Development of a Concise, Scalable Synthesis of a CCR1 Antagonist Utilizing a Continuous Flow Curtius Rearrangement

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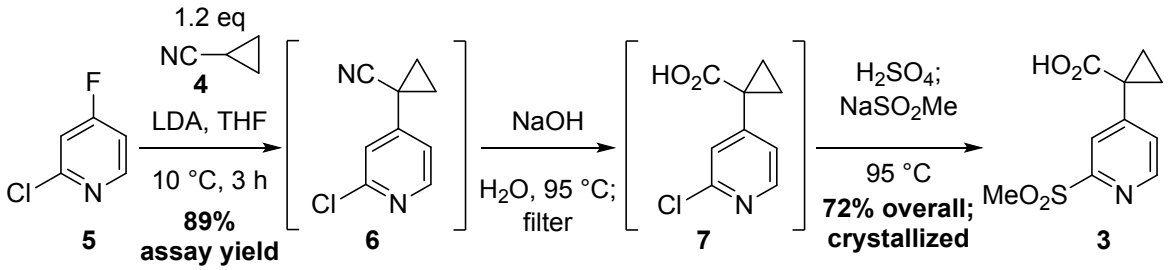
Supporting Information

General	**S1**
Procedures and data	**S2-S9**
Green Aspiration Level calculations/Scorecard	**S9-S12**
^{1}H and ^{13}C NMR spectra for all isolated compounds	**S13-S21**
References	**S22**

General. All reactions were performed under anhydrous conditions unless otherwise stated with oven-dried glassware and under an argon atmosphere. Anhydrous solvents (THF, MeOH, 1-PrOH, toluene, NMP, MeCN, and EtOAc) were purchased from Sigma-Aldrich or Fisher and were used without further purification. LDA (2 M solution in THF/EtPh/heptane) was purchased from Sigma Aldrich and used without further purification. All other starting materials and reagents were purchased from commercial sources and used as received unless otherwise noted. Melting points are uncorrected. HPLC analysis was performed on an Agilent 1200 binary pump HPLC equipped with a Zorbax Eclipse XDB-C18 4.6x50 mm column eluted at 15 °C with a mobile phase consisting of 90:10 MeCN/MeOH and water containing 0.1% H_3PO_4 and 0.2% $HClO_4$. Flash chromatography was performed on a Combi-Flash system with silica column cartridges using either a dichloromethane/hexanes or ethyl acetate/hexanes solvent system. TLC was performed on EMD silica gel F_{254} 2.5x7.5 cm plates and visualized with UV (254 nm) and/or a cerium molybdate or potassium permanganate stain. NMR spectra were recorded on Bruker 400 or 500 MHz instruments. All ^{1}H and ^{13}C NMR data were referenced to the internal deuterated solvent relative to TMS at 0 ppm. High resolution mass spectroscopy (HRMS) was performed on a TOF instrument with ESI in positive ionization mode. Flash chromatography was performed on a Combi-Flash

automated system with silica columns. FT-IR spectra were measured on a Mettler Toledo "ReactIR IC10" Fourier spectrometer with a silicon probe. Absorbance was measured with intervals of 15 sec.

Procedures and Data



1-(2-chloropyridin-4-yl)cyclopropane-1-carbonitrile 6. To a stirred solution of cyclopropanecarbonitrile **4** (3.06 kg, 45.6 mol, 1.2 eq.) and 2-chloro-4-fluoropyridine **5** (5 kg, 38.0 mol, 1.0 eq.) in THF (75 L) at 10 °C is added LDA (16.2 kg, 40.7 mol, 1.07 eq., 26 wt% solution in THF/heptane/ethylbenzene) over 4 h while maintaining the internal temperature ~10 °C. After reaction completion (as judged by HPLC analysis), the mixture is quenched with water (350 mL). The desired product **6** is obtained in ~89% assay yield and taken directly into the next step. (An analytical sample was obtained after EtOAc extraction and chromatographic purification (0-30% EtOAc in hexanes) to obtain nitrile **6** as a light yellow solid; see below for data).

1-(2-chloropyridin-4-yl)cyclopropane-1-carboxylic acid 7. The solution of **6** is concentrated under vacuum at 55-60 °C to minimum stirrable volume. Water (50 L) is added, followed by 50% aqueous NaOH (5.12 kg, 63.8 mol, 2 eq.). The mixture is heated to 95-100 °C over 1 h in order to control THF distillation, and further stirred at this temperature for 5 h. The resulting thin slurry is cooled to 10-15 °C over 3 h, after which it is filtered through Celite to remove LiF salts. The resulting solution of sodium-carboxylate **7** is taken directly into the next step. (An analytical sample was obtained after acidic quench, EtOAc extraction and chromatographic purification (0-30% EtOAc in hexanes) to obtain acid **7** as an off-white solid; see below for data).

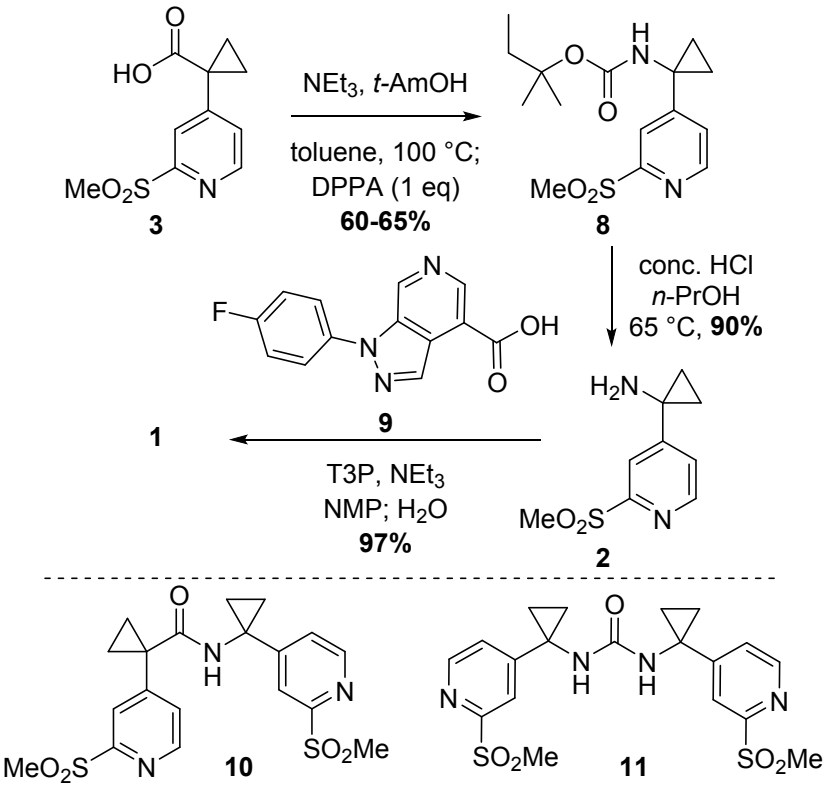
1-(2-chloropyridin-4-yl)cyclopropane-1-carbonitrile 3. The aqueous filtrate containing **7** is returned back to the reactor, heated to 70-75 °C, and treated with H_2SO_4 (5.59 kg, 55.9 mol, 1.75 eq.) slowly to control splattering and the resulting exotherm. After addition, the batch is heated to 80-85 °C, and a solution of $NaSO_2Me$ (4.93 kg, 47. 9 mol, 1.6 eