), ester (149 mg, 0.612 mmol, 2 equiv), PhMe (0.612 mL), LiHMDS (0.612 mL [1 M in THF], 0.612 mmol, 2 equiv), and DABCO (515 mg, 4.59 mmol, 15 equiv) stirring at 100 °C for 22 h, purified by flash column chromatography (0-100% EtOAc:heptane) to afford title compound **26** (51 mg, 54% yield) as a clear gum.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{25}N_2O_2$ 313.1911; Found 313.1913.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 8.6, 0.9 Hz, 1H), 8.03 (dq, *J* = 8.4, 0.9 Hz, 1H), 7.78 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.69 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.49 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 4.29 (s, 2H), 3.06 (tt, *J* = 11.9, 3.7 Hz, 1H), 2.90 (t, *J* = 12.8 Hz, 2H), 2.03 – 1.94 (m, 2H), 1.91 – 1.78 (m, 2H), 1.49 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 155.0, 148.0, 136.7, 129.6, 129.2, 127.6, 127.2, 126.1, 119.5, 79.6, 51.9, 45.7, 44.2, 43.4, 41.2, 31.8, 28.7, 28.6, 28.1.



***tert*-butyl 4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperidine-1-carboxylate (27):**

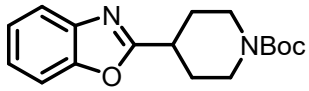
Following **GP1**, using aryl chloride (85.1 mg, 0.300 mmol, 1 equiv), ester (146 mg, 0.600 mmol, 2 equiv), PhMe (0.600 mL), LiHMDS (0.600 mL [1 M in THF], 0.600 mmol, 2 equiv), and DABCO (505 mg, 4.50 mmol, 15 equiv) stirring at 100 °C for 26 h, purified by flash column chromatography (0-20% EtOAc:heptane) to afford title compound **27** (68 mg, 52% yield) as a clear oil.

R_f = 0.42 (3:1 heptanes/EtOAc)

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{22}H_{37}N_4O_3Si$ 433.2629; found 433.2628.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.31 (d, *J* = 3.7 Hz, 1H), 6.63 (d, *J* = 3.7 Hz, 1H), 5.63 (s, 2H), 4.28 (s, 2H), 3.59 – 3.44 (m, 2H), 3.28 – 3.14 (m, 1H), 2.96 – 2.80 (m, 2H), 2.06 – 1.84 (m, 4H), 1.47 (s, 9H), 0.94 – 0.84 (m, 2H), -0.08 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 154.9, 151.7, 151.6, 128.0, 116.5, 100.2, 79.6, 73.0, 66.7, 44.0, 42.5, 30.6, 28.6, 17.9, -1.4.



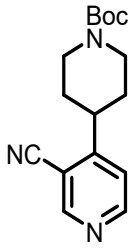
***tert*-butyl 4-(benzo[d]oxazol-2-yl)piperidine-1-carboxylate (28):**

Following **GP3**, using aryl chloride (50.0 mg, 0.326 mmol, 1 equiv), ester (158 mg, 0.651 mmol, 2 equiv), PhMe (0.651 mL), LiHMDS (0.651 mL [1 M in THF], 0.651 mmol, 2 equiv), and DABCO (548 mg, 4.88 mmol, 15 equiv) stirring at 100 °C for 24 h, purified by flash column chromatography (0-100% EtOAc:heptane) to afford title compound **28** (84.5 mg, 86% yield) as a clear gum.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{23}N_2O_3$ 303.1703; Found 303.1701.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.66 (m, 1H), 7.52 – 7.45 (m, 1H), 7.34 – 7.28 (m, 2H), 4.14 (d, *J* = 13.5 Hz, 2H), 3.12 (tt, *J* = 11.0, 3.9 Hz, 1H), 2.99 (t, *J* = 12.4 Hz, 2H), 2.14 (dd, *J* = 13.5, 3.5 Hz, 2H), 1.91 (dtd, *J* = 13.5, 11.3, 4.2 Hz, 2H), 1.48 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 154.9, 150.8, 141.3, 124.8, 124.4, 119.9, 110.5, 79.8, 43.3, 36.2, 29.5, 28.6.



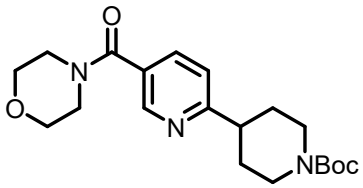
tert-butyl 4-(3-cyanopyridin-4-yl)piperidine-1-carboxylate (29):
Following **GP3**, using aryl chloride (50 mg, 0.36 mmol, 1 equiv), ester (263 mg, 1.08 mmol, 2 equiv), PhMe (1.08 mL), LiHMDS (1.08 mL [1 M in THF], 1.08 mmol, 2 equiv), and DABCO (405 mg, 3.61 mmol, 10 equiv) stirring at 85 °C for 18 h, purified by flash column chromatography (0-100% EtOAc:heptane) to afford title compound **29** (86 mg, 83% yield) as a clear oil.

R_f = 0.24 (50% EtOAc/Heptane)

HRMS (ESI-TOF) m/z: [M+H]+ calcd for $C_{16}H_{22}N_3O_2$ 288.1707; Found 288.1707.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.72 (d, *J* = 5.3 Hz, 1H), 7.29 (d, *J* = 5.3 Hz, 1H), 4.30 (d, *J* = 13.4 Hz, 2H), 3.10 (tt, *J* = 12.2, 3.5 Hz, 1H), 2.87 (t, *J* = 12.8 Hz, 2H), 1.92 – 1.82 (m, 2H), 1.64 (qd, *J* = 11.5, 10.6, 3.4 Hz, 2H), 1.48 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 155.1, 153.5, 153.4, 121.7, 116.1, 110.4, 80.4, 44.2, 41.2, 32.0, 28.9.

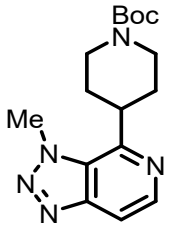


***tert*-butyl 4-(5-(morpholine-4-carbonyl)pyridin-2-yl)piperidine-1-carboxylate (30):**
Following **GP3** except no work-up was performed and the reaction mixture was directly purified, using aryl chloride (68.0 mg, 0.300 mmol, 1 equiv), ester (146 mg, 0.600 mmol, 2 equiv), PhMe (0.600 mL), LiHMDS (0.600 mL [1 M in THF], 0.600 mmol, 2 equiv), and DABCO (505 mg, 4.50 mmol, 15 equiv) stirring at 100 °C for 93 h, purified by flash column chromatography (0-20% DCM:MeOH) to afford title compound **30** (97 mg, 86% yield) as a clear oil.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{30}N_3O_4$ 376.2234; Found 376.2231.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (dd, *J* = 2.2, 0.9 Hz, 1H), 7.75 (dd, *J* = 8.0, 2.3 Hz, 1H), 7.24 (s, 1H), 4.26 (s, 2H), 3.71 (s, 6H), 3.47 (s, 2H), 2.99 – 2.74 (m, 3H), 1.97 – 1.85 (m, 2H), 1.71 (qd, *J* = 12.5, 4.4 Hz, 2H), 1.47 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 165.8, 154.9, 146.8, 137.0, 129.5, 121.4, 79.7, 66.9, 50.9, 44.1, 31.6, 28.6.

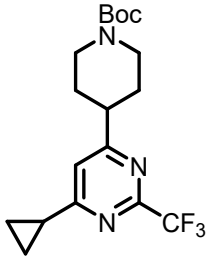


tert-butyl 4-(3-methyl-3H-[1,2,3]triazolo[4,5-c]pyridin-4-yl)piperidine-1-carboxylate (31):
Following **GP3** except no work-up was performed and the reaction mixture was directly purified, using aryl chloride (50.6 mg, 0.300 mmol, 1 equiv), ester (146 mg, 0.600 mmol, 2 equiv), PhMe (0.600 mL), LiHMDS (0.600 mL [1 M in THF], 0.600 mmol, 2 equiv), and DABCO (505 mg, 4.50 mmol, 15 equiv) stirring at 100 °C for 22 h, purified by flash column chromatography (0-20% DCM:MeOH) to afford title compound **31** (73 mg, 77% yield) as a waxy solid.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{24}N_5O_2$ 318.1925; Found 318.1927.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 5.8 Hz, 1H), 7.82 (d, *J* = 5.9 Hz, 1H), 4.57 (s, 3H), 4.35 (t, *J* = 10.5 Hz, 2H), 3.57 – 3.44 (m, 1H), 2.93 (t, *J* = 12.9 Hz, 2H), 2.14 (d, *J* = 12.6 Hz, 2H), 1.90 (d, *J* = 12.9 Hz, 2H), 1.48 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 150.7, 150.6, 140.8, 128.9, 112.7, 80.0, 43.9, 40.8, 38.0, 31.4, 28.6.



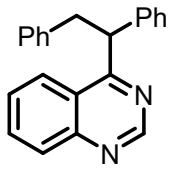
***tert*-butyl 4-(6-cyclopropyl-2-(trifluoromethyl)pyrimidin-4-yl)piperidine-1-carboxylate (32):**
Following **GP3**, using aryl chloride (66.8 mg, 0.300 mmol, 1 equiv), ester (146 mg, 0.600 mmol, 2 equiv), PhMe (0.600 mL), LiHMDS (0.600 mL [1 M in THF], 0.600 mmol, 2 equiv), and DABCO (505 mg, 4.50 mmol, 15 equiv) stirring at 100 °C for 67 h, purified by flash column chromatography (0-25% EtOAc:heptane) to afford title compound **32** (81 mg, 70% yield) as a clear oil.

R_f = 0.33 (3:1 Heptanes:EtOAc)

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{25}F_3N_3O_2$ 372.1893; Found 372.1894.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 1H), 4.25 (d, J = 13.2 Hz, 2H), 2.89 – 2.77 (m, 3H), 2.07 – 1.98 (m, 1H), 1.98 – 1.88 (m, 2H), 1.78 – 1.62 (m, 2H), 1.47 (s, 9H), 1.26 – 1.19 (m, 2H), 1.17 – 1.10 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 172.9, 156.6 (q, J = 35.9 Hz), 154.9, 119.8 (q, J = 275.8 Hz), 117.7, 79.8, 43.8, 30.9, 28.6, 17.3, 12.1. (note: one sp3 signal missing, potentially due to signal overlap)



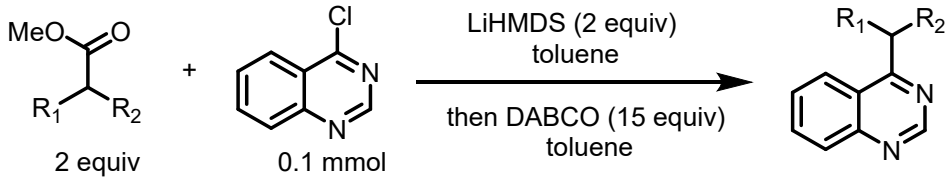
4-(1,2-diphenylethyl)quinazoline (35):
To an oven dried flask containing LiHMDS (1.37 mL [1 M in THF], 1.37 mmol, 3 equiv) and PhMe (0.911 mL) was added methyl phenylacetate (96.3 µL, 0.683 mmol, 1.5 equiv). This solution was allowed to stir for 10 min before the addition of benzyl bromide (81.3 µL, 0.683 mmmol, 1.5 equiv). After stirring for 30 min, aryl chloride (75.0 mg, 0.456 mmol, 1 equiv) was added. This solution was allowed to stir for 1 h before the addition of DABCO (767 mg, 6.83 mmol, 15 equiv) and heating to 100 °C while stirring. After 23 h, the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride and extracted with EtOAc (3x). The combined organic layers were dried with sodium sulfate, filtered, concentrated, and purified using flash column chromatography (0-100% EtOAc:heptane) to afford title compound **35** (65 mg, 46% yield) as a yellow oil.

HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{22}H_{19}N_2$ 311.1543; Found 311.1542.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.70 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.43 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.29 – 7.25 (m, 2H), 7.20 – 7.14 (m, 2H), 7.12 – 7.05 (m, 3H), 7.05 – 6.99 (m, 3H), 5.08 (t, *J* = 7.4 Hz, 1H), 3.80 (dd, *J* = 13.7, 7.5 Hz, 1H), 3.41 (dd, *J* = 13.7, 7.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 154.5, 150.3, 141.9, 140.2, 133.4, 129.3, 129.3, 128.7, 128.3, 128.2, 127.7, 127.1, 126.2, 124.5, 124.1, 50.7, 41.5.

V. Library Procedure



Stock solution A: To a vial conaining 4-chloroquinazoline (1 equiv. per reaction, 16.5 mg, 0.10 mmol) was added THF (0.4 mL per reaction) and the resulting mixture was stirred for 5 minutes to provide a pale pink solution.

Stock solution B: (Prepared in a glovebox under N_2) To a vial was added solid LiHMDS (2 equiv. per reaction, 36.0 mg, 0.20 mmol) followed by toluene (0.2 mL per reaction). The resulting mixture was stirred for 5 minutes to provide a colorless solution.

A plate of 1-dram vials with septum caps under air atmosphere were charged with stock solution A and a stir bar. The solutions were concentrated in parallel under a stream of nitrogen. To each vial containing 200 µmol of methyl ester monomer was added 200 µL of toluene and the monomer mixtures were then stirred for 15 minutes. During this time, stock solution B was added (0.2 mL per reaction) to each vial

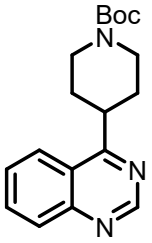
containing 4-chloroquinazoline (0.1 mmol). After 15 minutes, most monomers were in solution, 50 uL of THF was added to monomers that were insoluble in toluene and then stirred for 5 minutes. Monomer solutions (200 uL or 250 uL if THF was added) were then slowly transferred over approximately 10 seconds to the 4-chloroquinazoline vials using a pipette. Vials were then capped and removed from the glovebox. Plate was then stirred at room temperature for 18 hours.

After 18 h, many of the vials had turned into a thick slurry. An additional 300 uL of toluene was added to each vial. Approximately 172 mg of DABCO was then added to each vial (not individually measured, adjustable spatula used). The reactions were then stirred at 100 °C for 66 h.

After 66 h, the reactions were cooled to room temperature. The reactions were diluted with 1.0 mL of sat. NH_4Cl. The aqueous layers were then extracted with EtOAc (3 x 0.75 mL) and filtered through a 0.45 um polypropylene filter. Organic extractions for each reaction were concentrated in parallel under a stream of nitrogen to yield the crude products, which were dissolved in 1 mL of DMSO and submitted for high-throughput purification (column: XBridge C18 19x100mm, 5um; Mobile phase A: 0.03% NH_4OH in water (v/v); Mobile phase B: 0.03% NH_4OH in acetonitrile (v/v).

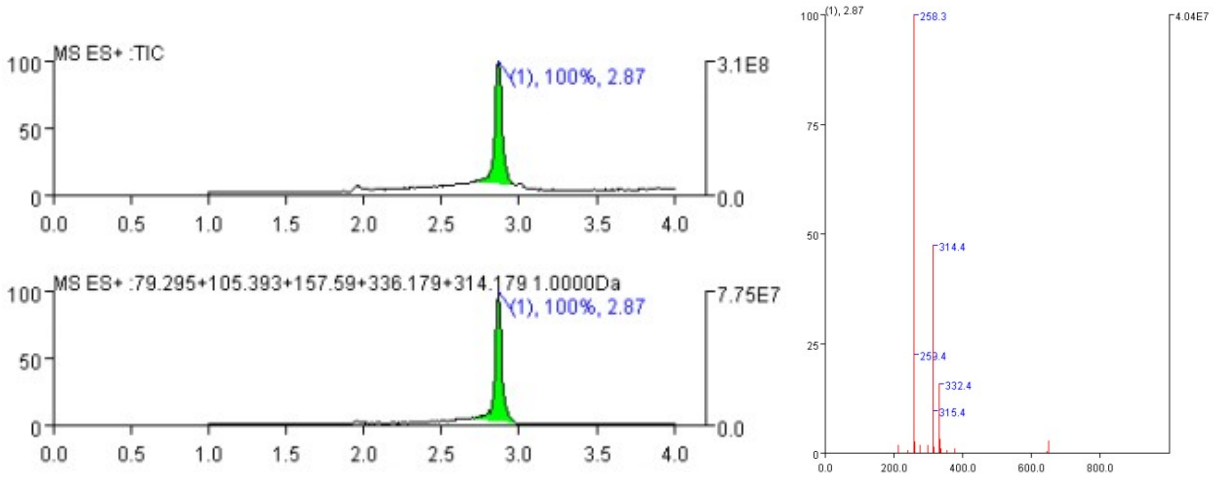
The isolated, desired products were characterized using LC-MS which is consistent with other reported library synthesis standard. For a library synthesis data characterization example, see *Angew. Chem. Int. Ed.* 2015, **54**, 1168. Some peak splitting and streaking was attributed to rotamers and/or differential protonation states.

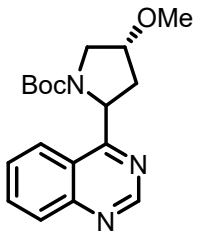
VI. Library Compound Characterization



***tert*-butyl 4-(quinazolin-4-yl)piperidine-1-carboxylate (6):**

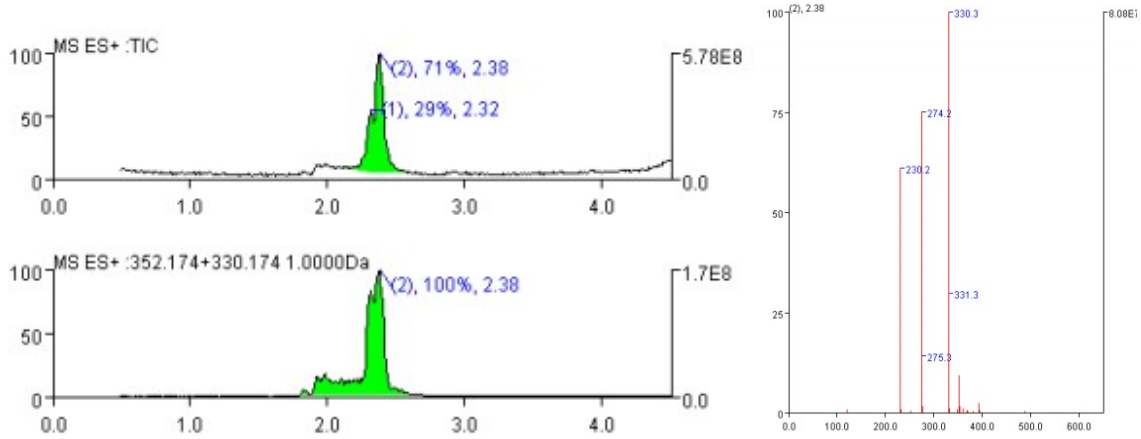
Product obtained: 22.8 mg, LC-MS data – Ret. time 2.87: ES+ m/z 314 ($[M+H]^+$).

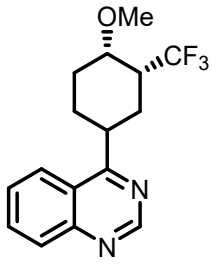




***tert*-butyl (4R)-4-methoxy-2-(quinazolin-4-yl)pyrrolidine-1-carboxylate (37):**

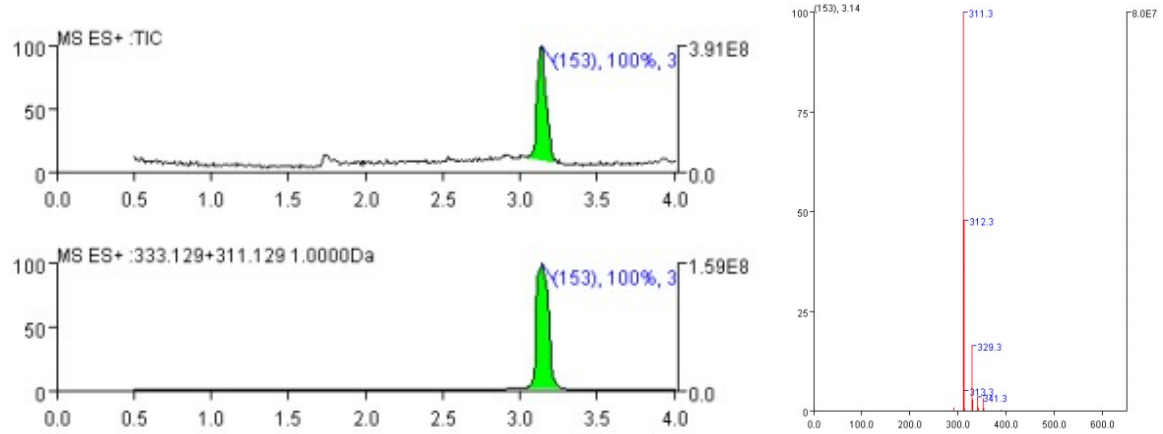
Product obtained: 18.8 mg, LC-MS data – Ret. time 2.38: ES+ m/z 330 ($[M+H]^+$).

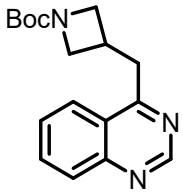




4-((3R,4S)-4-methoxy-3-(trifluoromethyl)cyclohexyl)quinazoline (38):

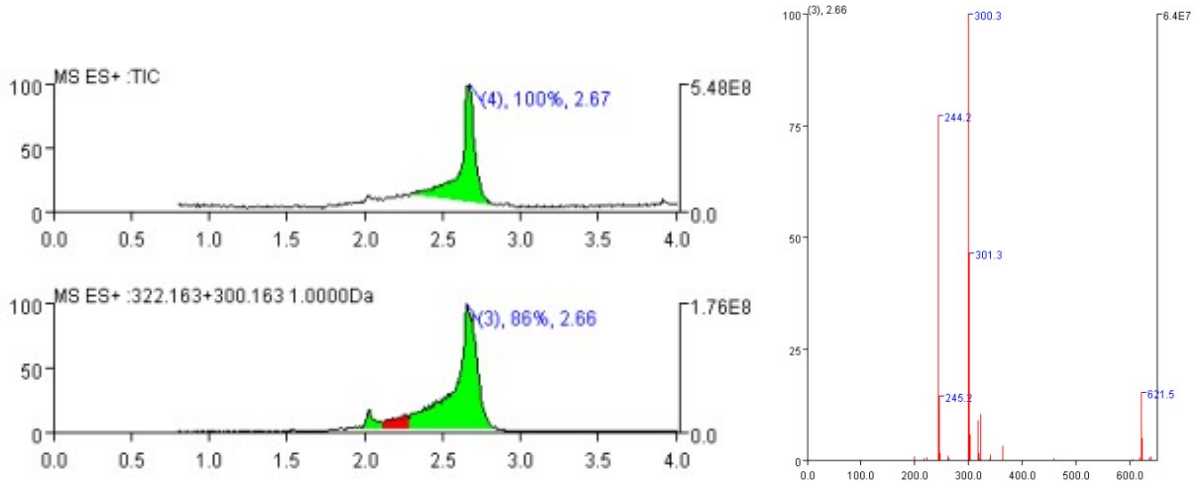
Product obtained: 15.3 mg, LC-MS data – Ret. time 3.14: ES+ m/z 311 ([M+H]$^+$).

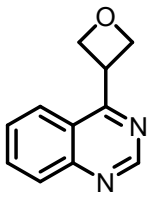




tert-butyl 3-(quinazolin-4-yl)azetidine-1-carboxylate (39):

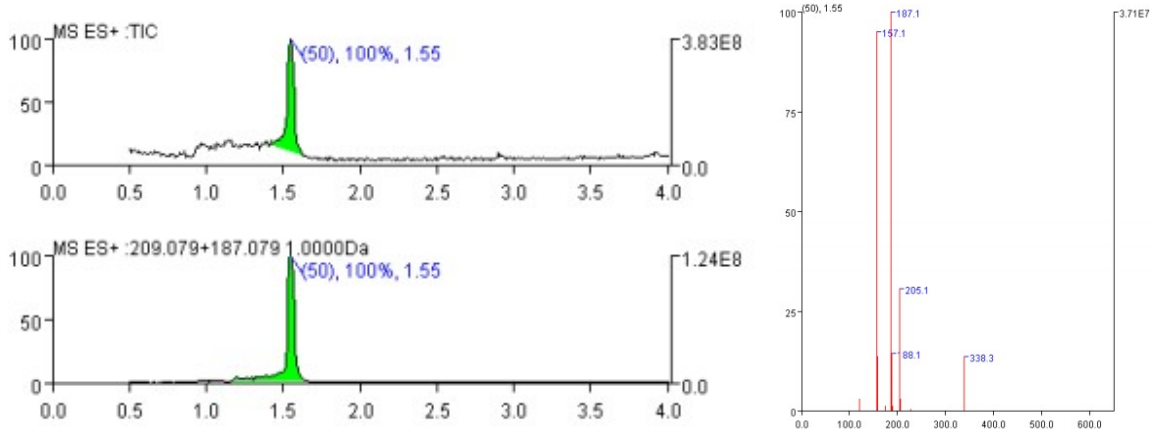
Product obtained: 14.2 mg, LC-MS data – Ret. time 2.66: ES+ m/z 300 ([M+H]$^+$).

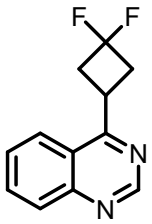




4-(oxetan-3-yl)quinazoline (40):

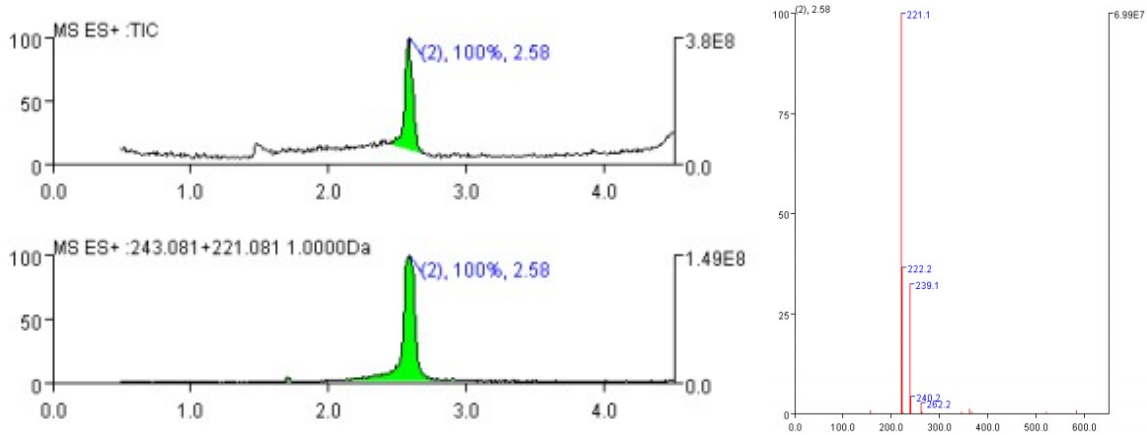
Product obtained: 8.1 mg, LC-MS data – Ret. time 1.55: ES+ m/z 187 ([M+H]$^+$).

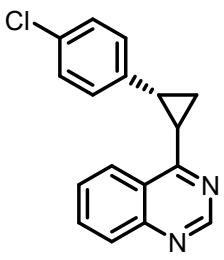




4-(3,3-difluorocyclobutyl)quinazoline (41):

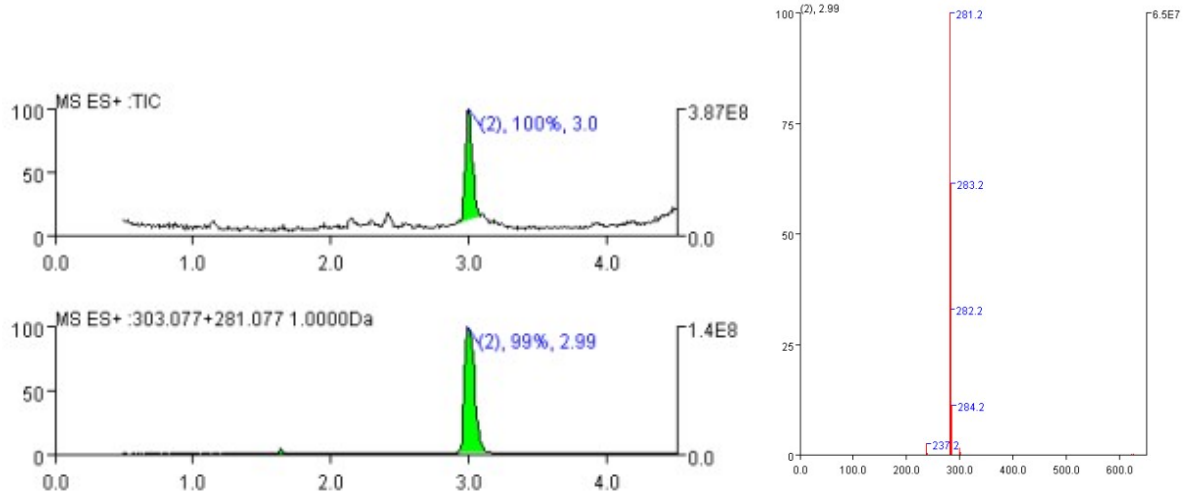
Product obtained: 7.1 mg, LC-MS data – Ret. time 2.58: ES+ m/z 221 ([M+H]$^+$).

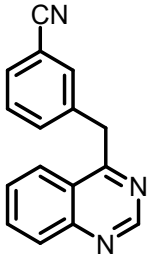




4-((2*R*)-2-(4-chlorophenyl)cyclopropyl)quinazoline (42):

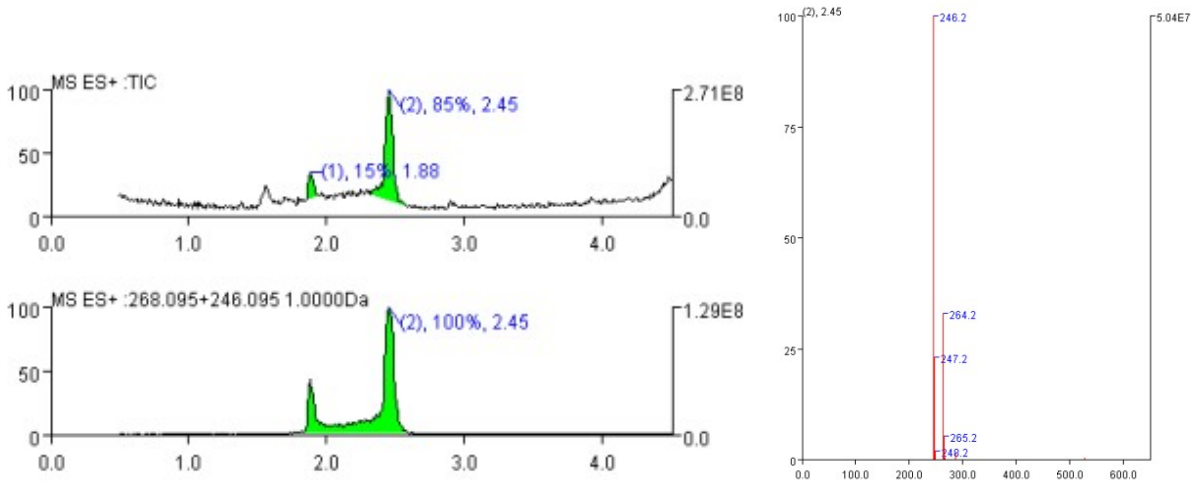
Product obtained: 1.6 mg, LC-MS data – Ret. time 2.99: ES+ m/z 281 ($[M+H]^+$).

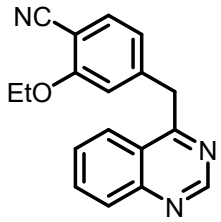




3-(quinazolin-4-ylmethyl)benzonitrile (43):

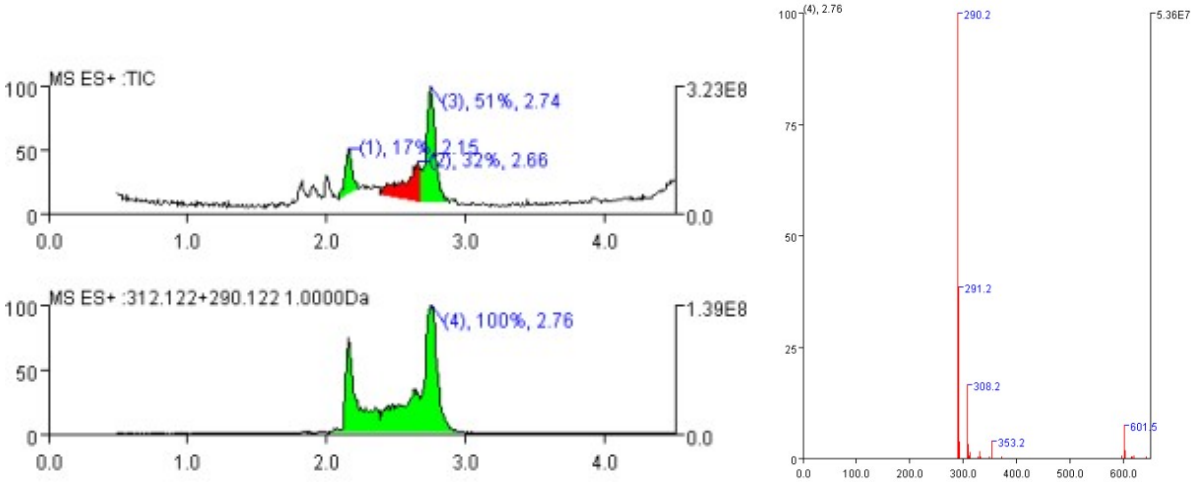
Product obtained: 1.7 mg, LC-MS data – Ret. time 2.45: ES+ m/z 246 ($[M+H]^+$).

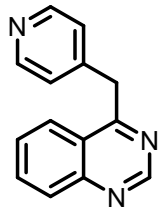




2-ethoxy-4-(quinazolin-4-ylmethyl)benzonitrile (44):

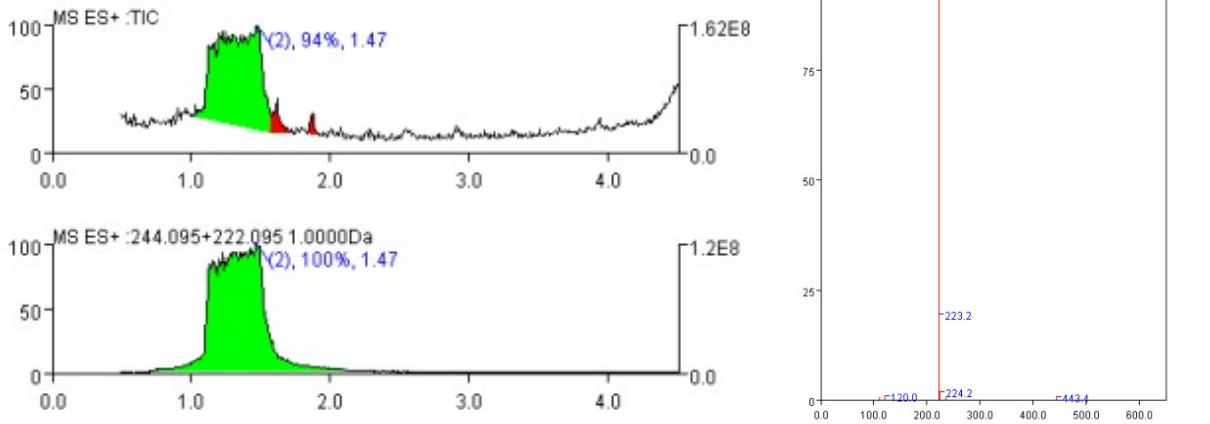
Product obtained: 3.4 mg, LC-MS data – Ret. time 2.76: ES+ m/z 290 ($[M+H]^+$).

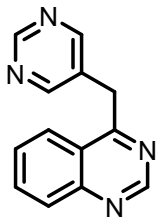




4-(pyridin-4-ylmethyl)quinazoline (45):

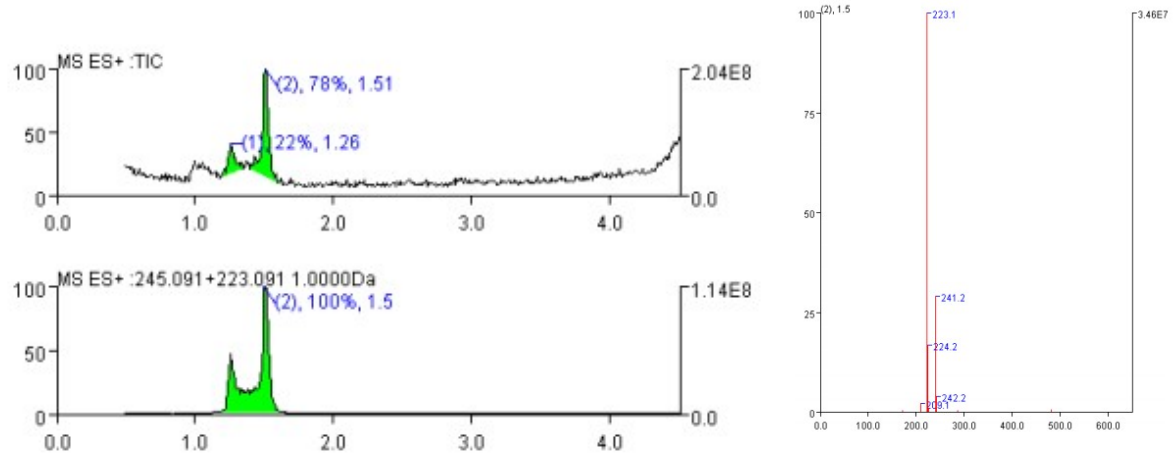
Product obtained: 3.7 mg, LC-MS data – Ret. time 1.47: ES+ m/z 222 ($[M+H]^+$).

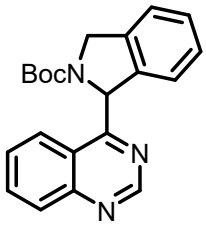




4-(pyrimidin-5-ylmethyl)quinazoline (46):

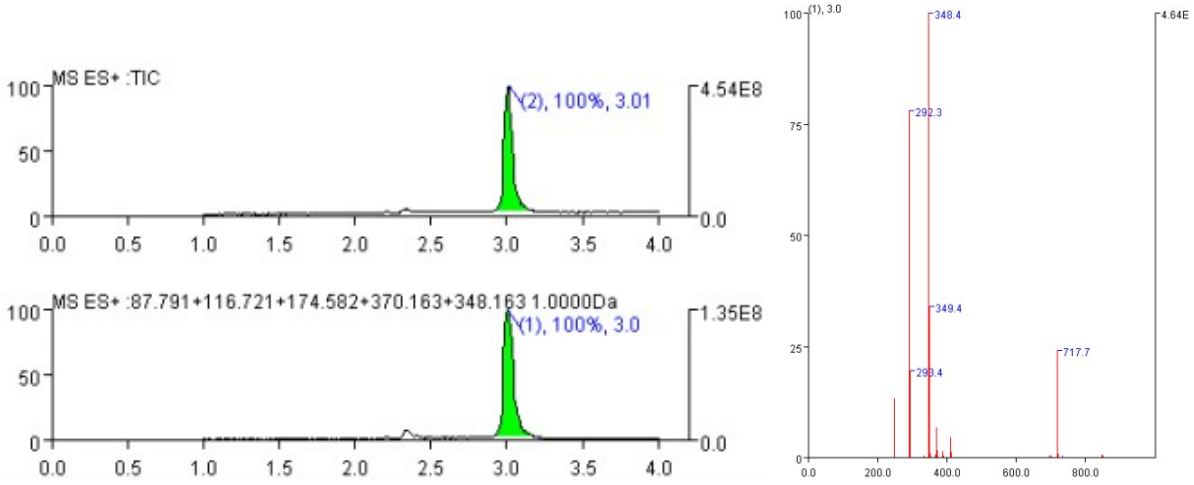
Product obtained: 2.3 mg, LC-MS data – Ret. time 1.50: ES+ m/z 223 ($[M+H]^+$).

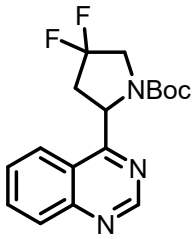




***tert*-butyl 1-(quinazolin-4-yl)isoindoline-2-carboxylate (47):**

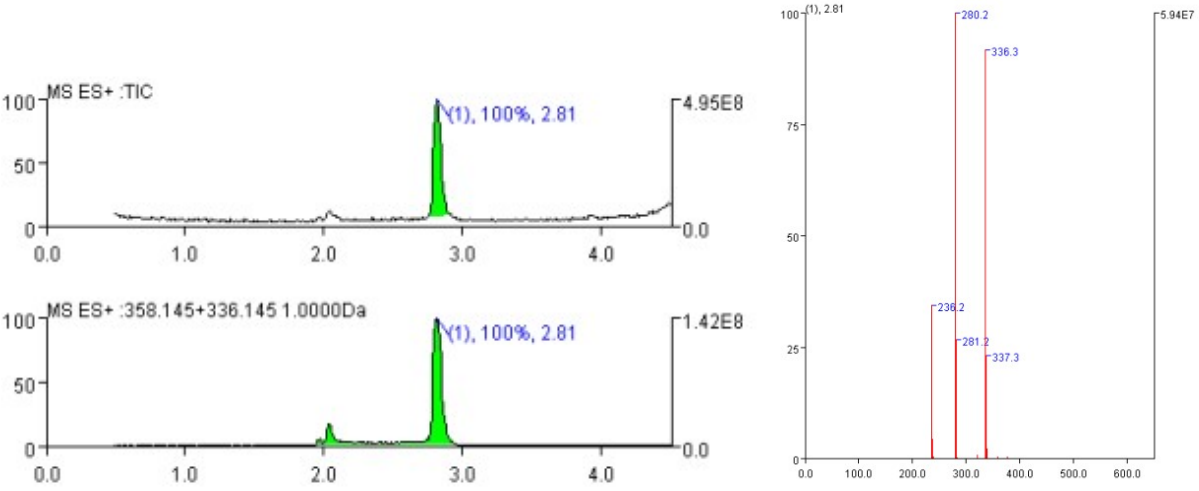
Product obtained: 25.2 mg, LC-MS data – Ret. time 3.00: ES+ m/z 348 ($[M+H]^+$).

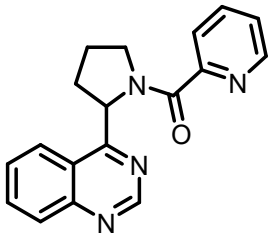




***tert*-butyl 4,4-difluoro-2-(quinazolin-4-yl)pyrrolidine-1-carboxylate (48):**

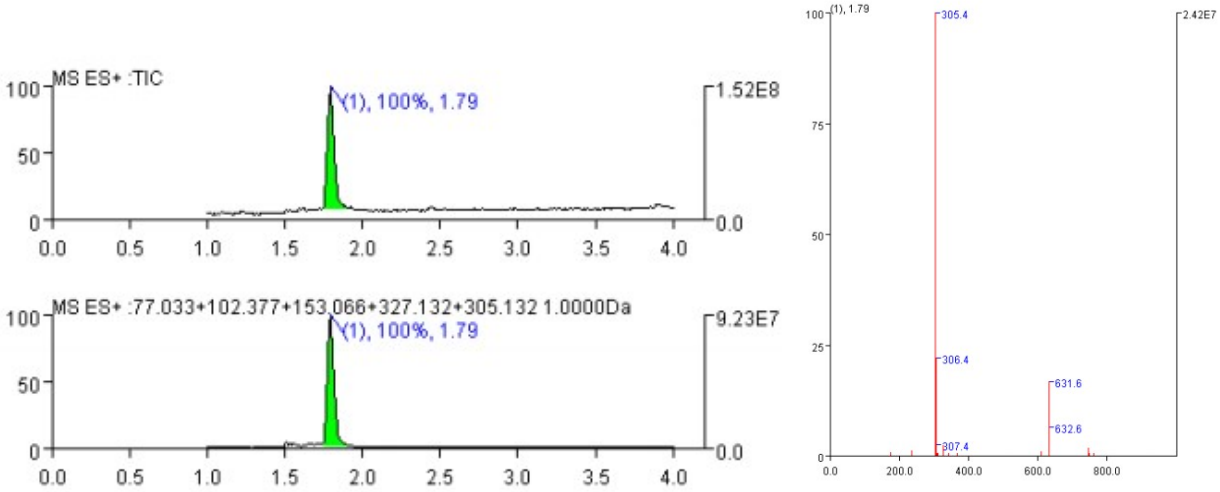
Product obtained: 16.0 mg, LC-MS data – Ret. time 2.81: ES+ m/z 336 ($[M+H]^+$).

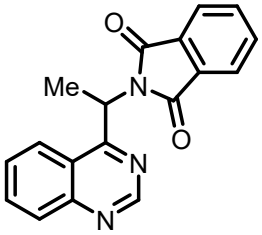




pyridin-2-yl(2-(quinazolin-4-yl)pyrrolidin-1-yl)methanone (49):

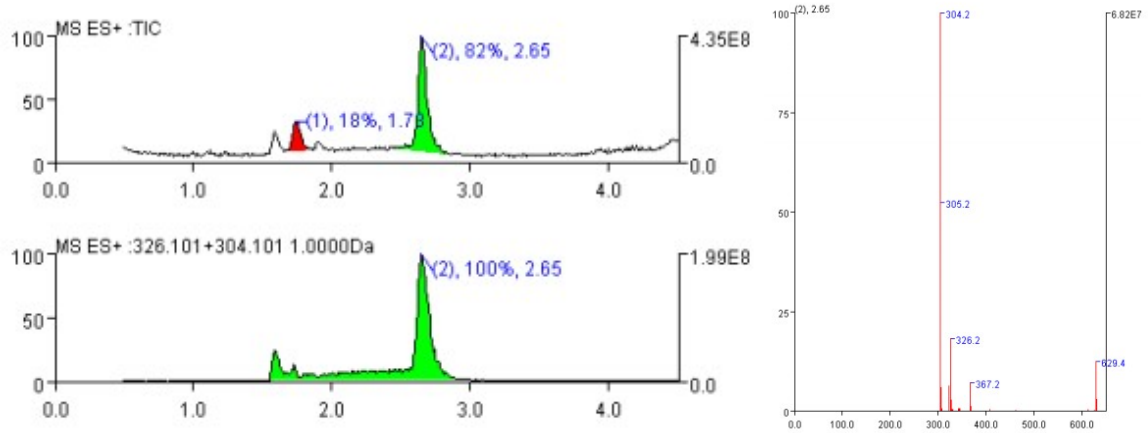
Product obtained: 2.8 mg, LC-MS data – Ret. time 1.79: ES+ m/z 305 ($[M+H]^+$).

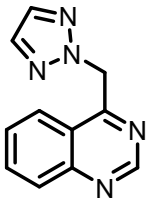




2-(1-(quinazolin-4-yl)ethyl)isoindoline-1,3-dione (50):

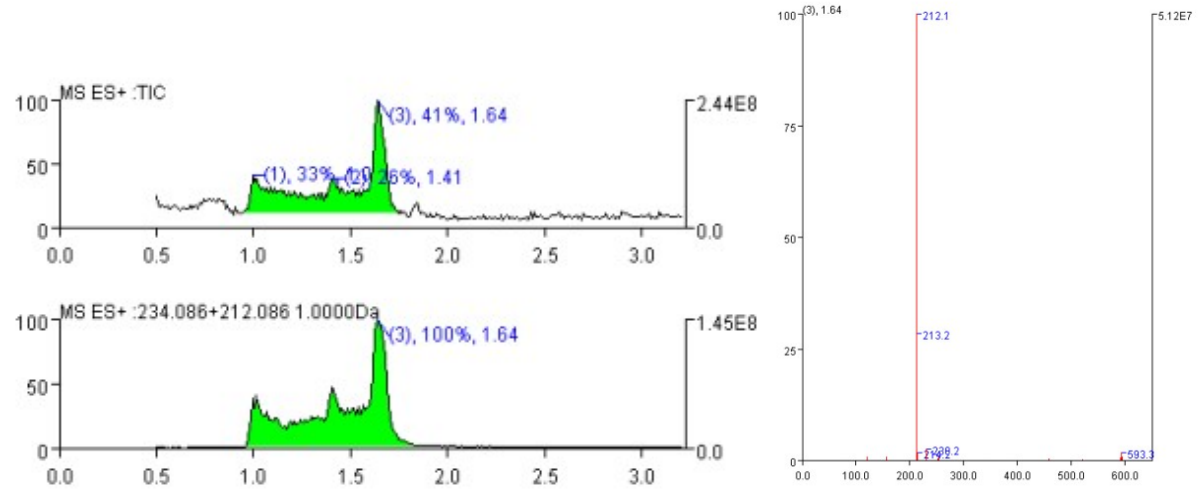
Product obtained: 8.5 mg, LC-MS data – Ret. time 2.65: ES+ m/z 304 ($[M+H)^+$).

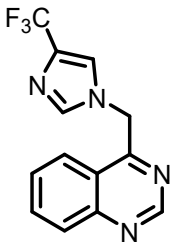




4-((2H-1,2,3-triazol-2-yl)methyl)quinazoline (51):

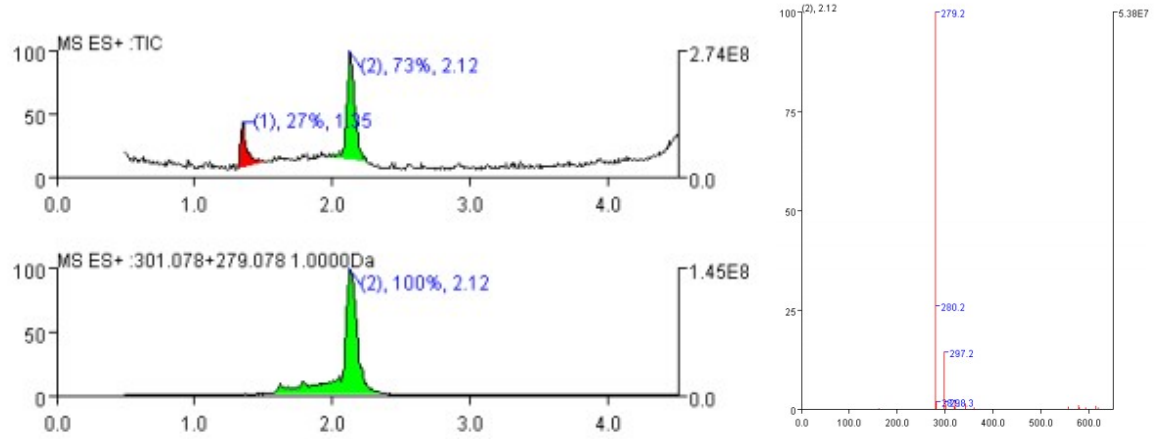
Product obtained: 5.6 mg, LC-MS data – Ret. time 1.64: ES+ m/z 212 ($[M+H]^+$).

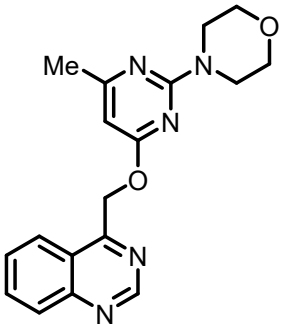




4-((4-(trifluoromethyl)-1H-imidazol-1-yl)methyl)quinazoline (52):

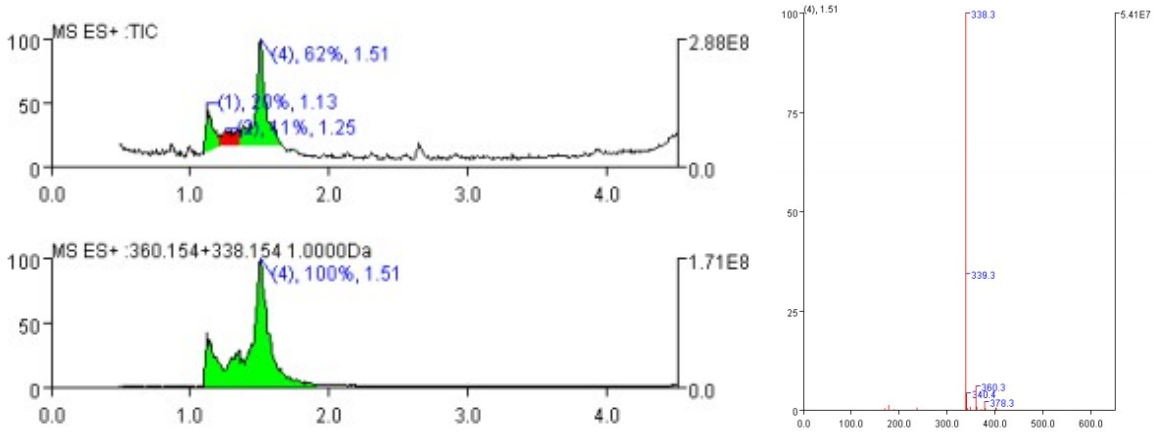
Product obtained: 9.0 mg, LC-MS data – Ret. time 2.12: ES+ m/z 279 ($[M+H]^+$).

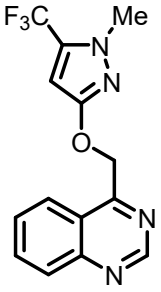




4-(4-methyl-6-(quinazolin-4-ylmethoxy)pyrimidin-2-yl)morpholine (53):

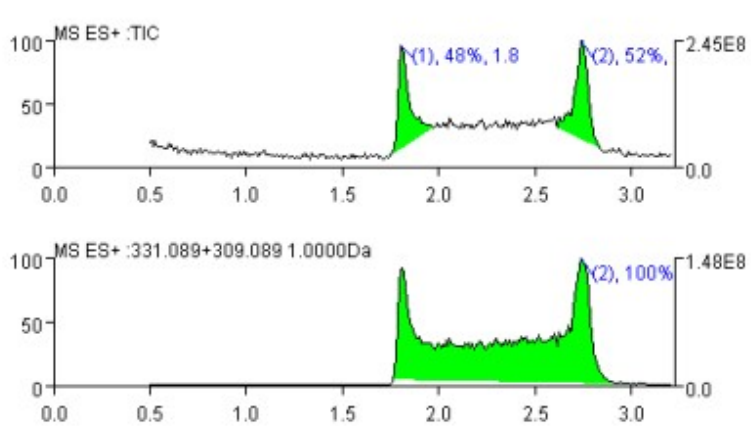
Product obtained: 7.7 mg, LC-MS data – Ret. time 1.51: ES+ m/z 338 ($[M+H)^+$).

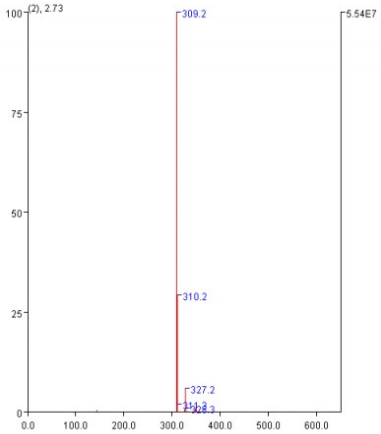




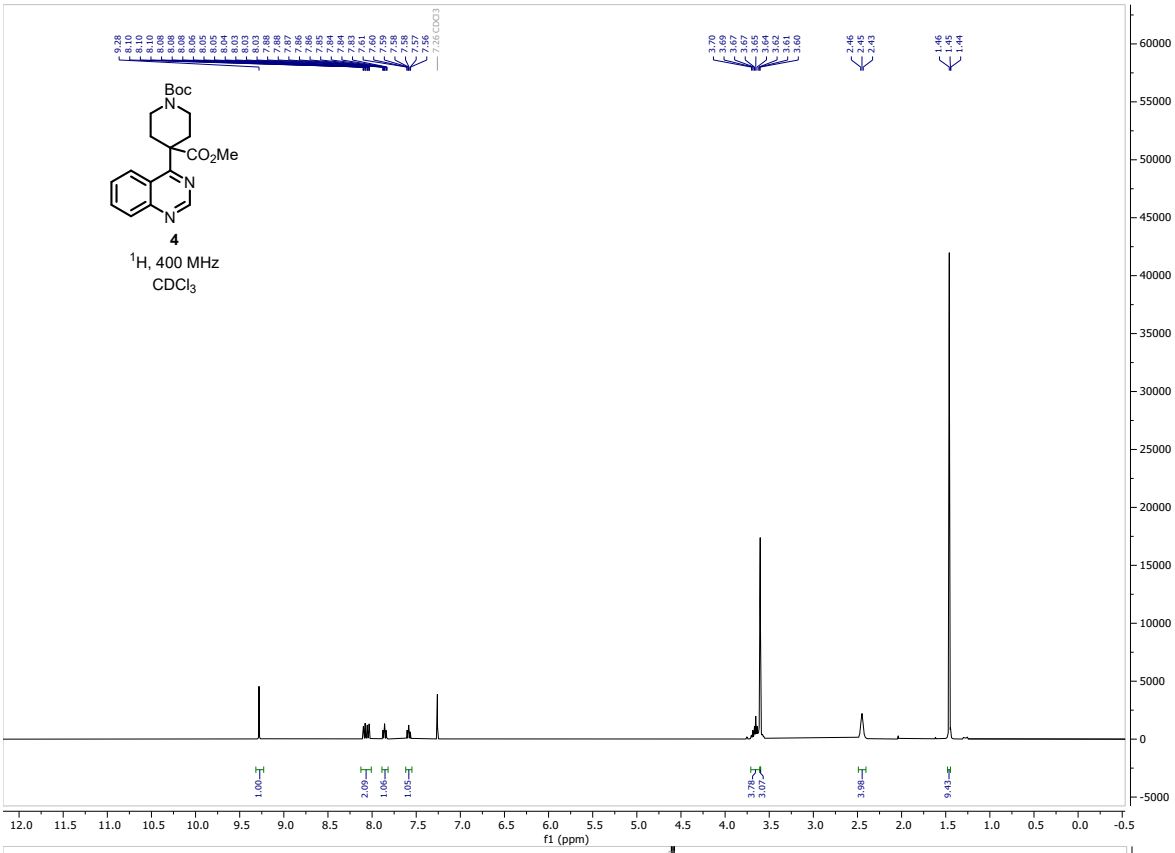
4-(((1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)oxy)methyl)quinazoline (54):

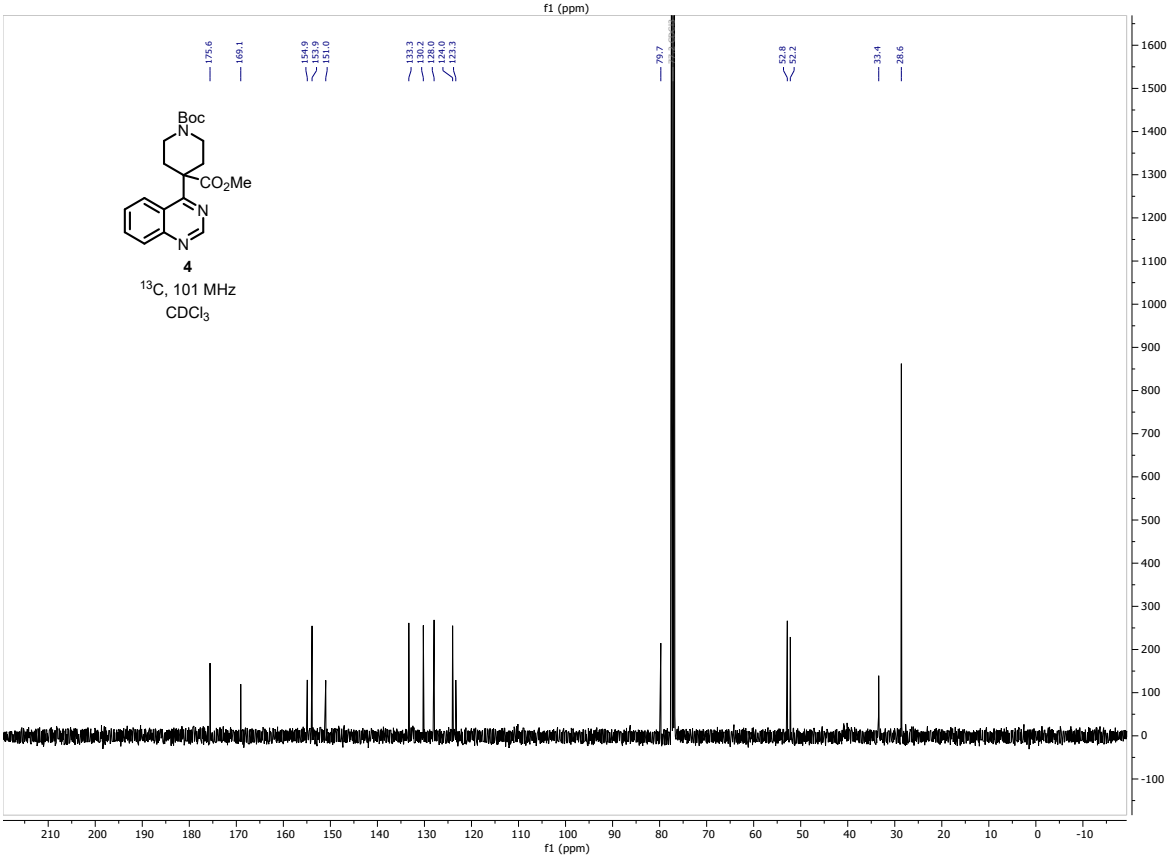
Product obtained: 5.6 mg, LC-MS data – Ret. time 2.73: ES+ m/z 309 ([M+H]$^+$).

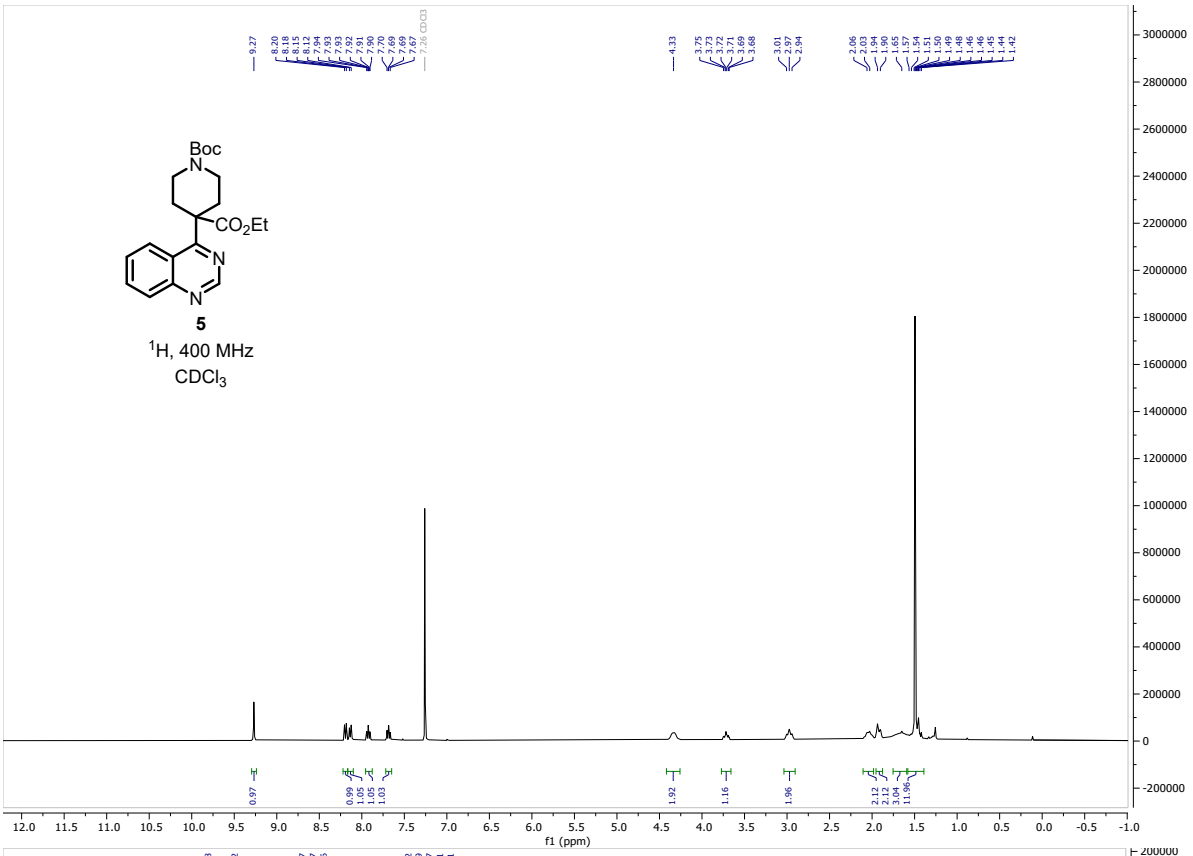


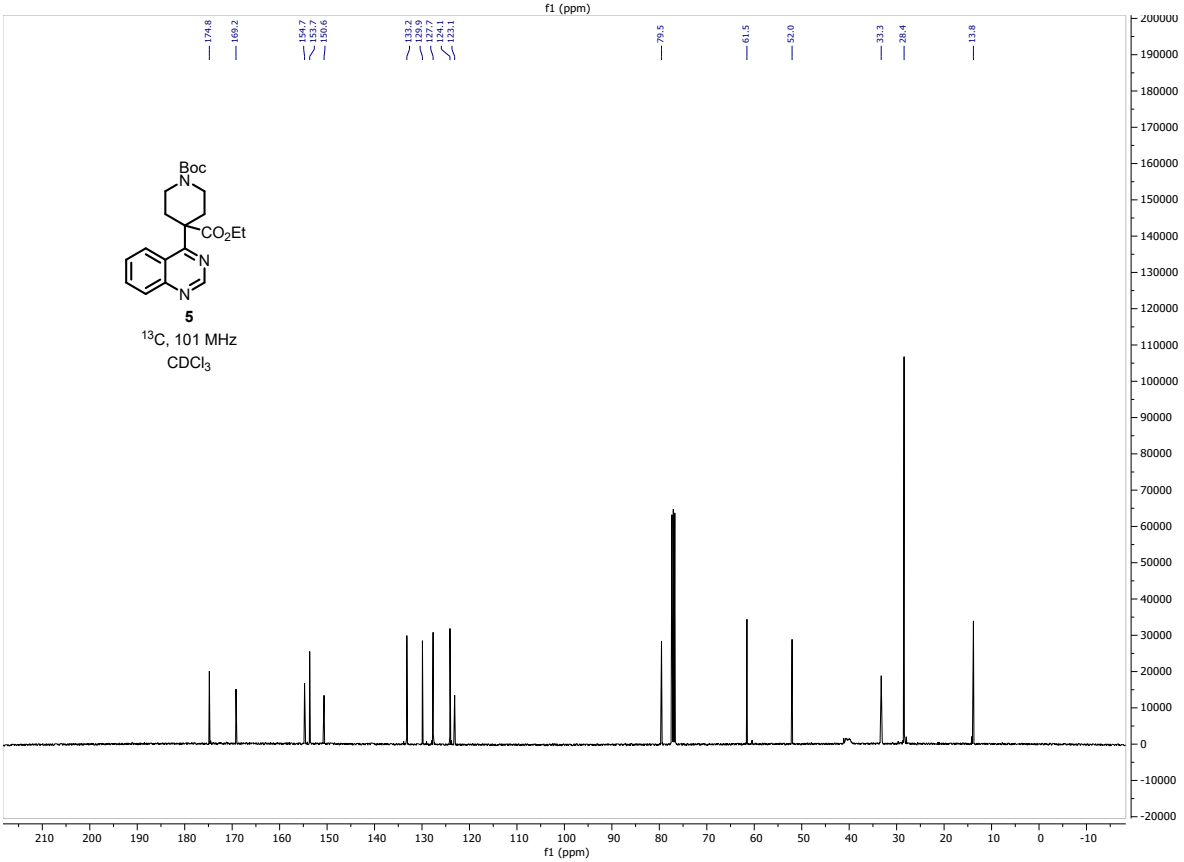


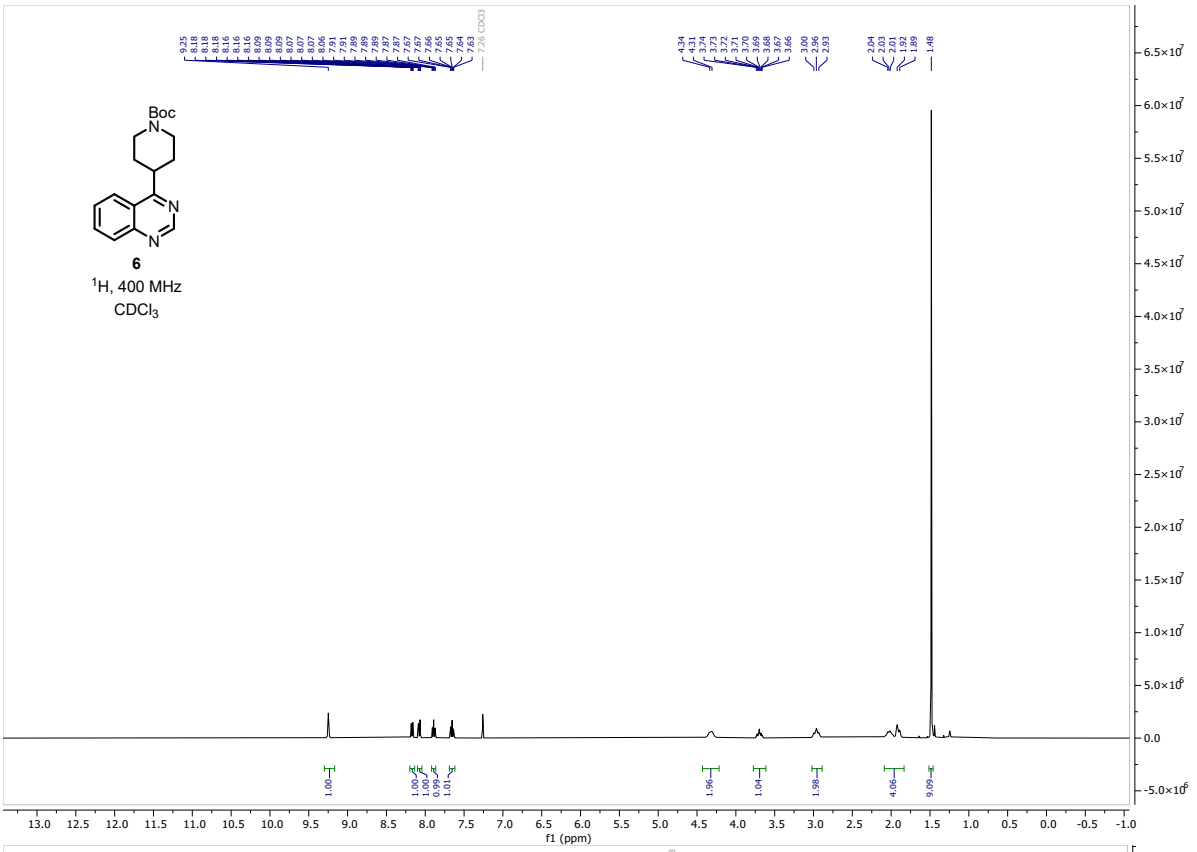
VII. NMR Spectra

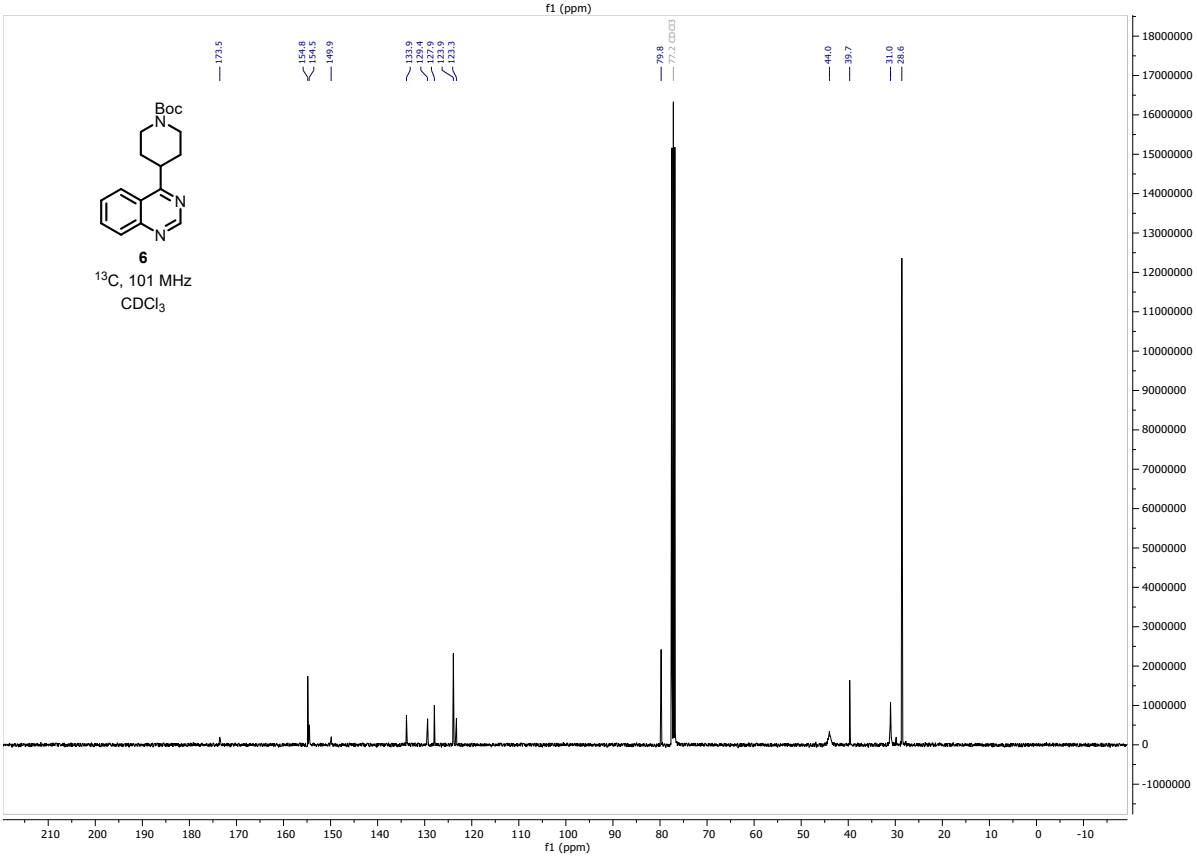


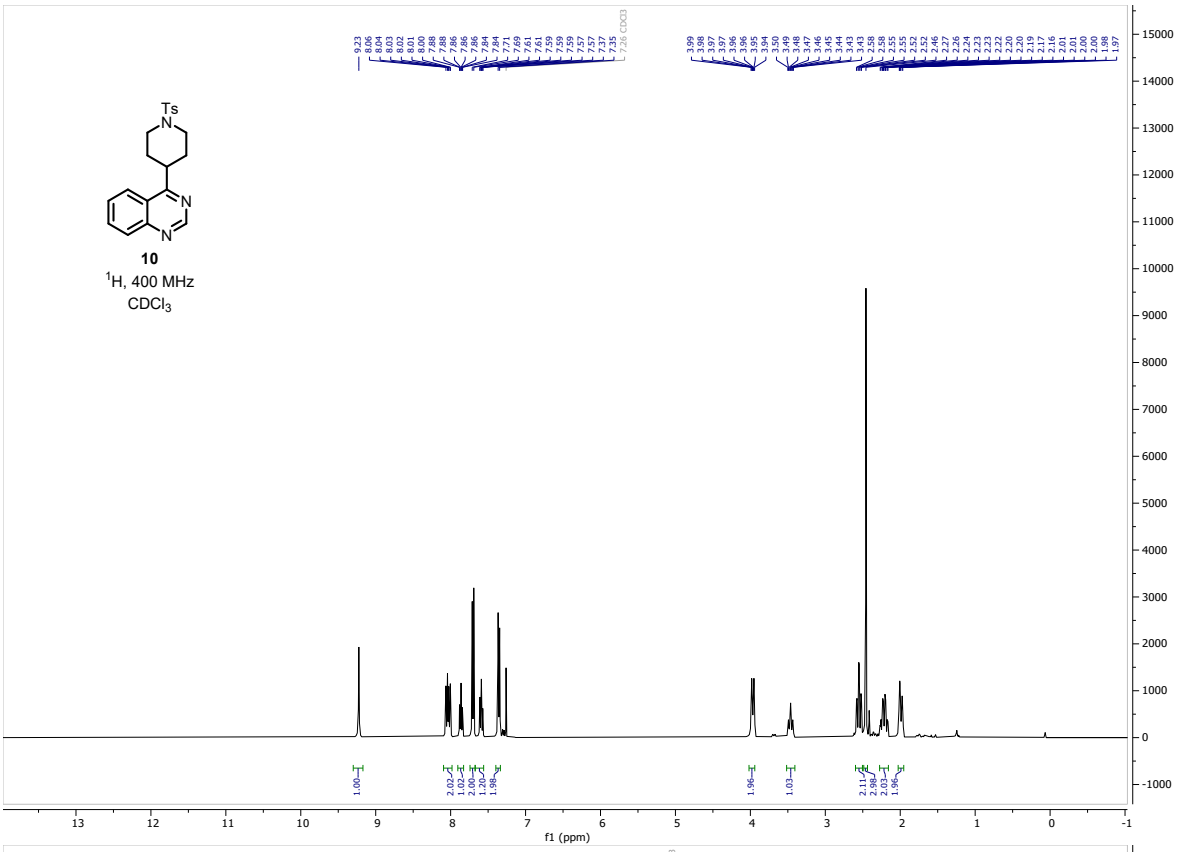


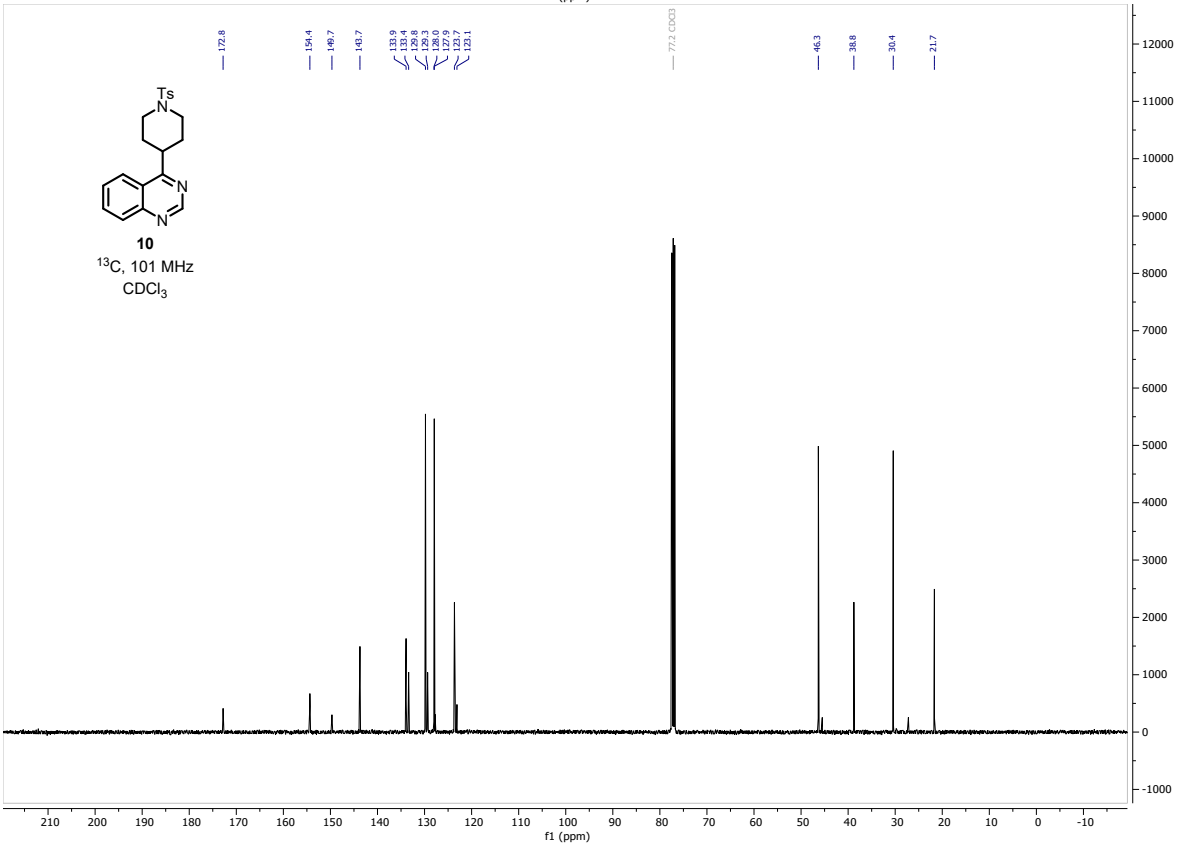

Boc
N
CO2Et
N
N
5
1H, 400 MHz
CDCl3
f1 (ppm)

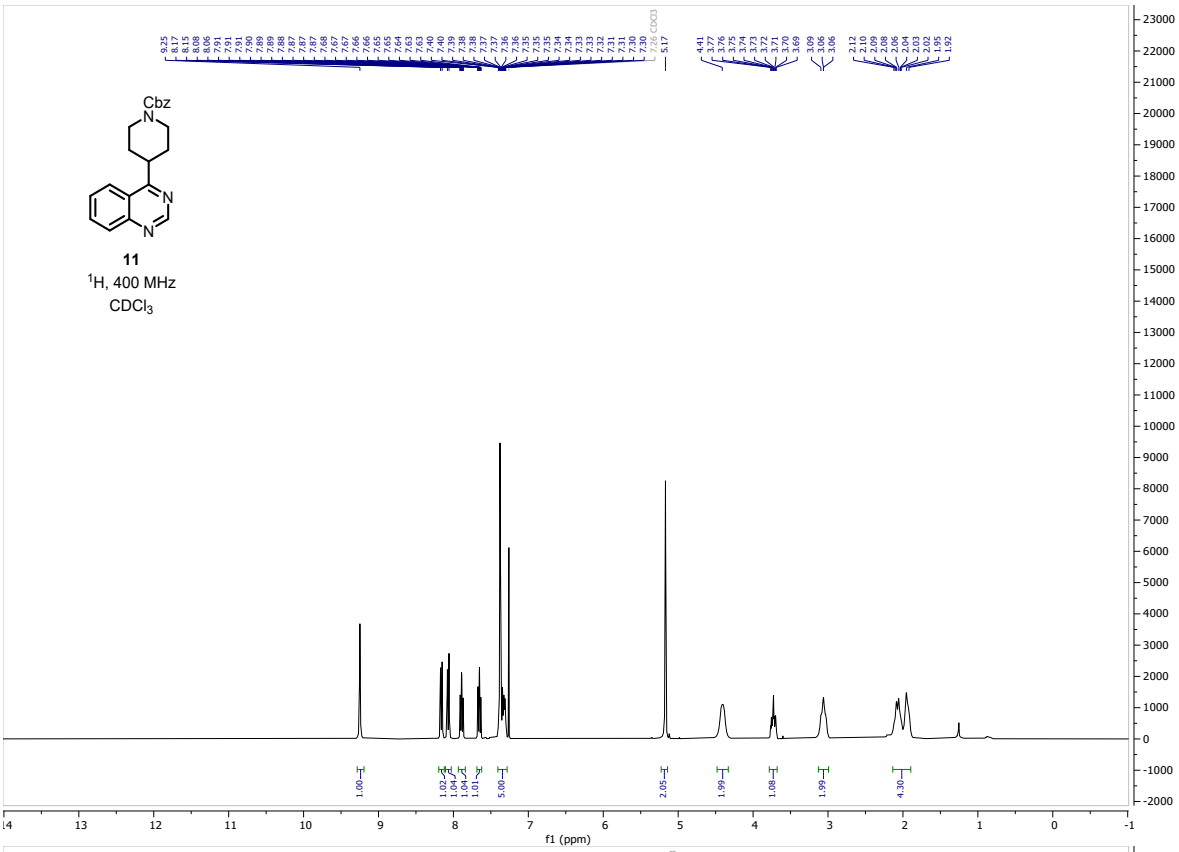

Boc
N
CO2Et
N
N
5
13C, 101 MHz
CDCl3
f1 (ppm)

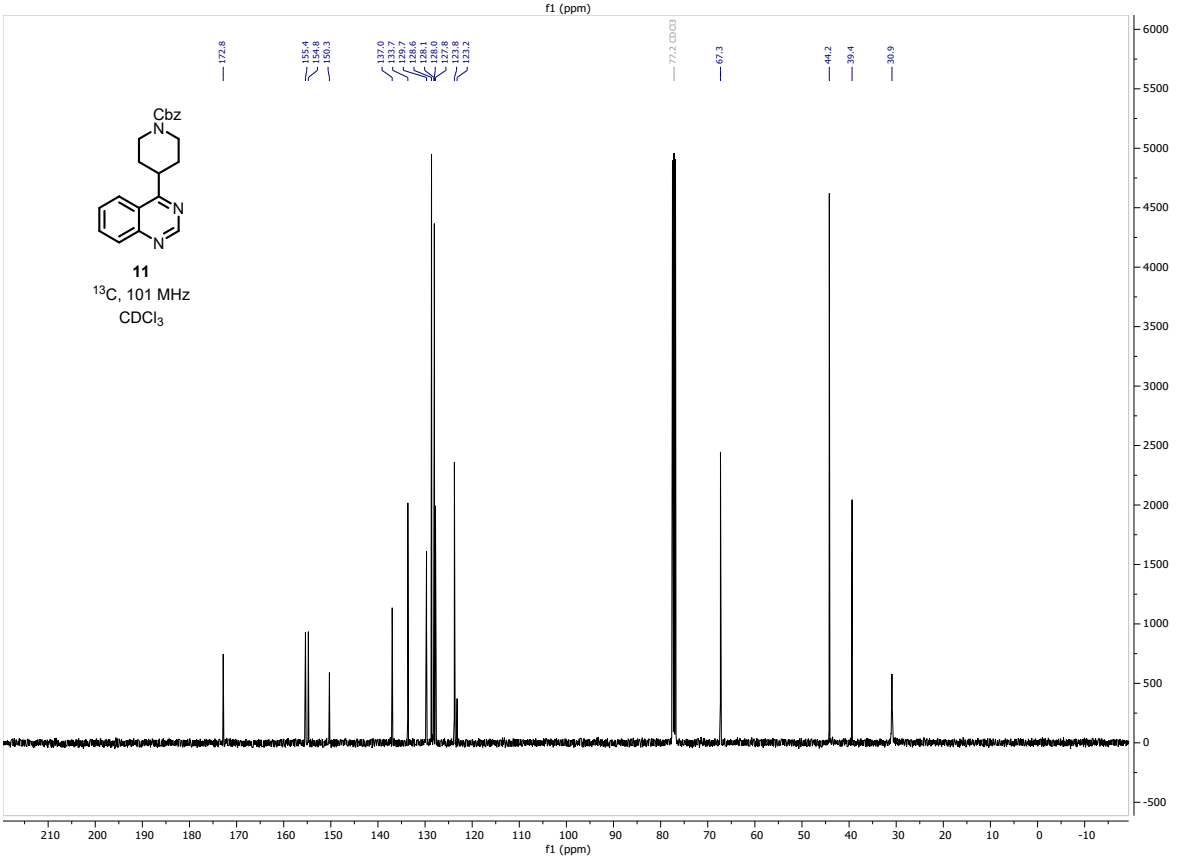

Boc
N
N
N
6
1H, 400 MHz
CDCl3
f1 (ppm)

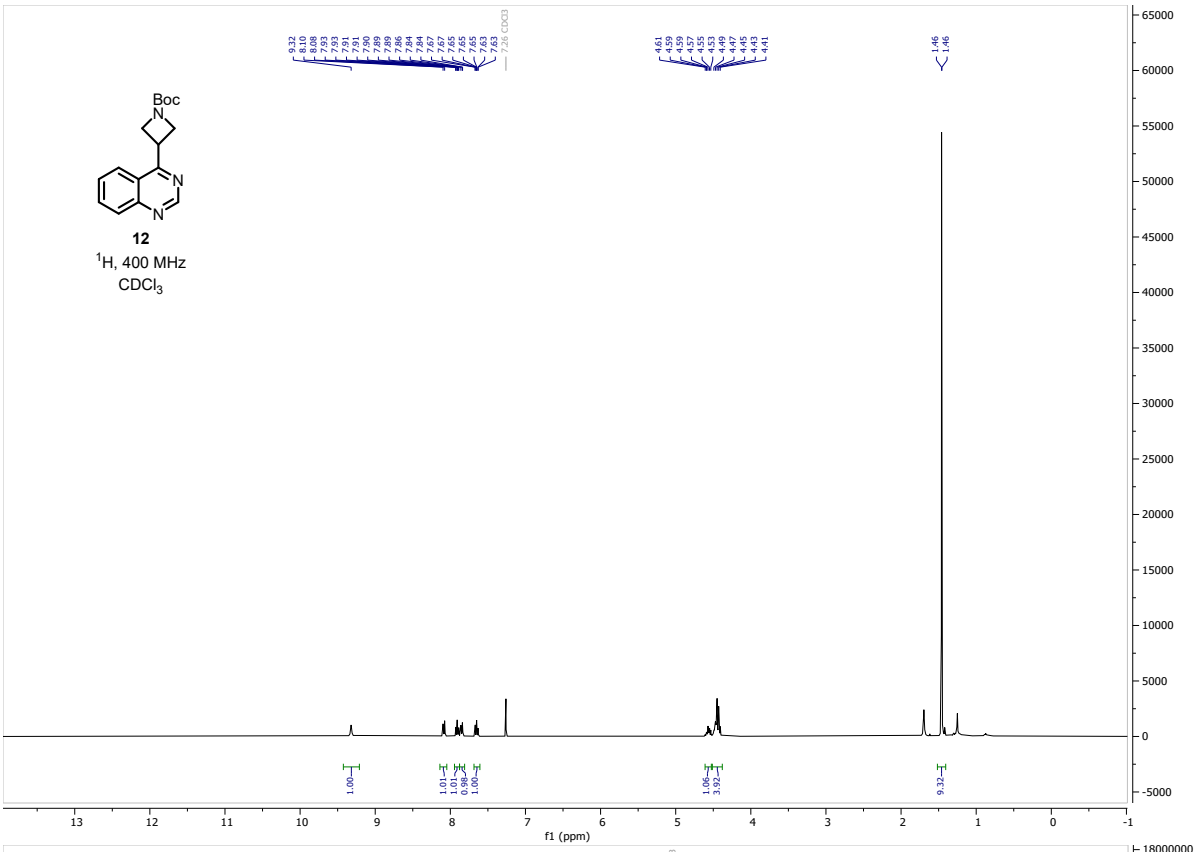

Boc
N
N
N
6
13C, 101 MHz
CDCl3
f1 (ppm)

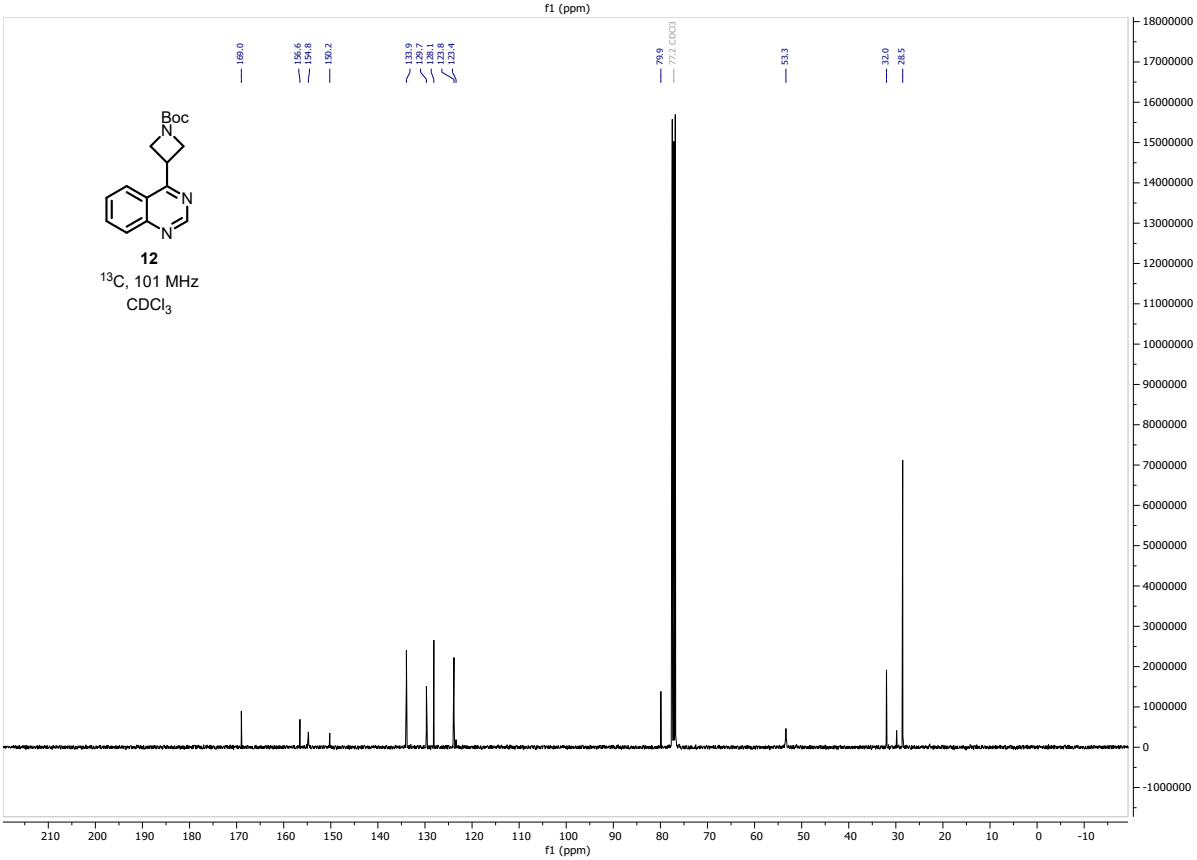

Ts
N
N
N
10
1H, 400 MHz
CDCl3
f1 (ppm)

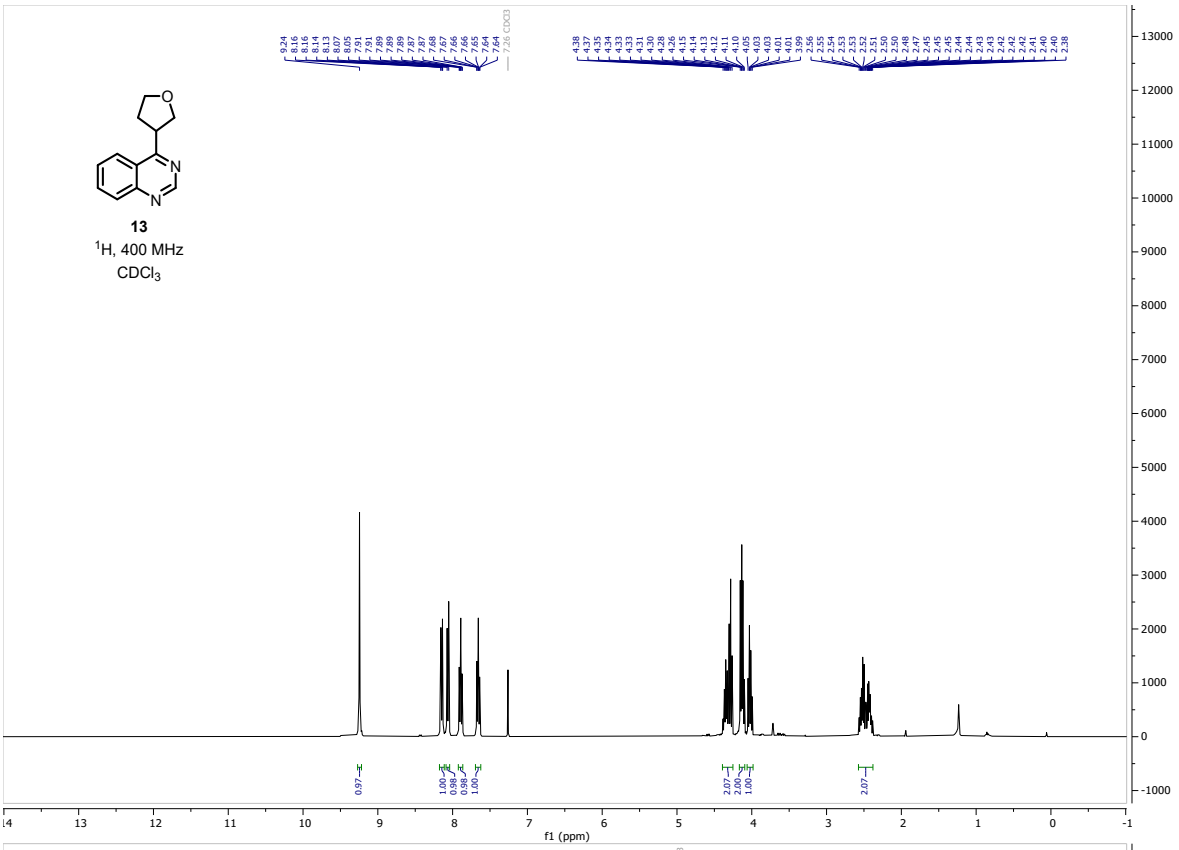

Ts
N
N
N
10
13C, 101 MHz
CDCl3
f1 (ppm)

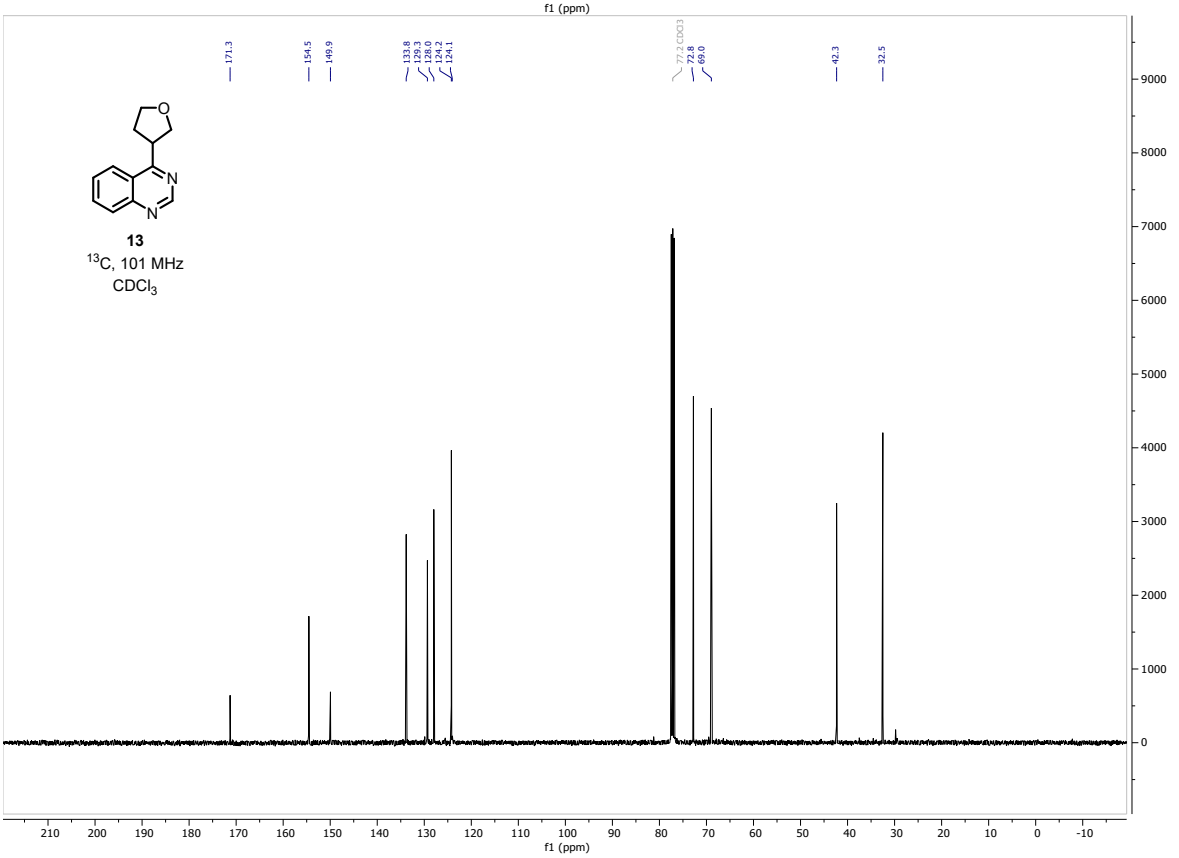

Cbz
N
N
N
11
1H, 400 MHz
CDCl3
f1 (ppm)

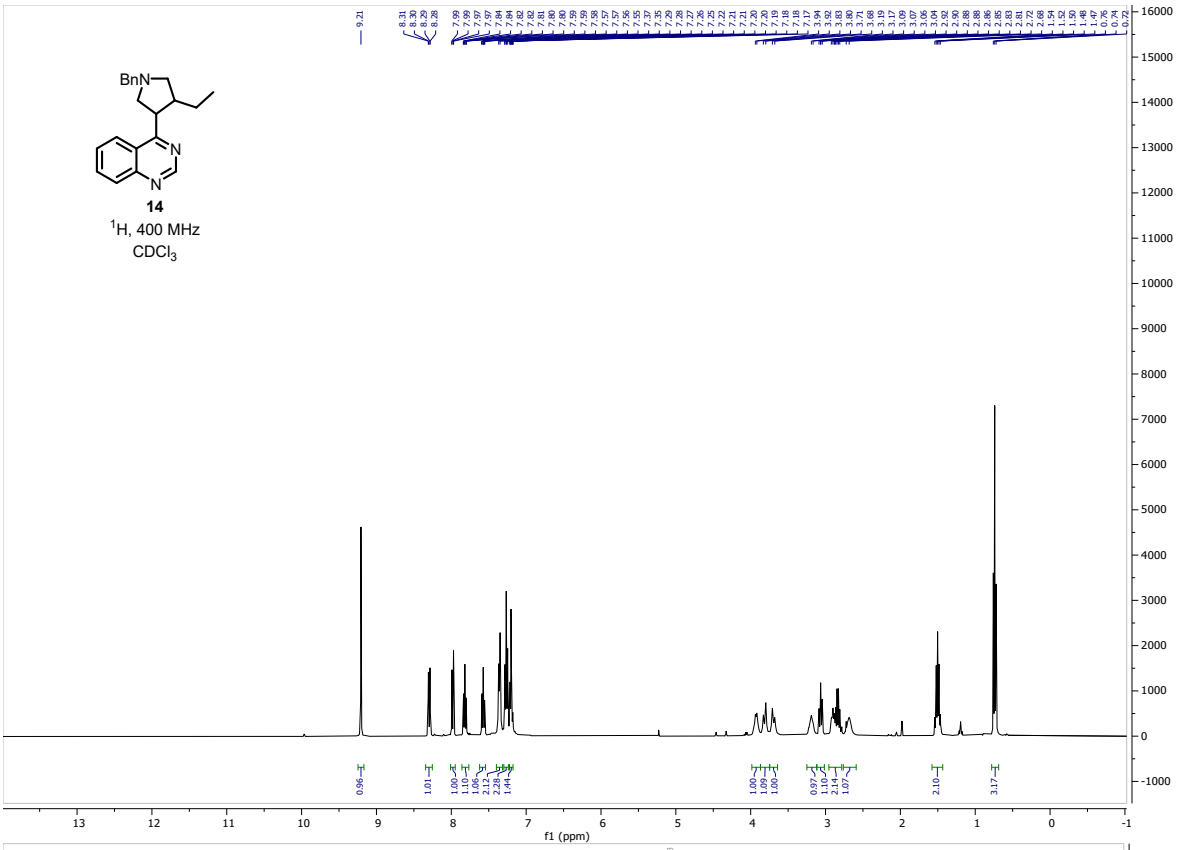

Cbz
N
N
N
11
13C, 101 MHz
CDCl3
f1 (ppm)

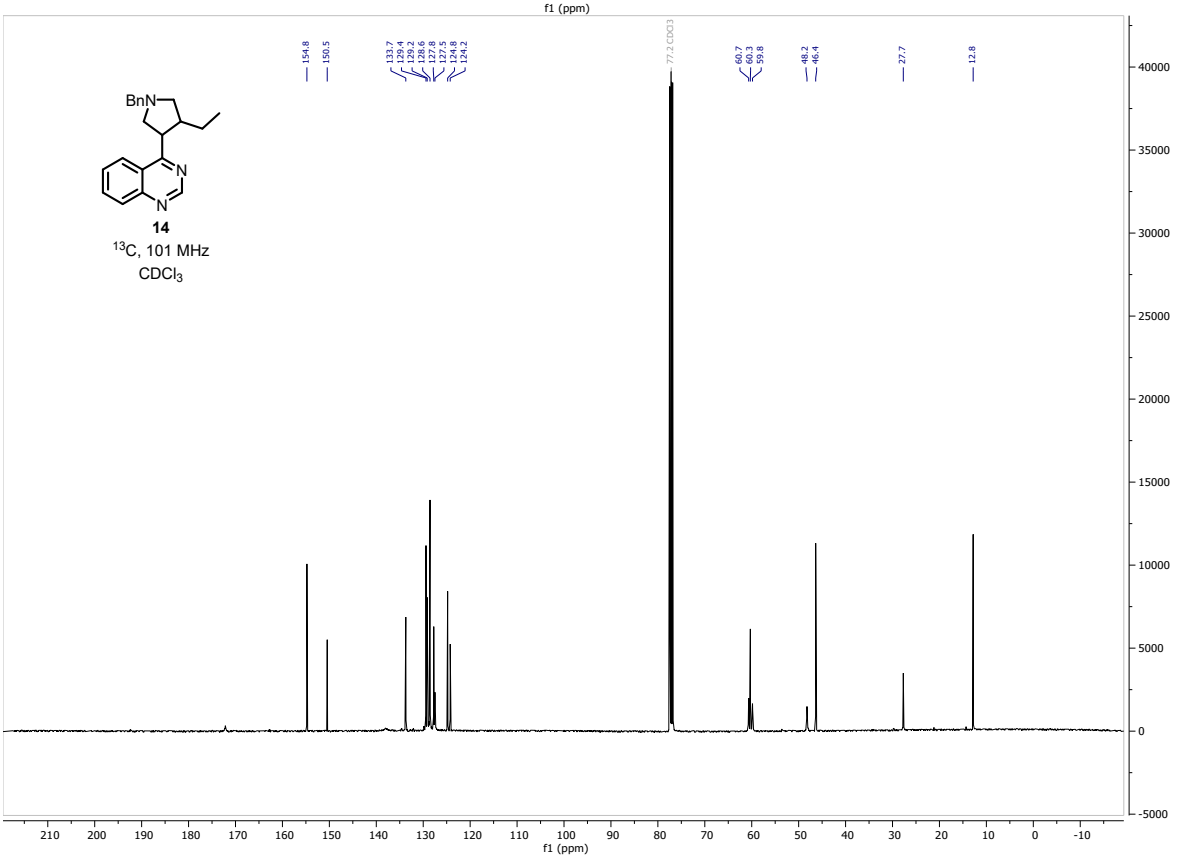

Boc
N
N
N
12
1H, 400 MHz
CDCl3
f1 (ppm)

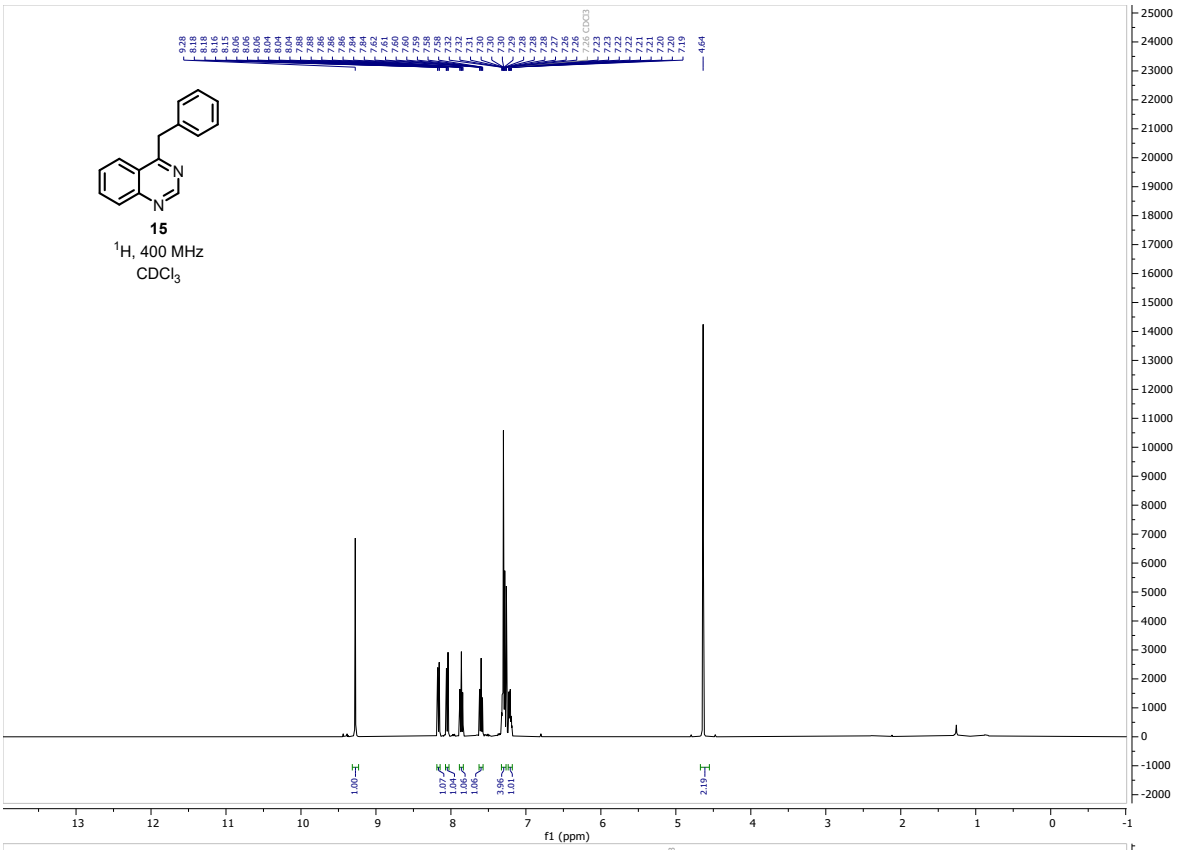

Boc
N
N
N
12
13C, 101 MHz
CDCl3
f1 (ppm)

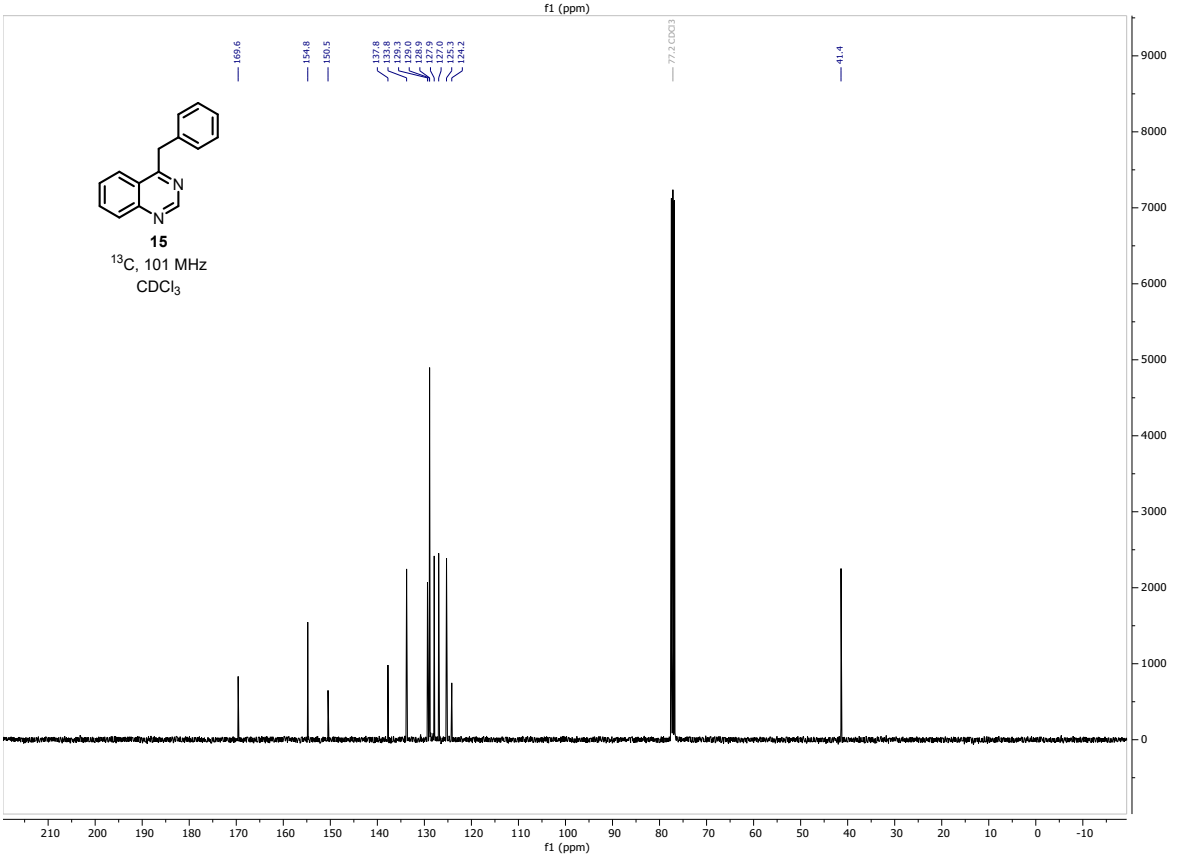

13
1H, 400 MHz
CDCl3
f1 (ppm)

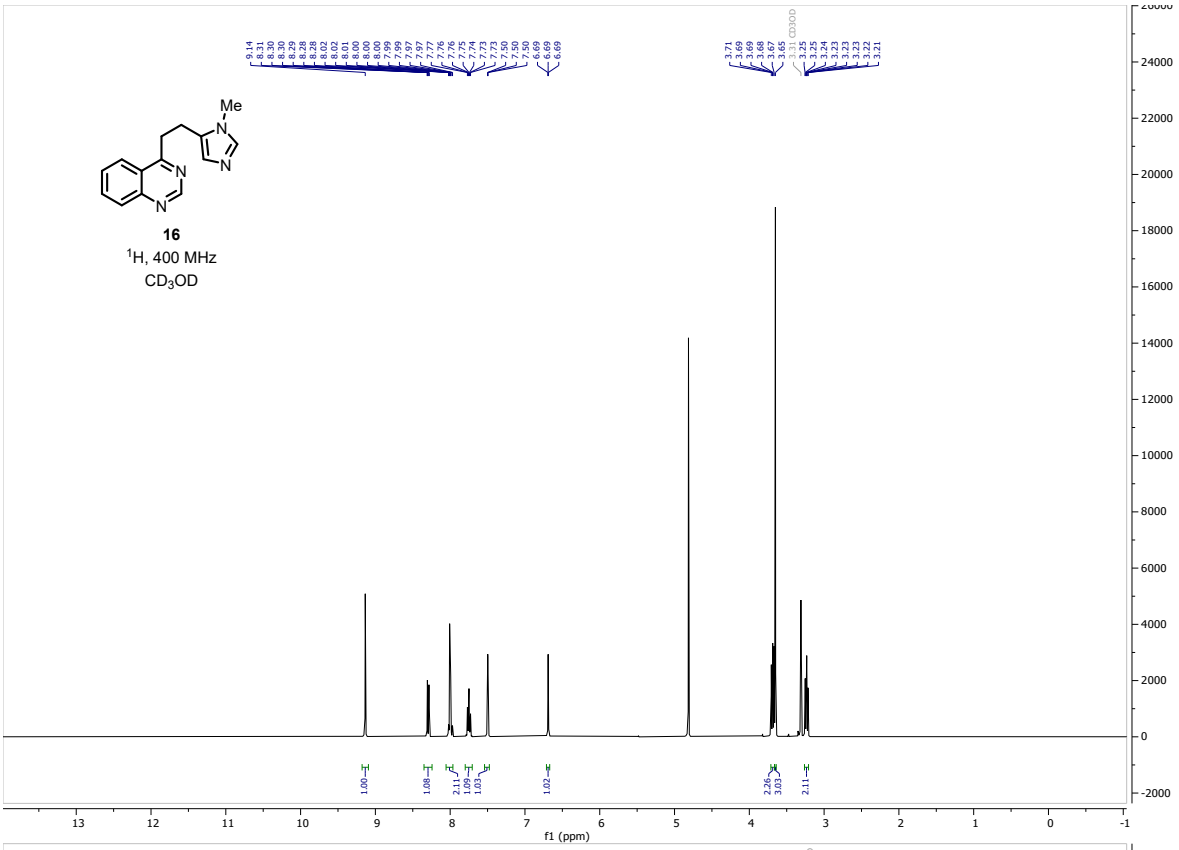

13
13C, 101 MHz
CDCl3
f1 (ppm)

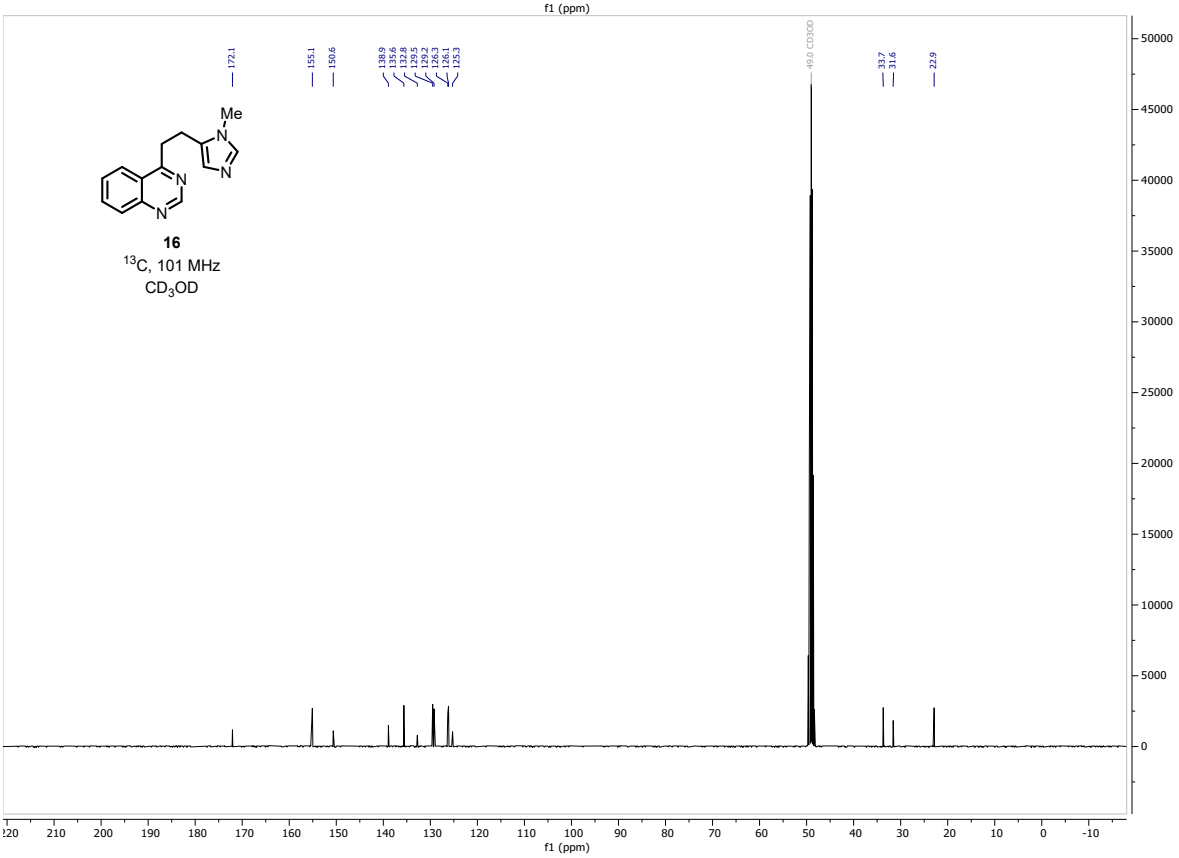

BnN
N
N
14
1H, 400 MHz
CDCl3
f1 (ppm)

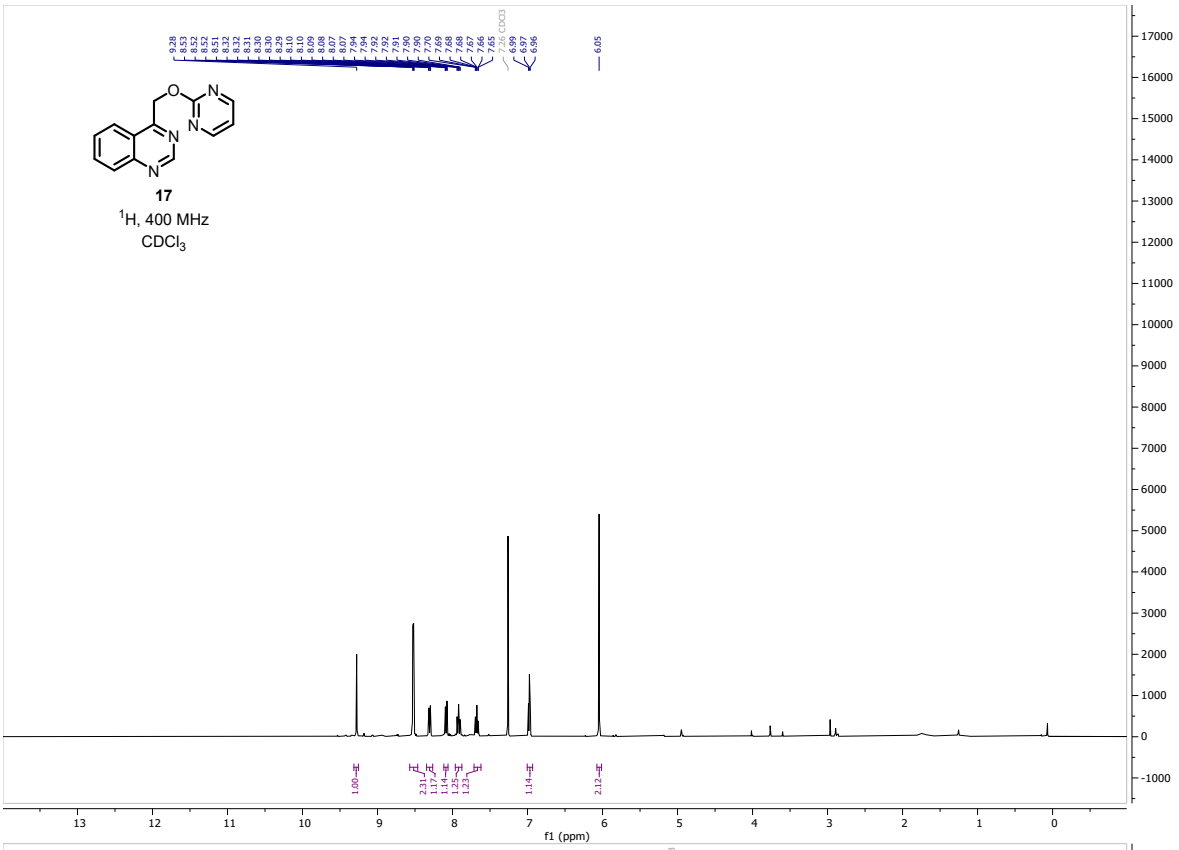

BnN
N
N
14
13C, 101 MHz
CDCl3
f1 (ppm)

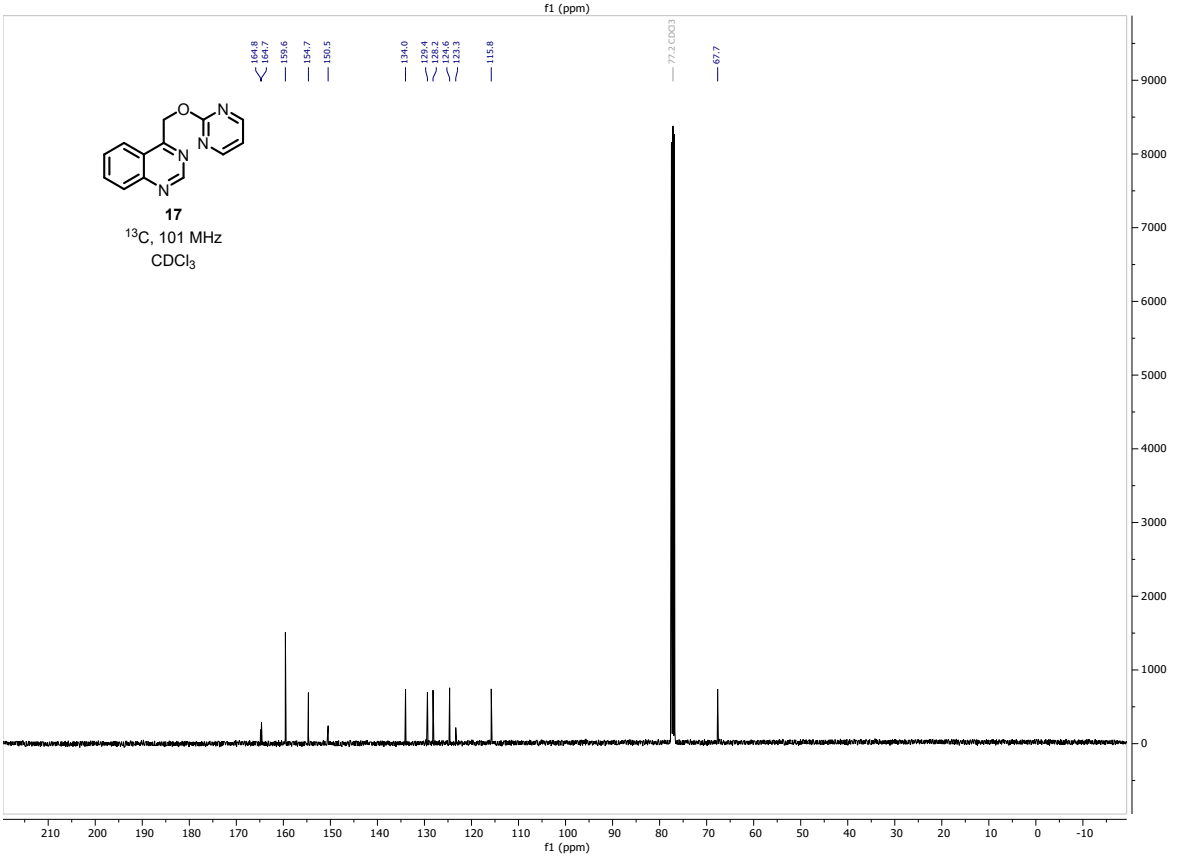

15
1H, 400 MHz
CDCl3
f1 (ppm)

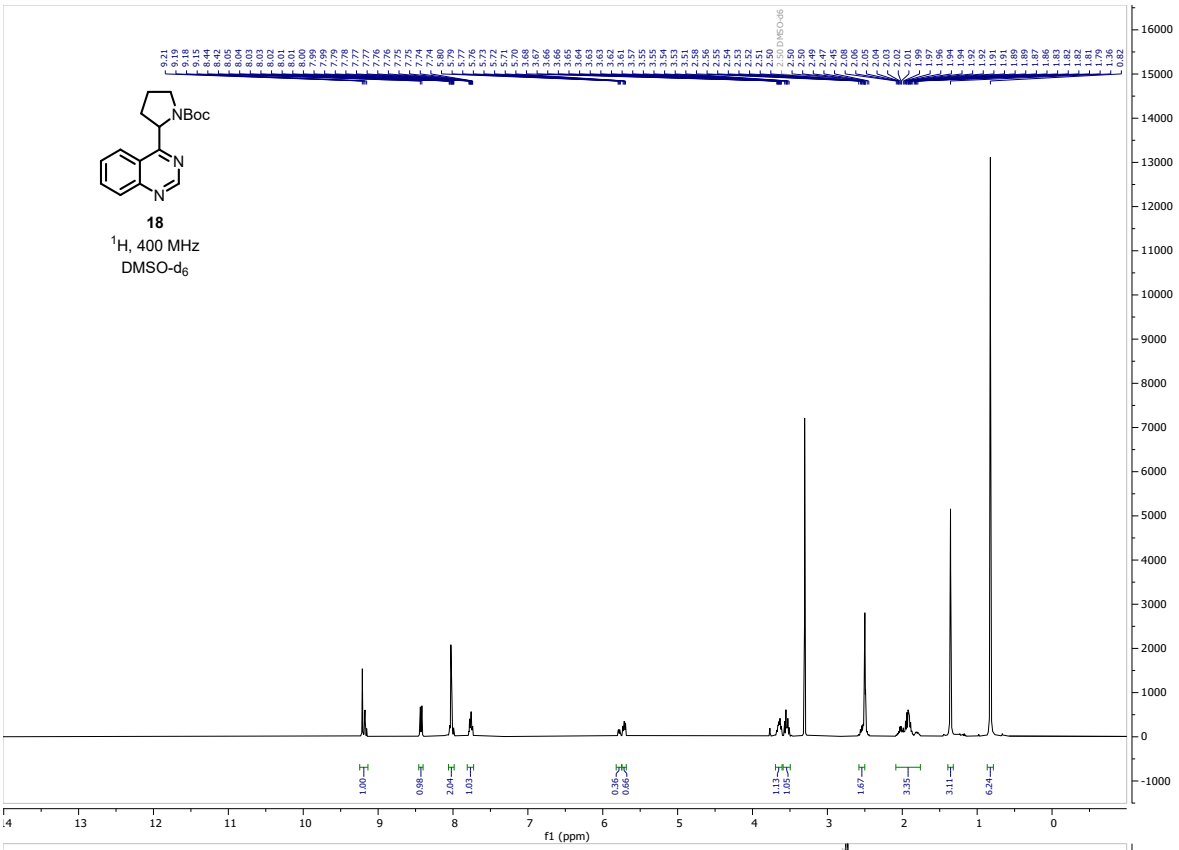

15
13C, 101 MHz
CDCl3
f1 (ppm)

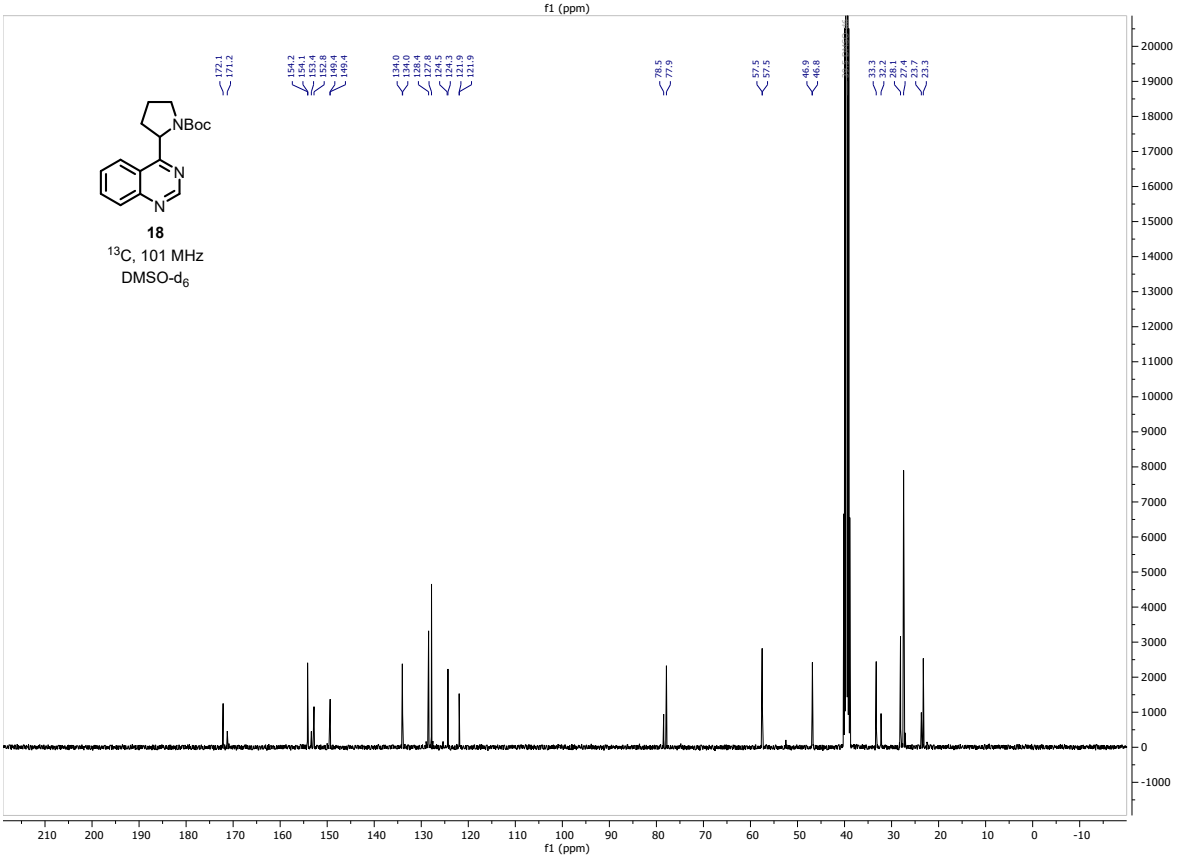

Me
N
N
N
N
16
1H, 400 MHz
CD3OD
f1 (ppm)

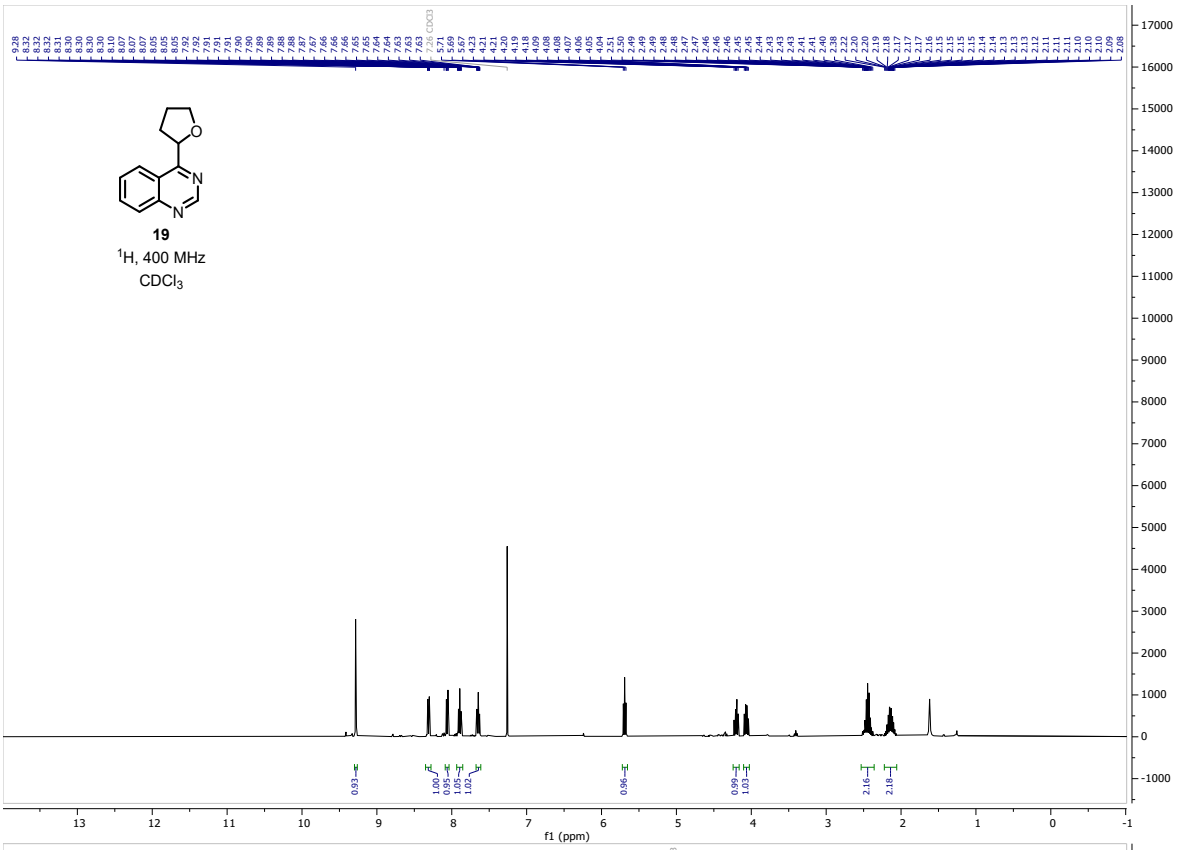

Me
N
N
N
N
16
13C, 101 MHz
CD3OD
f1 (ppm)

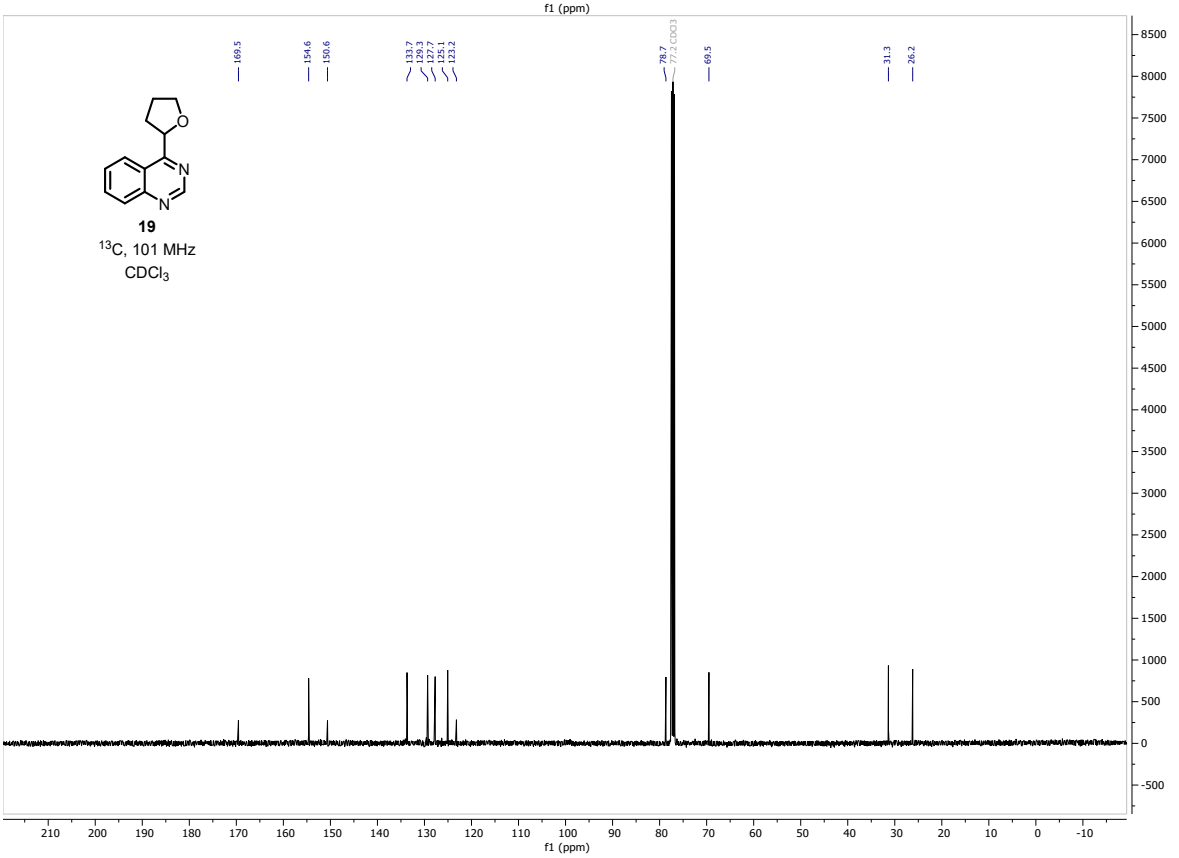

17
1H, 400 MHz
CDCl3
f1 (ppm)

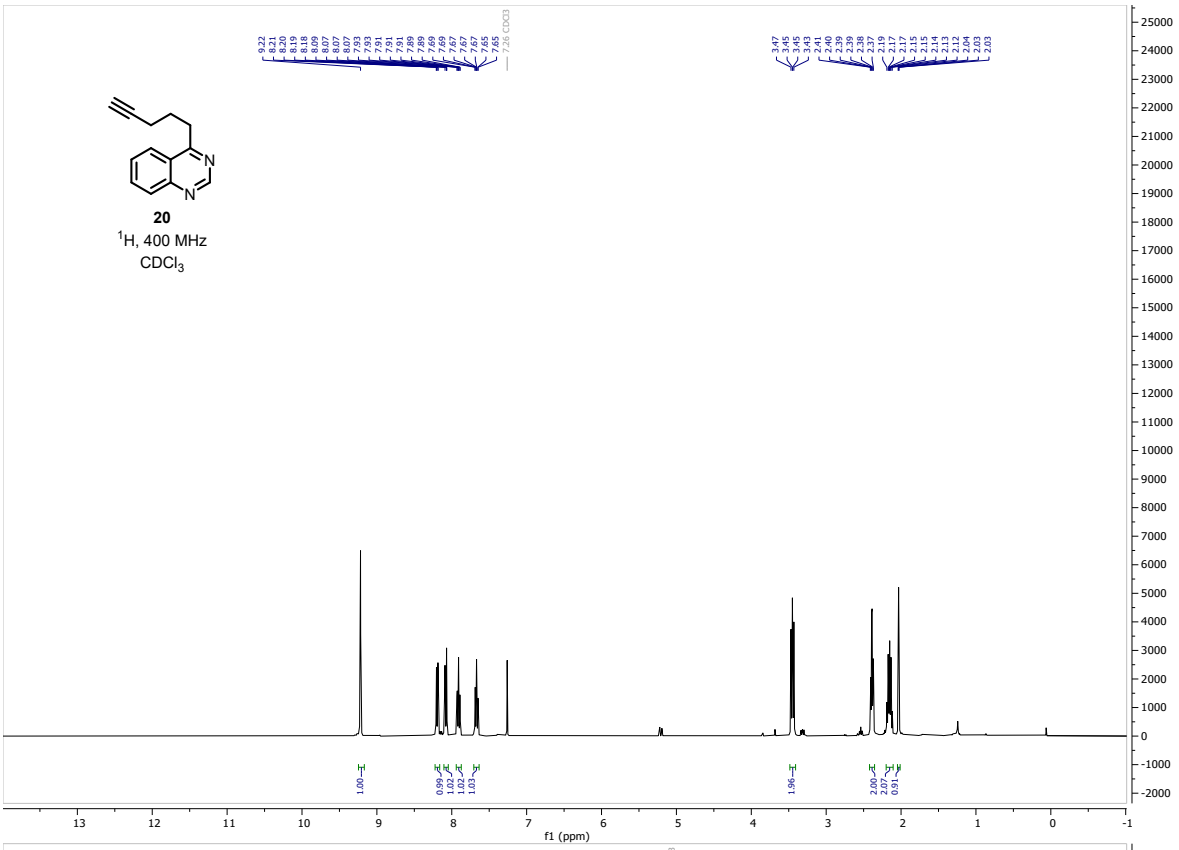

17
13C, 101 MHz
CDCl3
f1 (ppm)

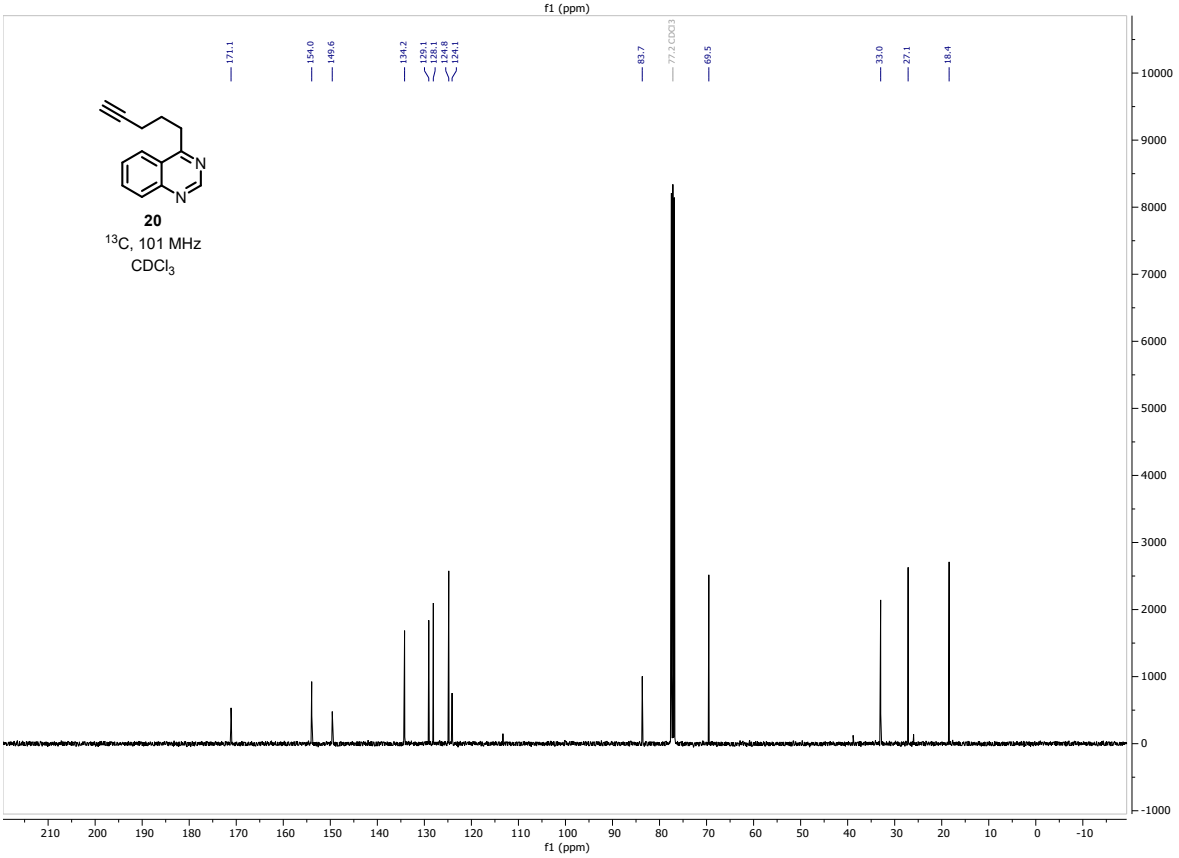

NBoc
N
N
18
1H, 400 MHz
DMSO-d6
f1 (ppm)

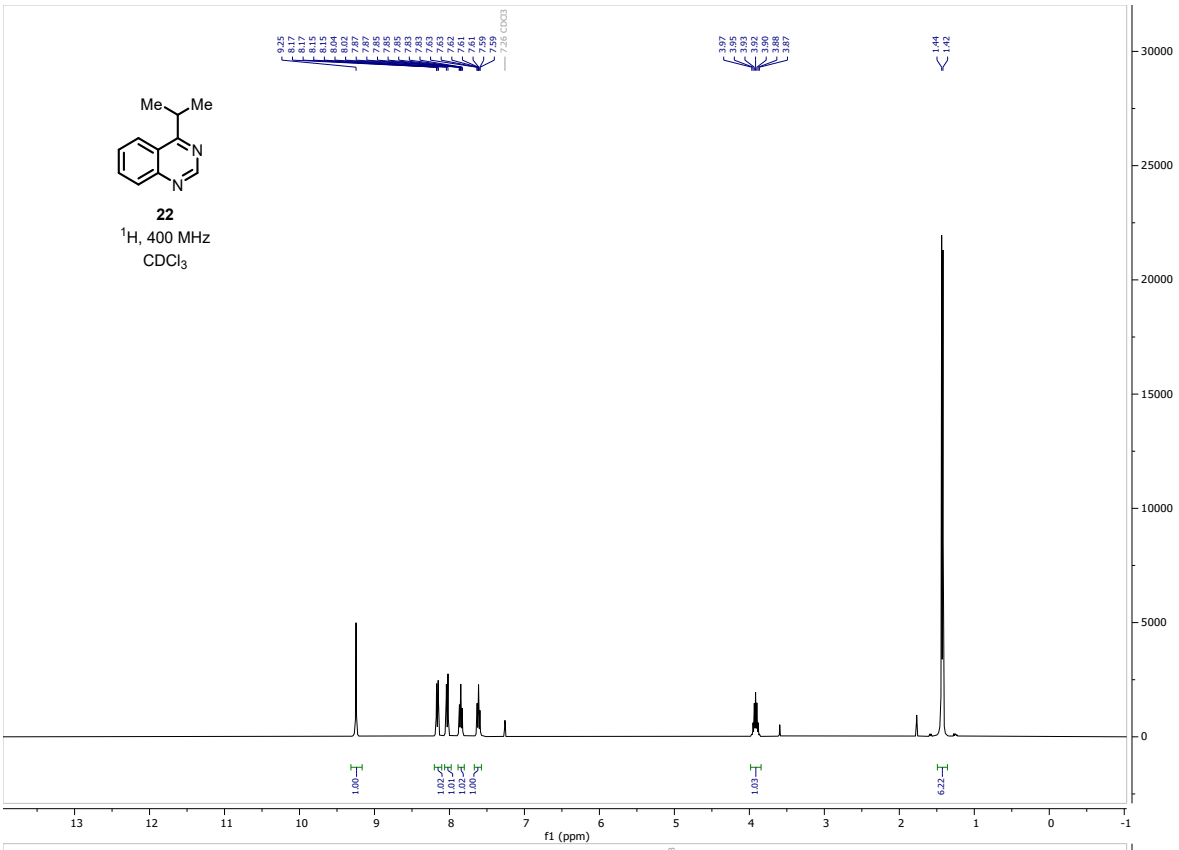

NBoc
N
N
18
13C, 101 MHz
DMSO-d6
f1 (ppm)

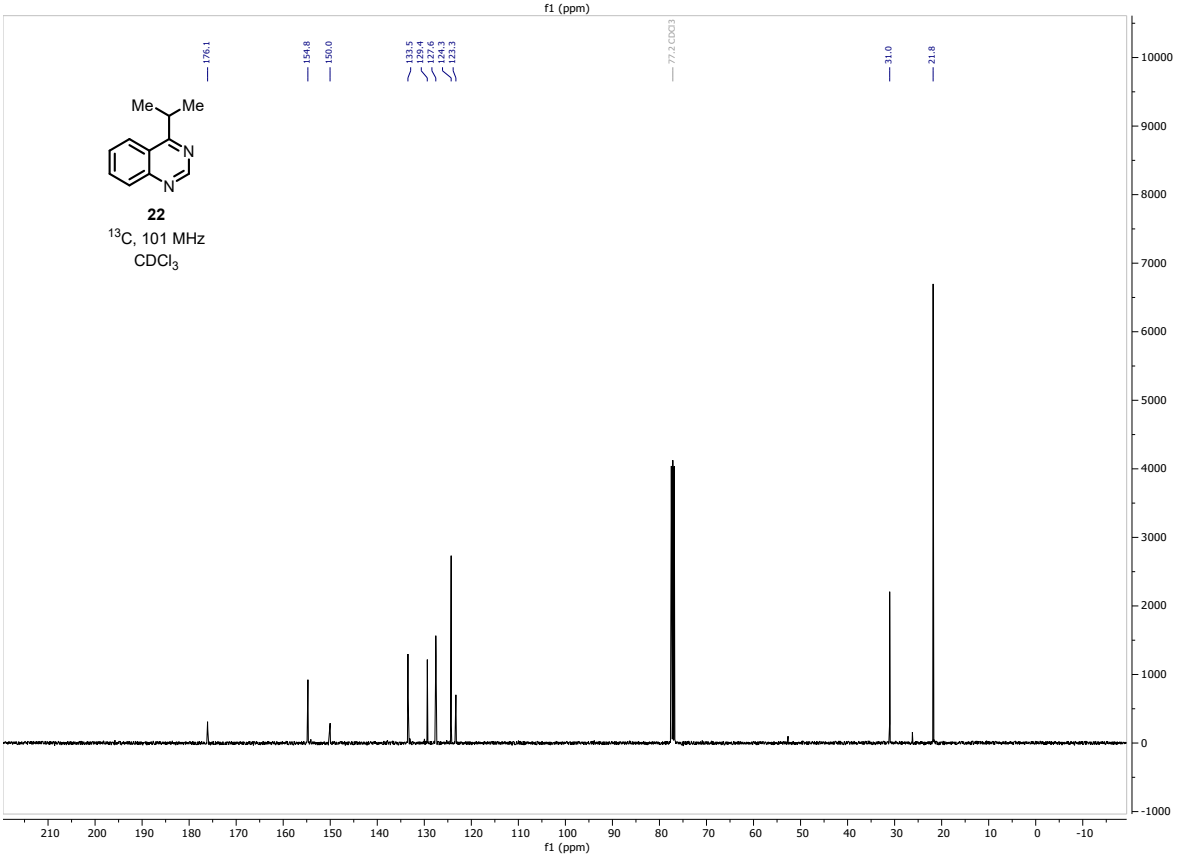

19
1H, 400 MHz
CDCl3
f1 (ppm)

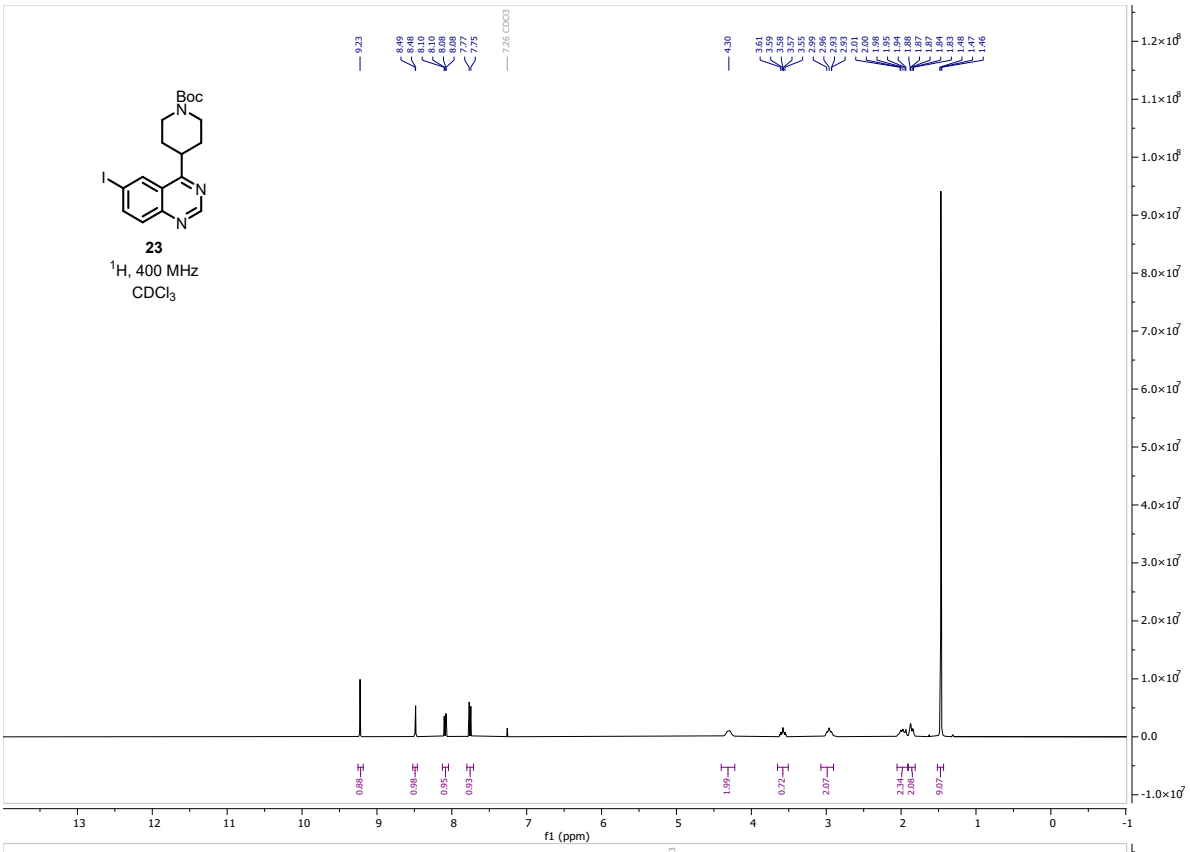

19
13C, 101 MHz
CDCl3
169.5
154.6
150.6
133.7
129.3
127.7
125.1
123.2
78.7
77.2 CDCl3
69.5
31.3
26.2
f1 (ppm)

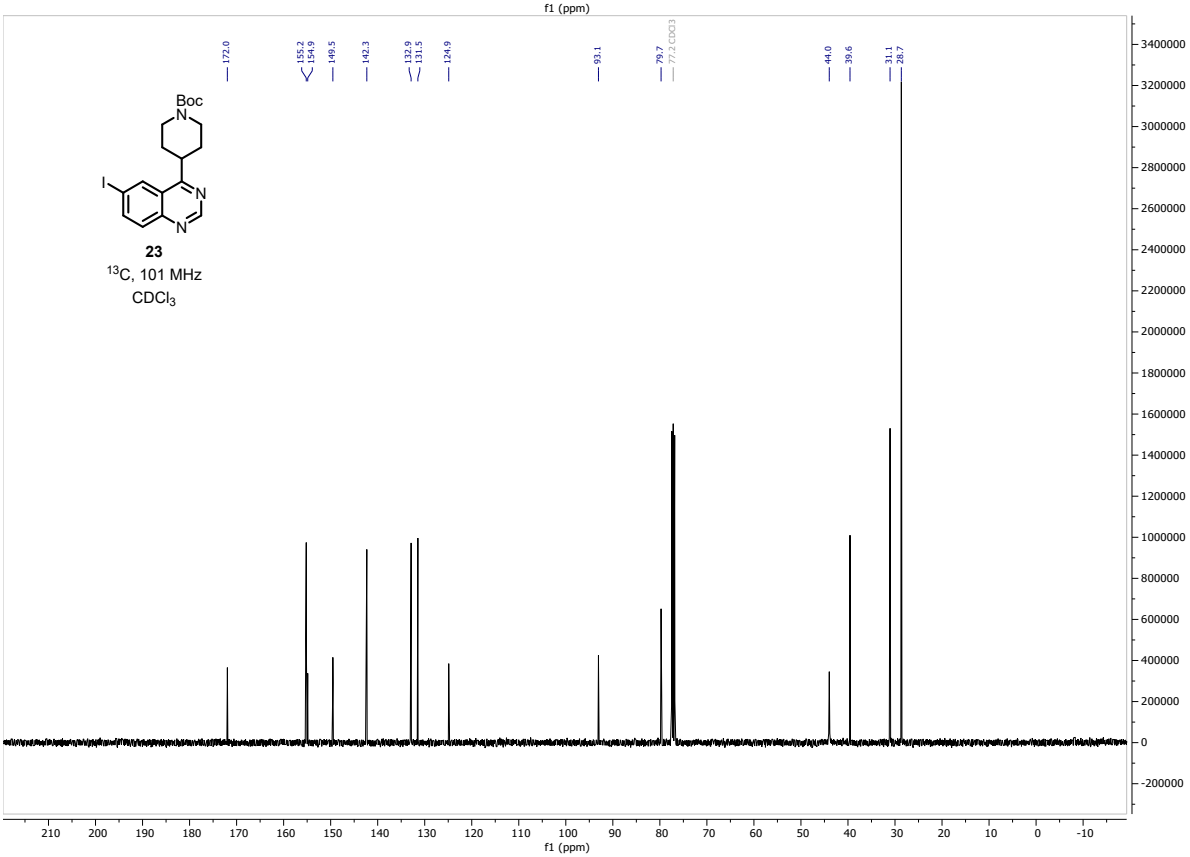

20
1H, 400 MHz
CDCl3
f1 (ppm)

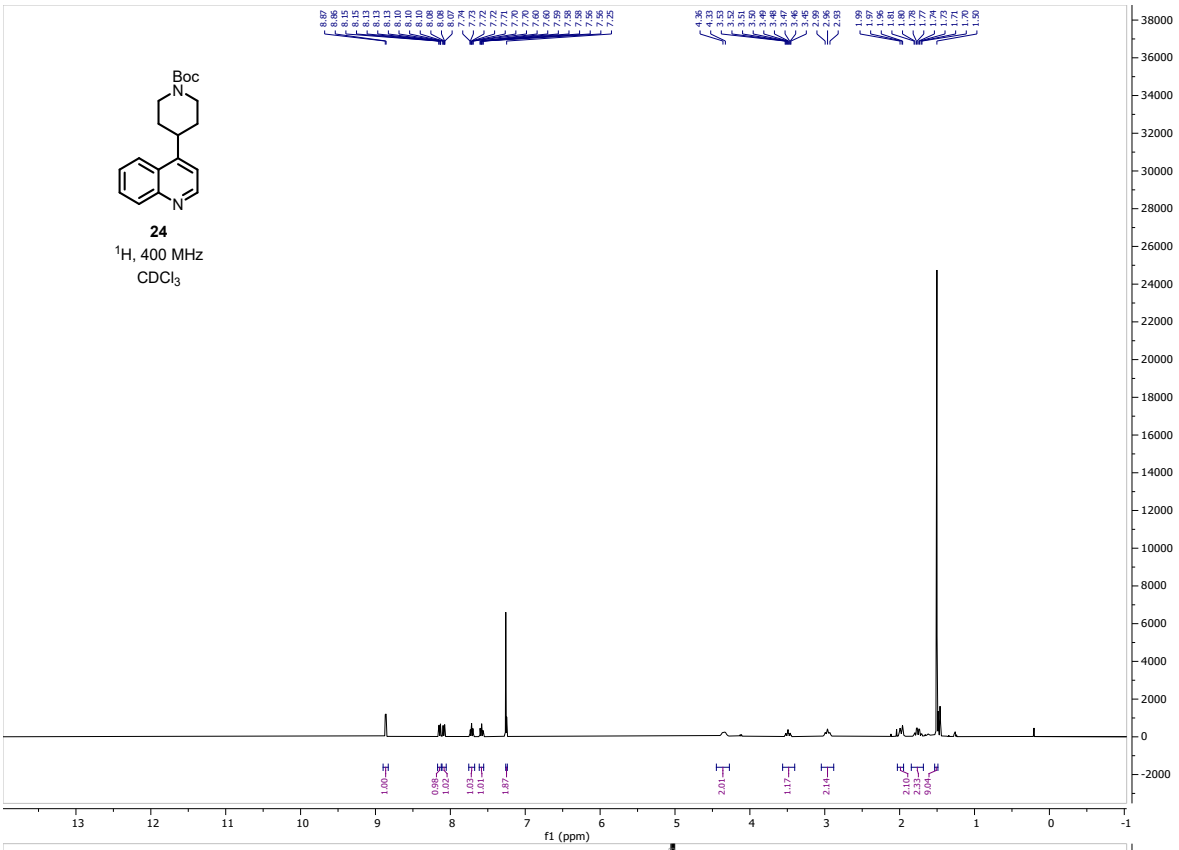

20
13C, 101 MHz
CDCl3
f1 (ppm)

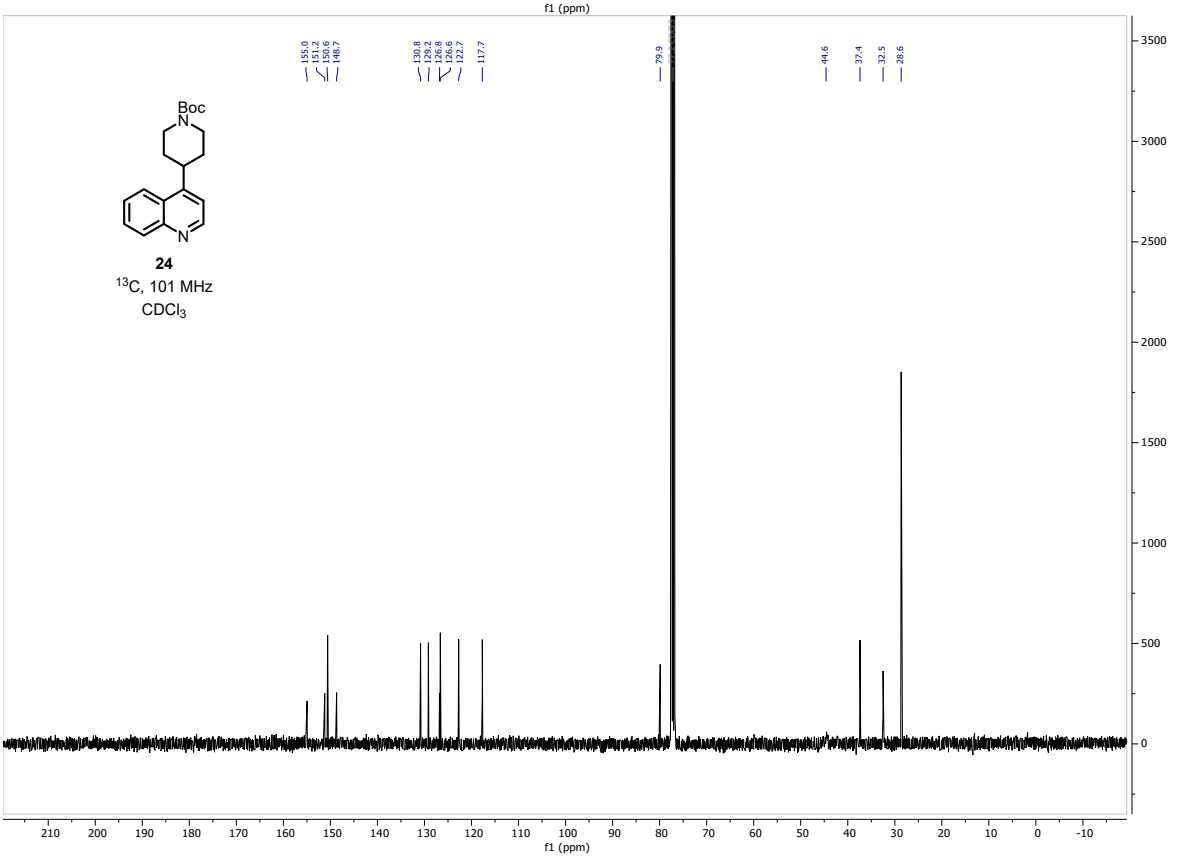

Me
Me
N
N
22
1H, 400 MHz
CDCl3
f1 (ppm)

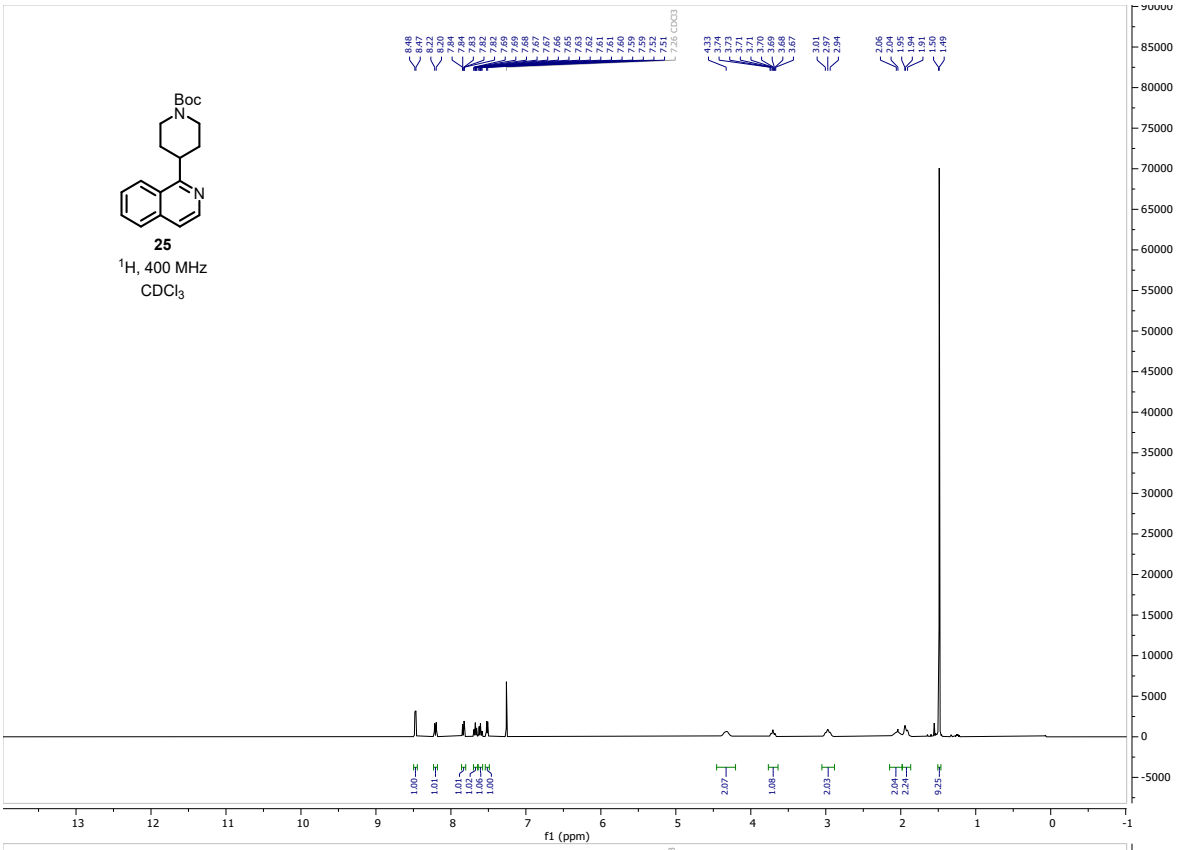

Me
Me
N
N
22
13C, 101 MHz
CDCl3
f1 (ppm)

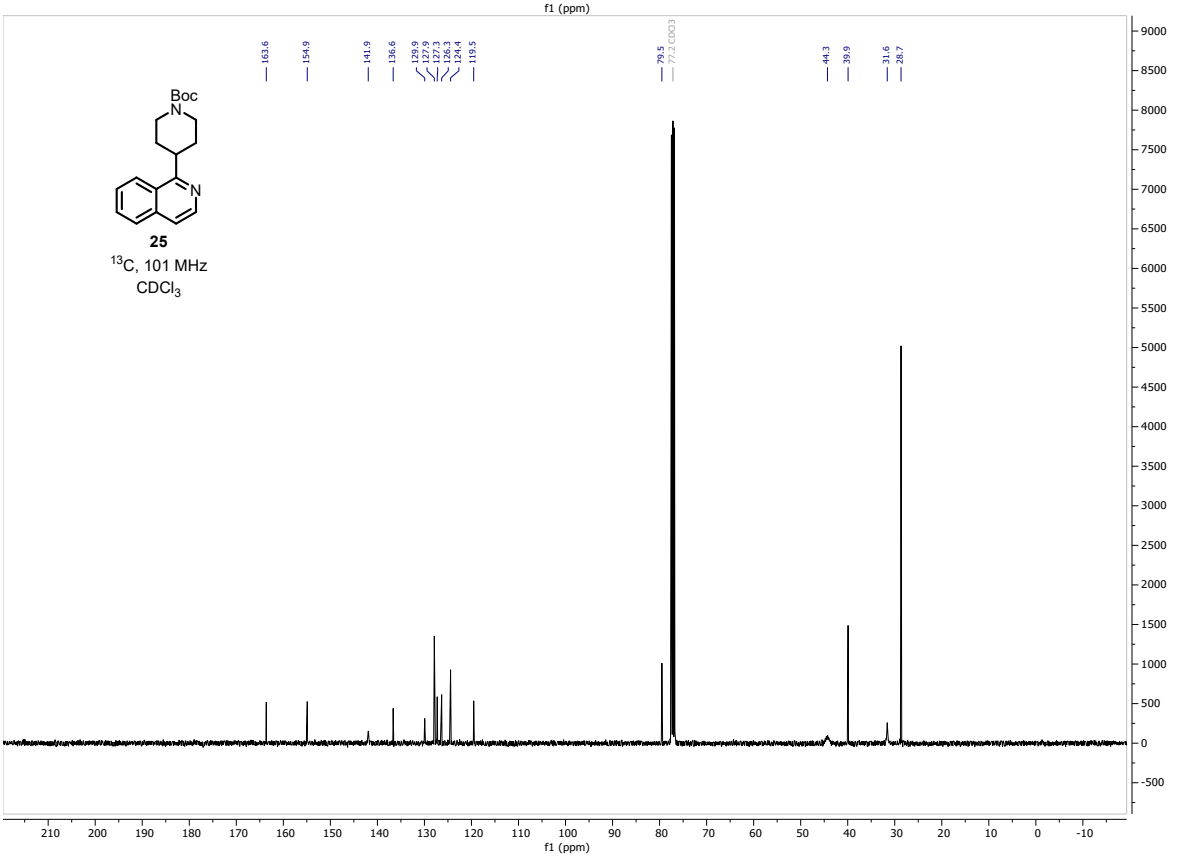

Boc
N
I
N
N
23
1H, 400 MHz
CDCl3
9.23
8.49
8.48
8.10
8.08
8.08
7.77
7.75
7.26 CDCl3
4.30
3.61
3.59
3.58
3.57
3.35
2.99
2.96
2.93
2.93
2.01
2.00
1.98
1.95
1.94
1.88
1.87
1.85
1.84
1.83
1.48
1.47
1.46
0.88
0.98
0.95
0.93
1.99
0.72
2.07
2.34
2.08
9.07
f1 (ppm)

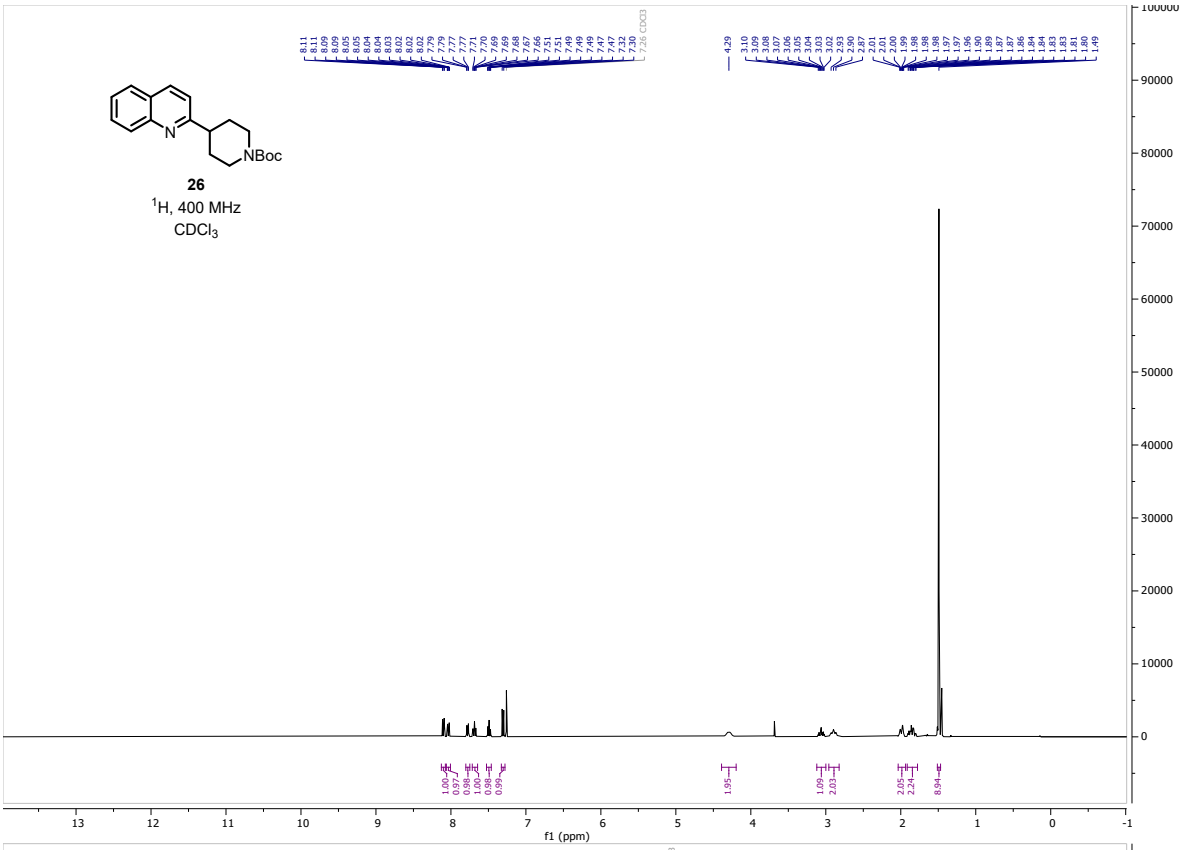

Boc
N
I
N
N
23
13C, 101 MHz
CDCl3
172.0
155.2
154.9
149.5
142.3
132.9
131.5
124.9
93.1
79.7
77.2 CDCl3
44.0
39.6
31.1
28.7
f1 (ppm)

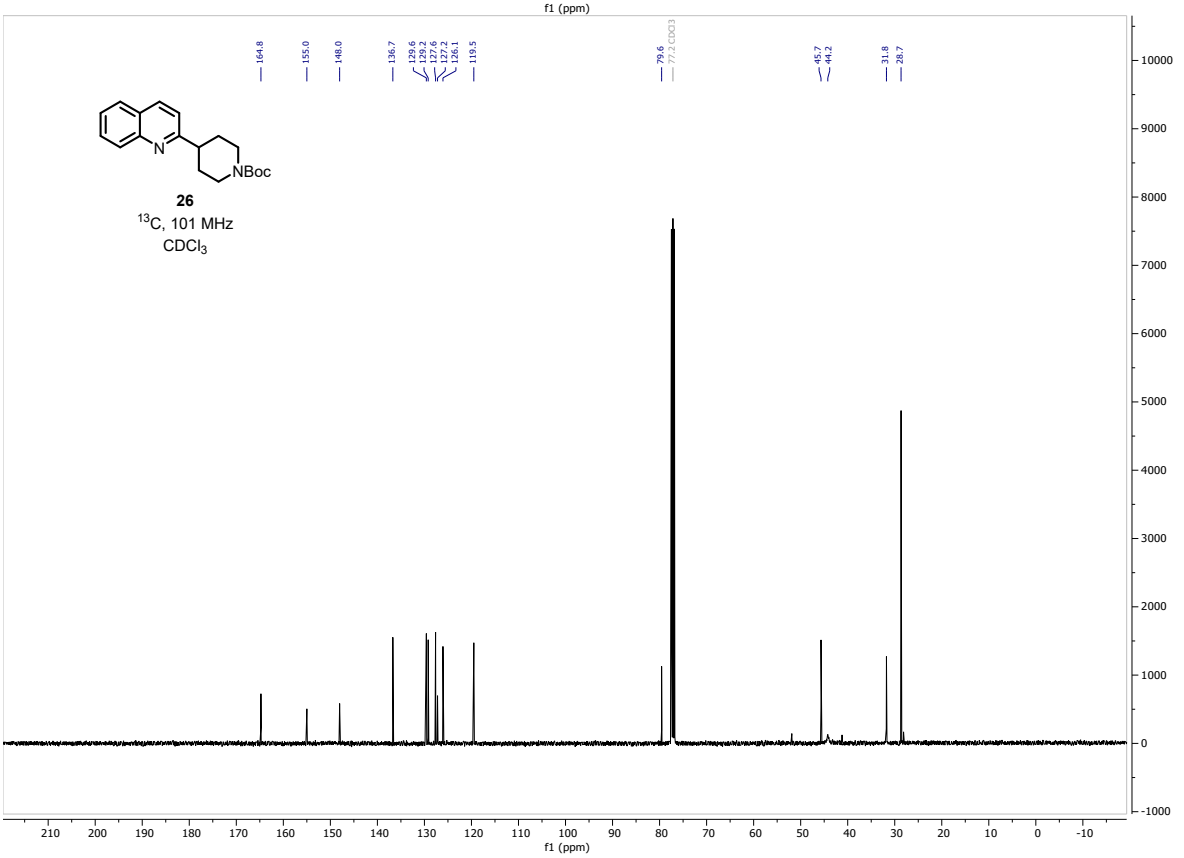

Boc
N
N
24
1H, 400 MHz
CDCl3
f1 (ppm)

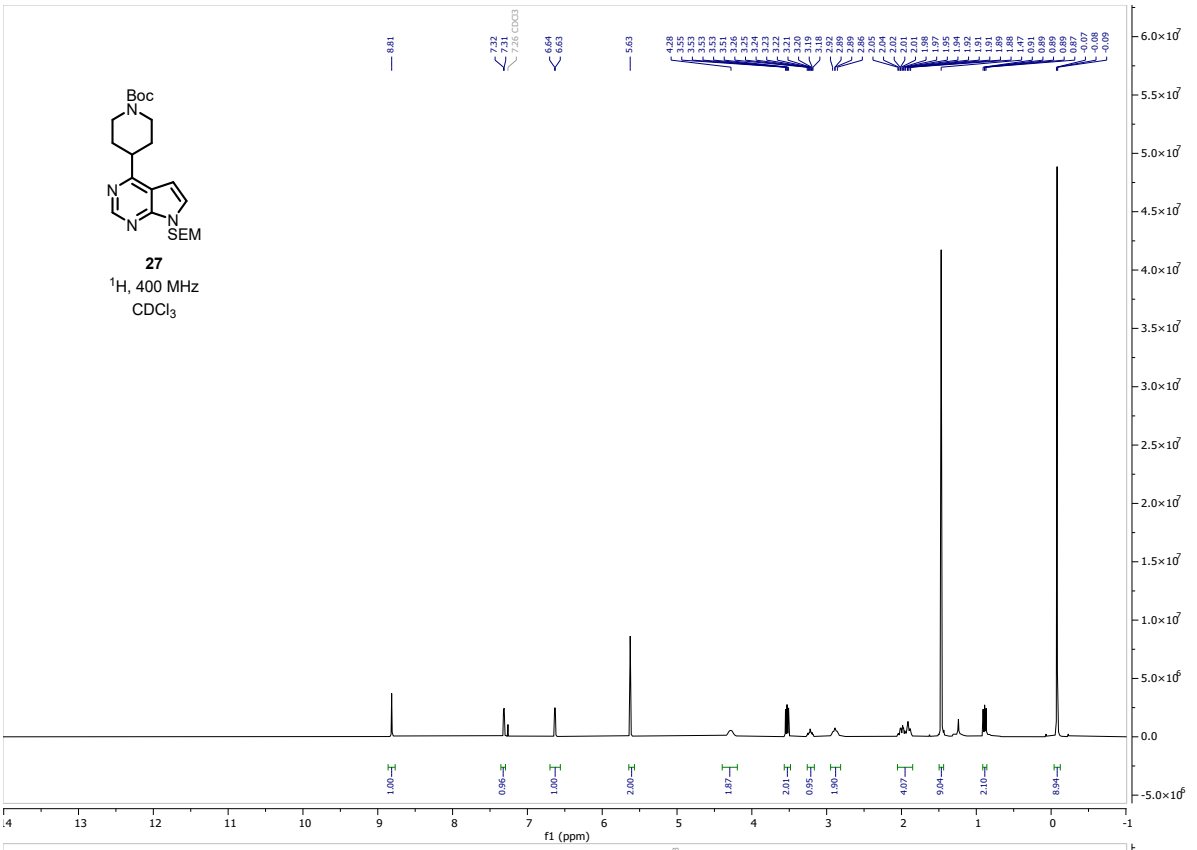

Boc
N
N
24
13C, 101 MHz
CDCl3
155.0
151.2
150.6
148.7
130.8
130.2
126.8
126.6
122.7
117.7
79.9
44.6
37.4
32.5
28.6
f1 (ppm)

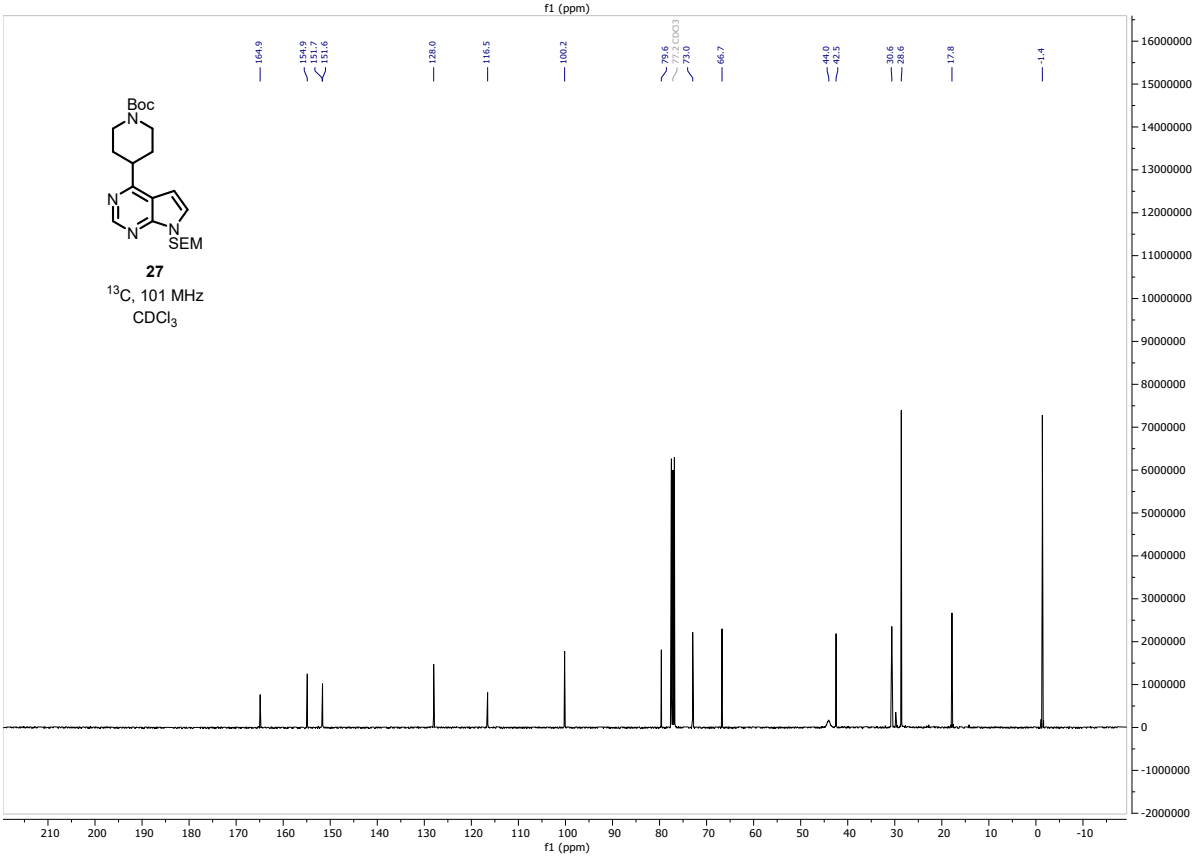

Boc
N
N
25
1H, 400 MHz
CDCl3
f1 (ppm)

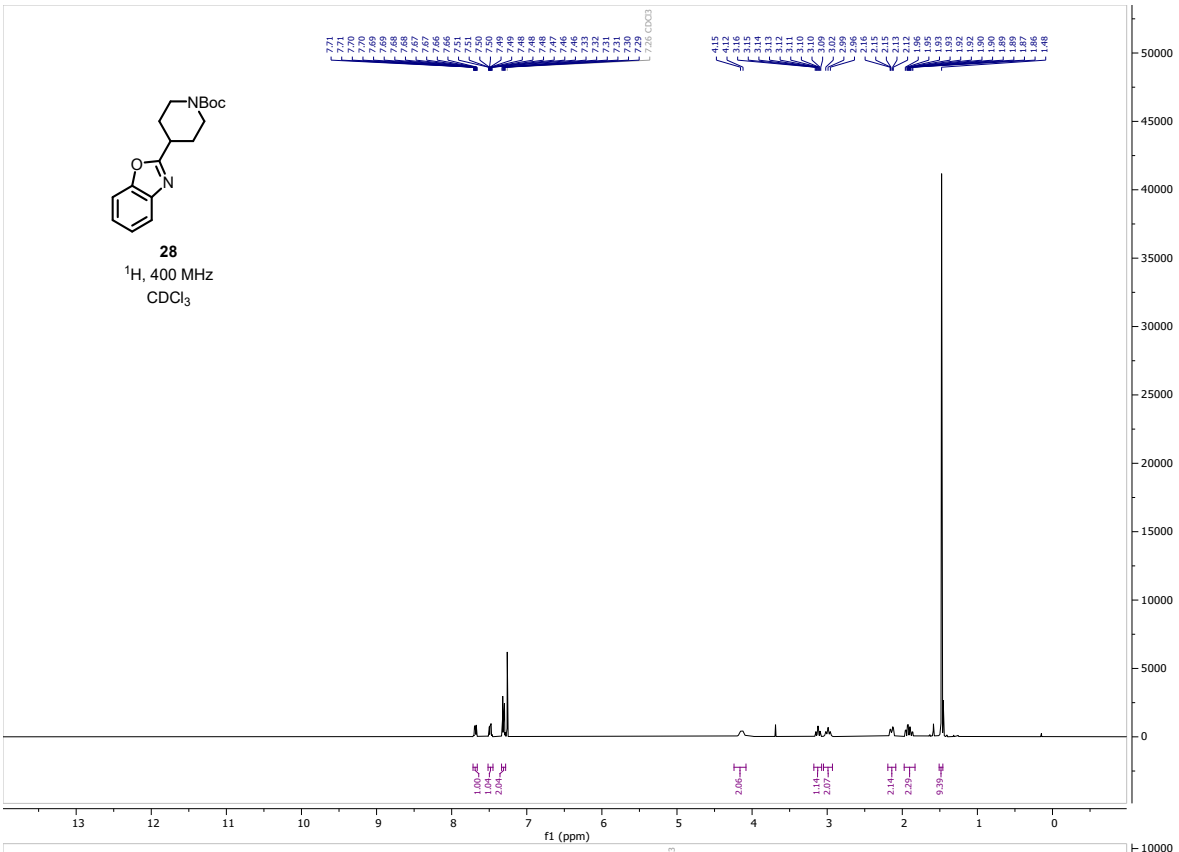

Boc
N
N
25
13C, 101 MHz
CDCl3
f1 (ppm)

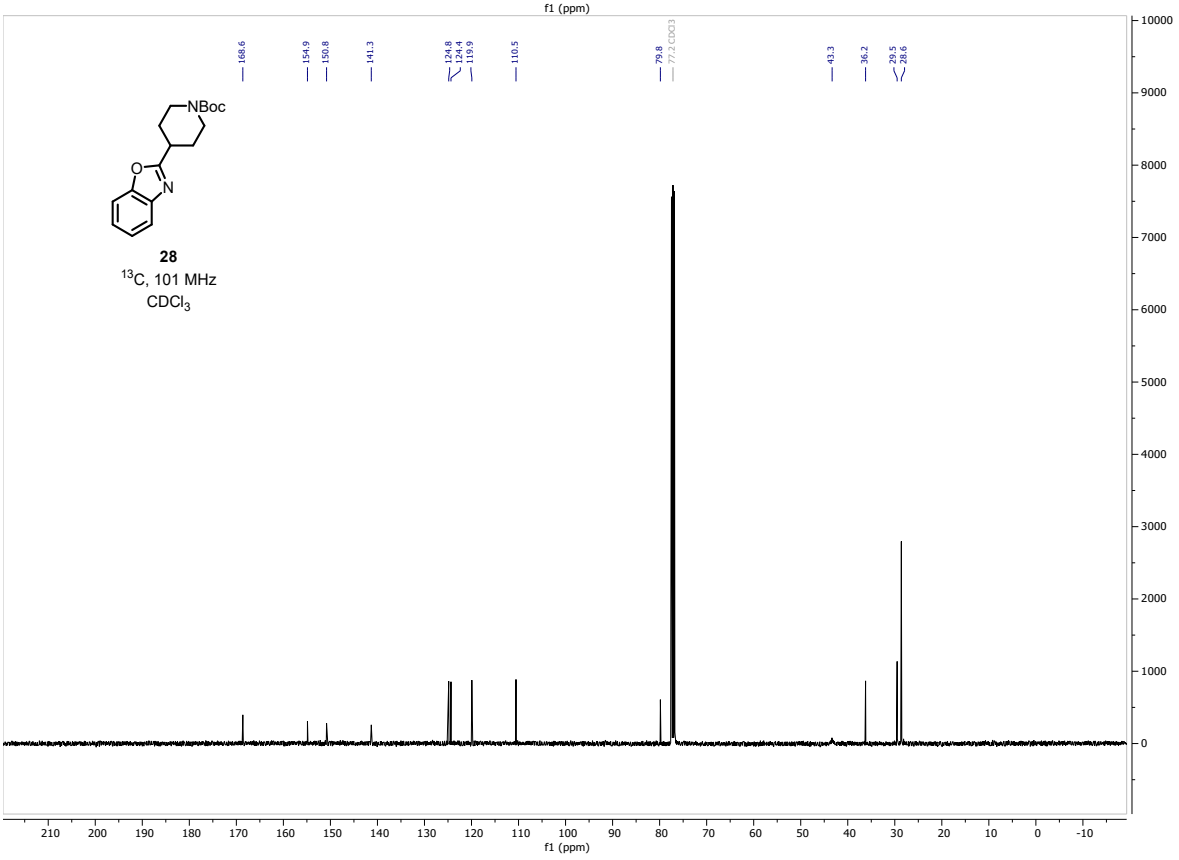

N
NBoc
26
1H, 400 MHz
CDCl3
f1 (ppm)

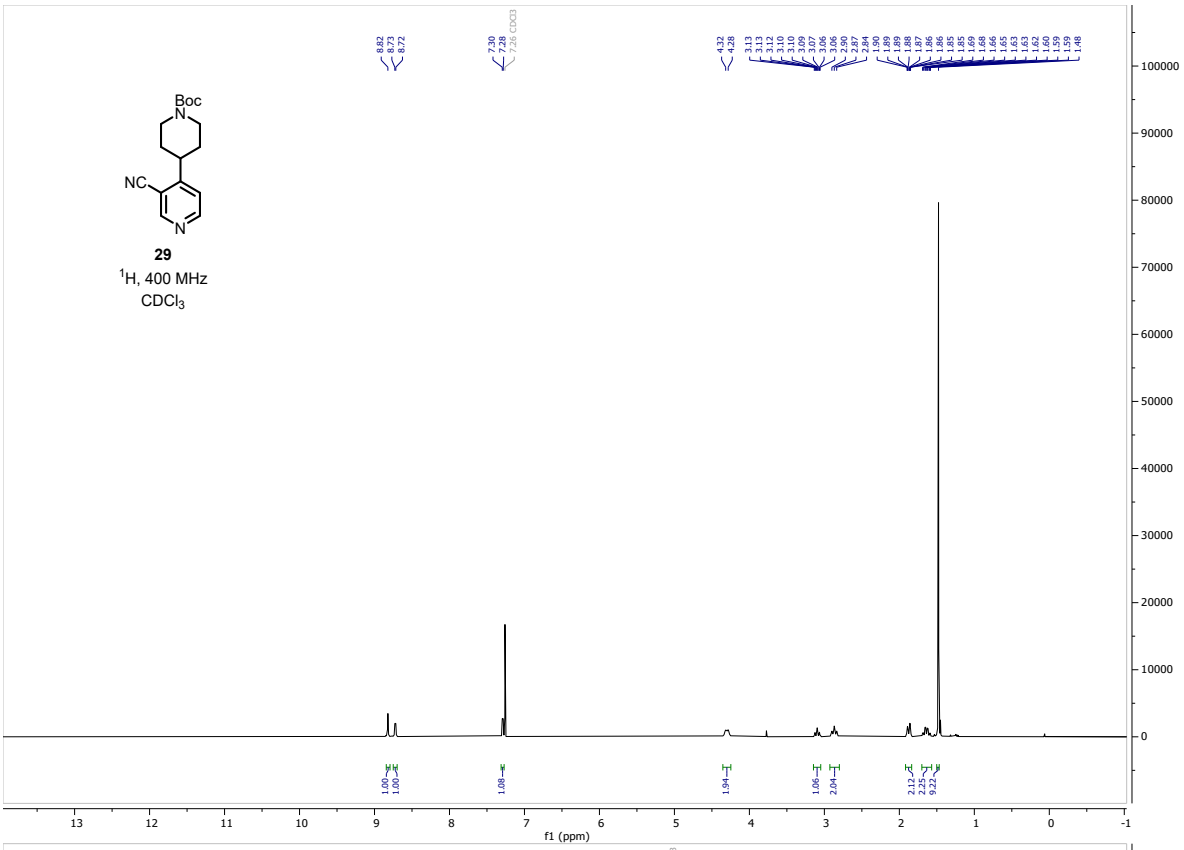

N
NBoc
26
13C, 101 MHz
CDCl3
f1 (ppm)

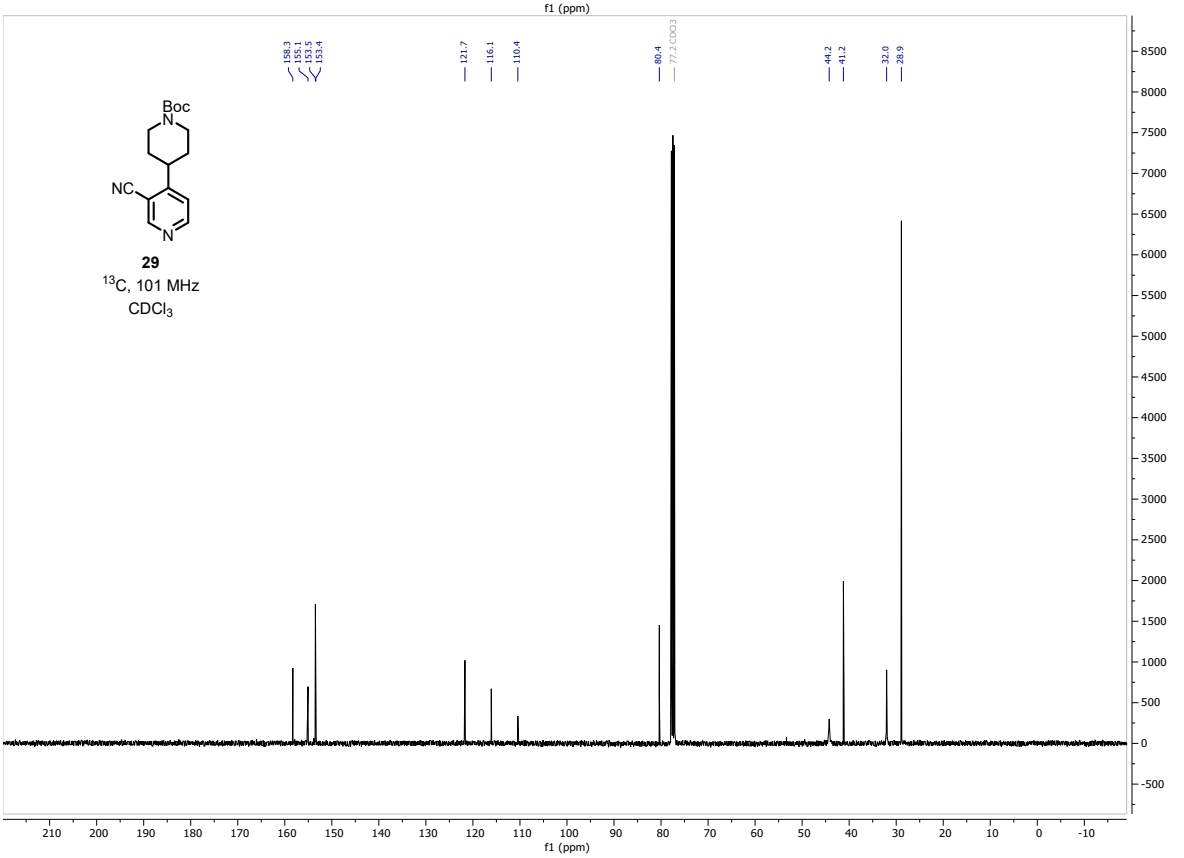

Boc
N
N
N
N
SEM
27
1H, 400 MHz
CDCl3
8.81
7.32
7.31
7.26 CDCl3
6.64
6.63
5.63
4.28
3.55
3.54
3.53
3.53
3.51
3.26
3.25
3.24
3.23
3.22
3.21
3.20
3.19
3.18
2.92
2.89
2.89
2.86
2.05
2.04
2.02
2.01
2.01
1.98
1.97
1.95
1.94
1.92
1.91
1.91
1.88
1.88
1.47
0.91
0.90
0.89
0.89
0.87
0.07
0.07
-0.08
-0.09
1.00
0.96
1.00
2.00
1.87
2.01
0.95
1.90
4.07
9.04
2.10
8.94
f1 (ppm)

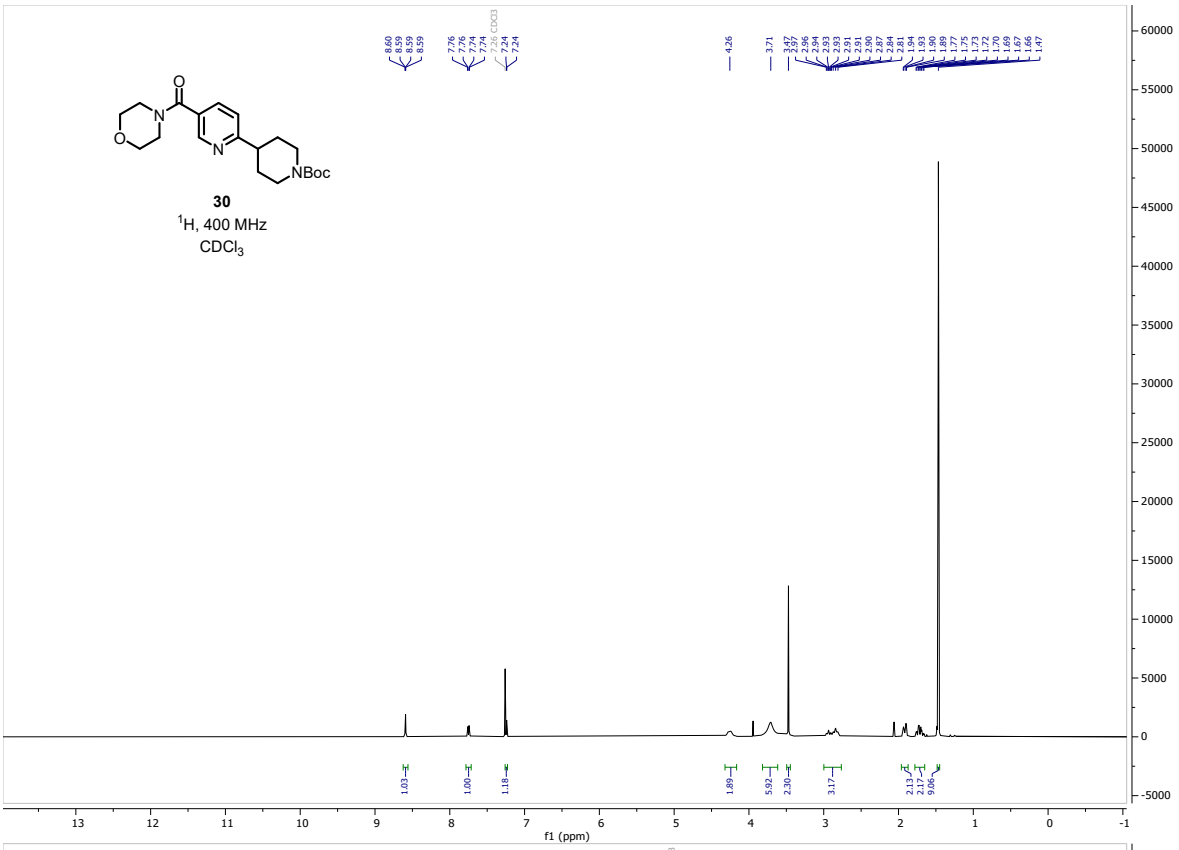

Boc
N
N
N
N
SEM
27
13C, 101 MHz
CDCl3
164.9
154.9
151.7
151.6
128.0
116.5
100.2
79.6
77.2 CDCl3
73.0
66.7
44.0
42.5
30.6
28.6
17.8
-1.4
f1 (ppm)

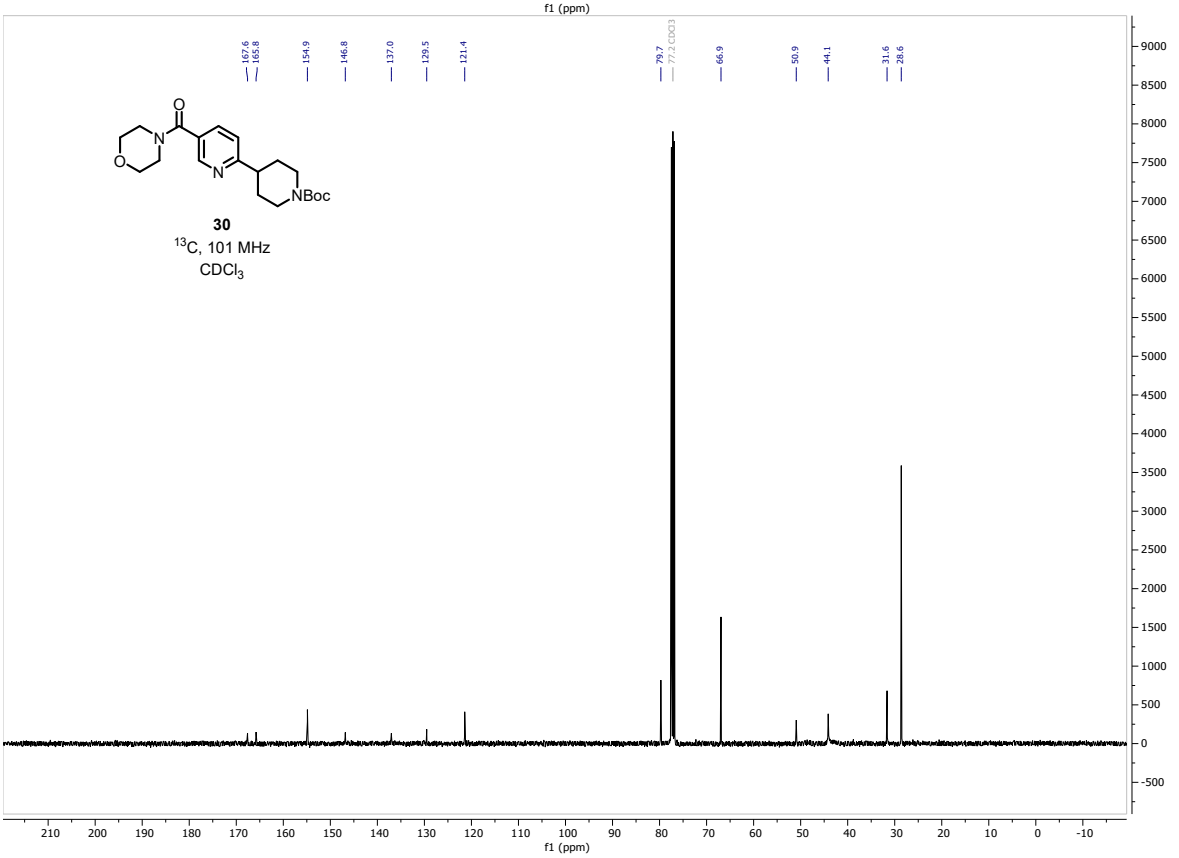

NBoc
O
N
28
1H, 400 MHz
CDCl3
f1 (ppm)

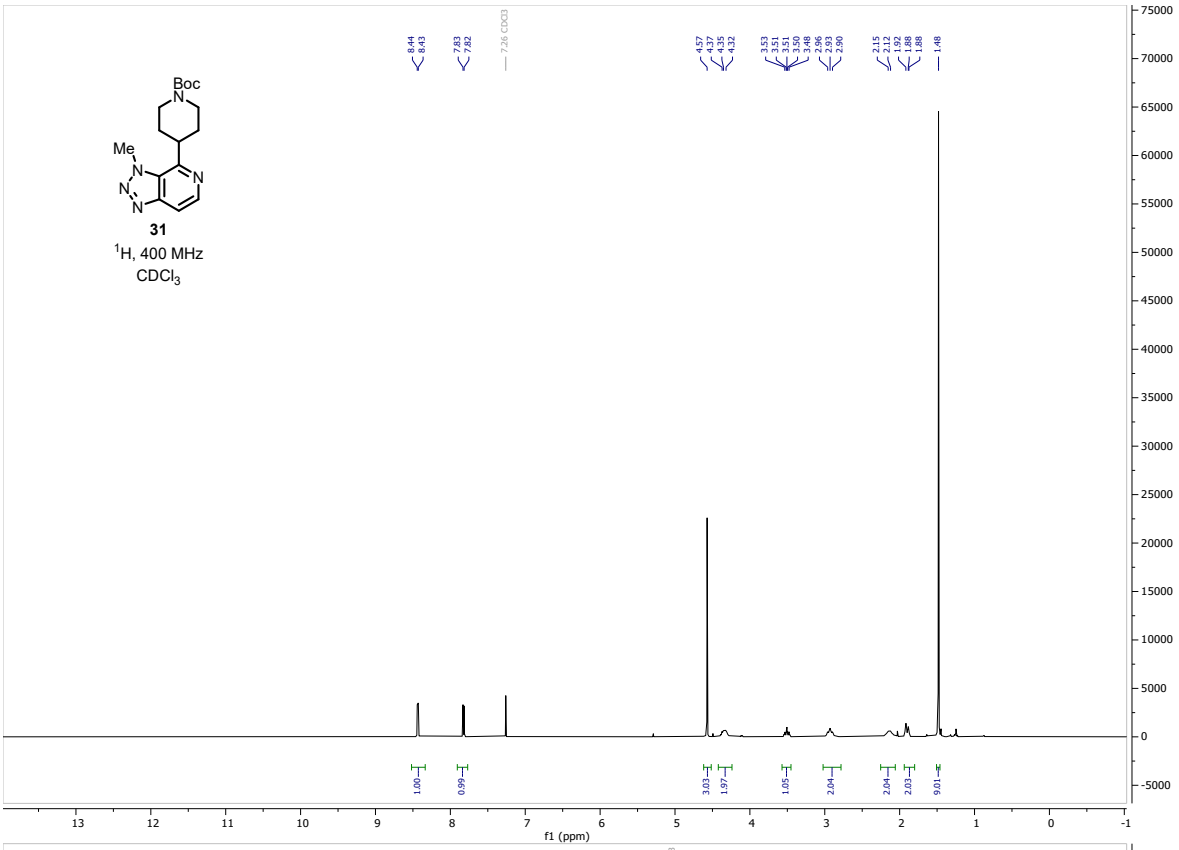

NBoc
O
N
28
13C, 101 MHz
CDCl3
f1 (ppm)

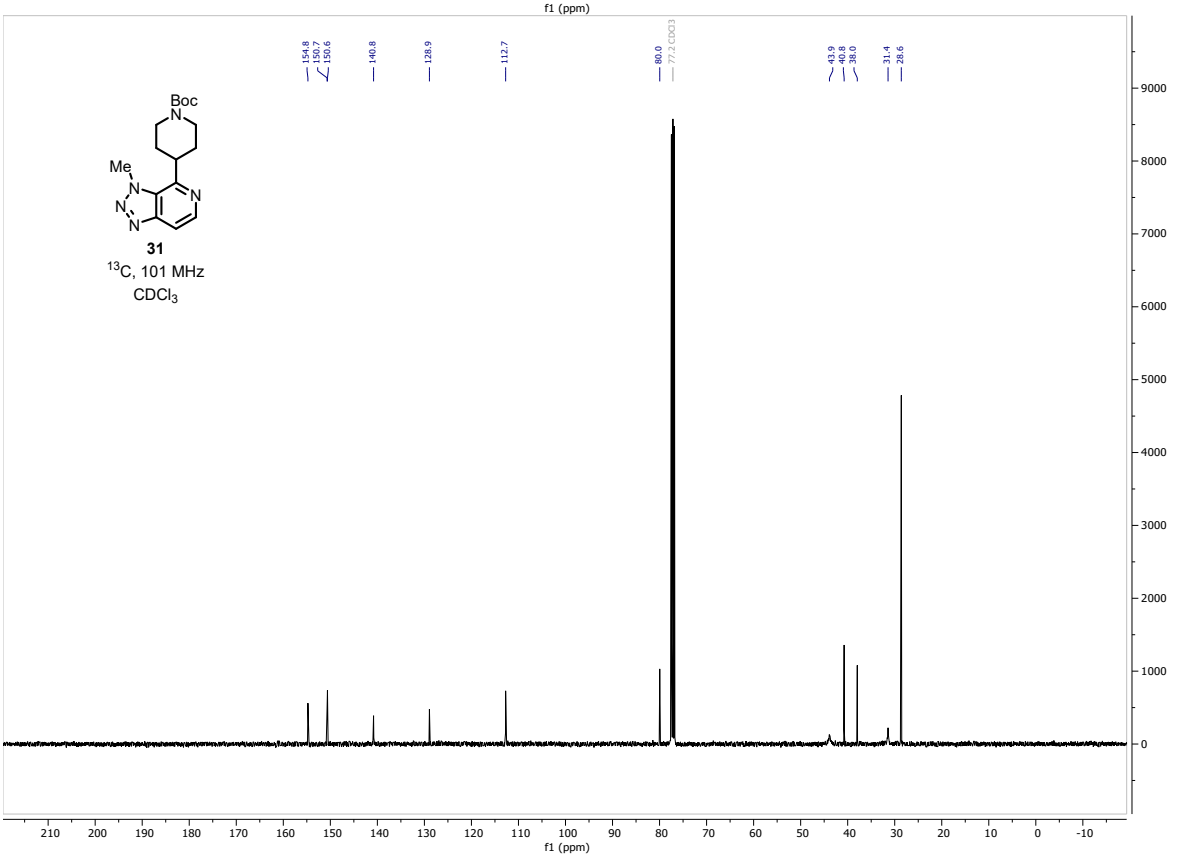

Boc
N
NC
N
29
1H, 400 MHz
CDCl3
f1 (ppm)

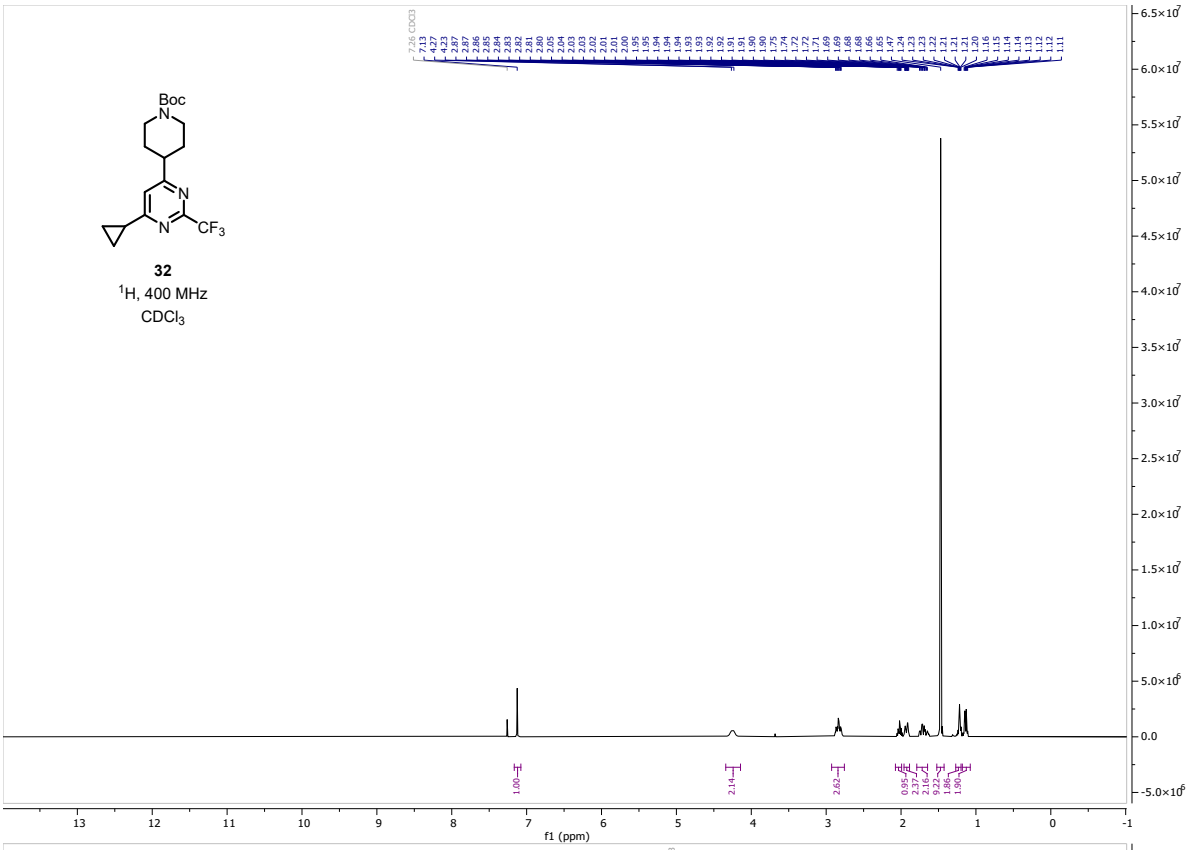

Boc
N
NC
N
29
13C, 101 MHz
CDCl3
f1 (ppm)

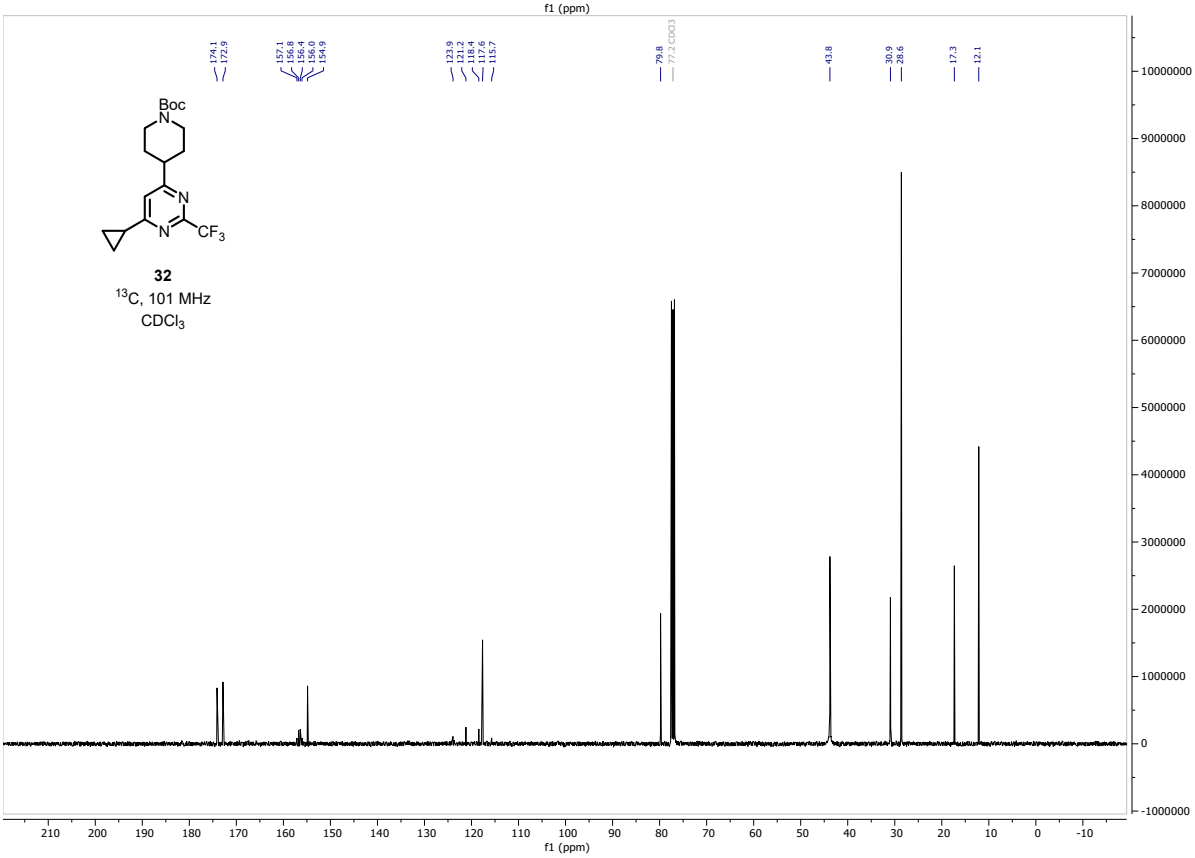

30
1H, 400 MHz
CDCl3
f1 (ppm)

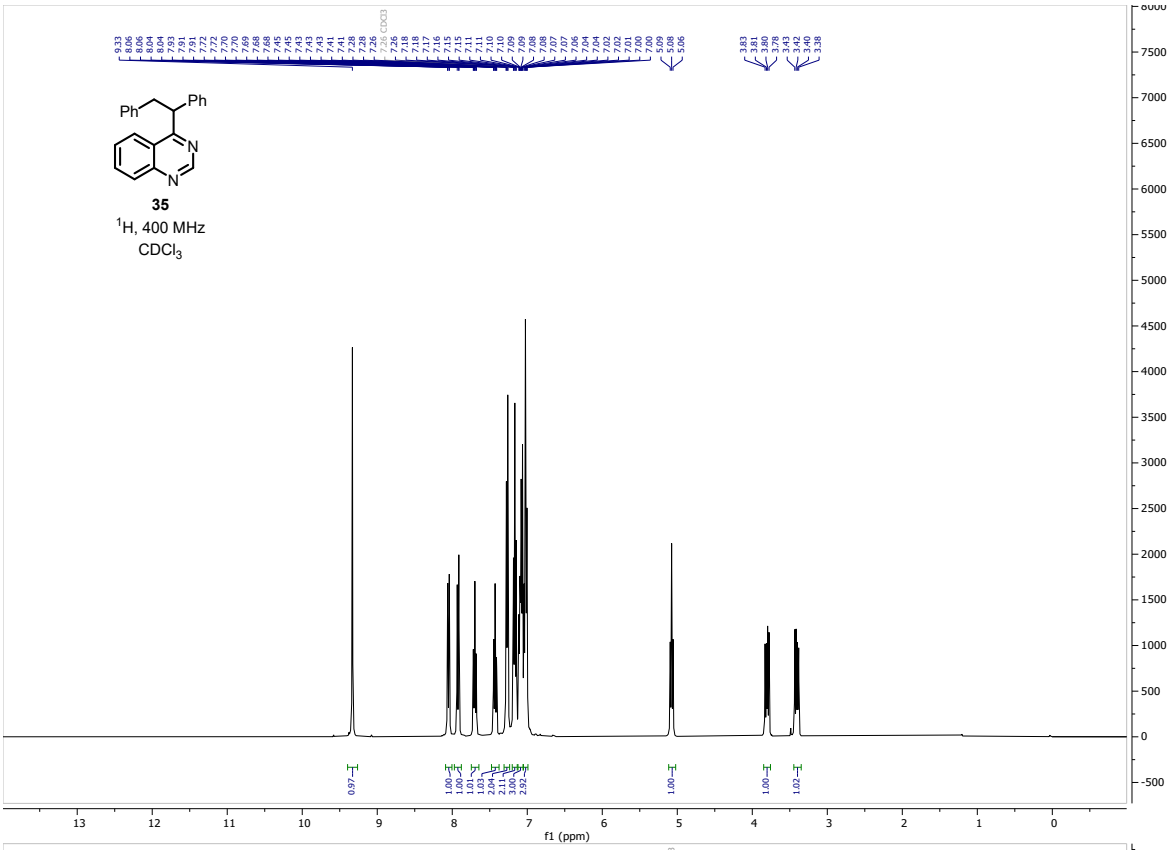

30
13C, 101 MHz
CDCl3
f1 (ppm)

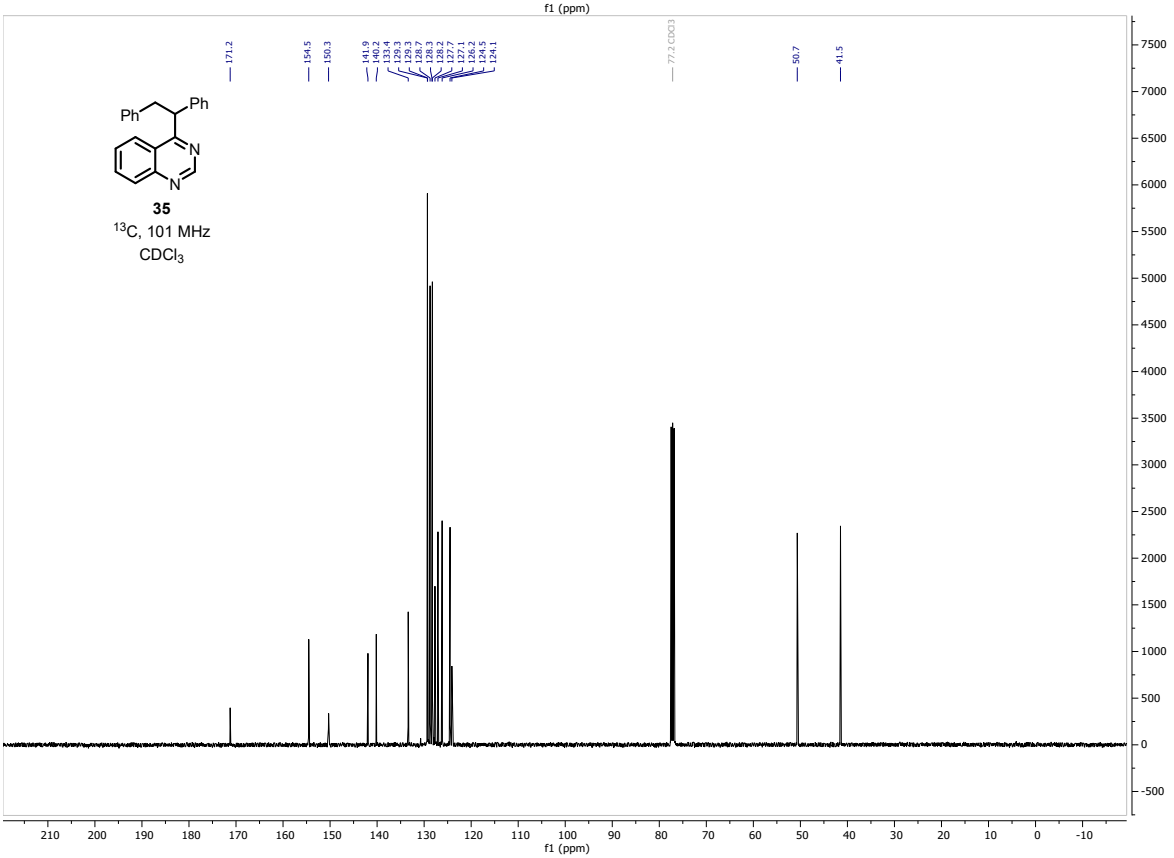

Boc
Me
31
1H, 400 MHz
CDCl3
8.44
8.43
7.83
7.82
7.26 CDCl3
4.57
4.37
4.35
4.32
3.53
3.51
3.51
3.50
3.48
3.36
2.93
2.90
2.15
2.12
1.92
1.88
1.88
1.48
1.00
0.99
3.03
1.97
1.05
2.04
2.04
2.03
9.01
f1 (ppm)


Boc
Me
31
13C, 101 MHz
CDCl3
154.8
150.7
150.6
140.8
128.9
112.7
80.0
77.2 CDCl3
43.9
40.8
38.0
31.4
28.6
f1 (ppm)


Boc
N
N
N
CF3
32
1H, 400 MHz
CDCl3
f1 (ppm)


Boc
N
N
N
CF3
32
13C, 101 MHz
CDCl3
f1 (ppm)


Ph
Ph
N
N
35
1H, 400 MHz
CDCl3
f1 (ppm)


Ph
Ph
N
N
35
13C, 101 MHz
CDCl3
f1 (ppm)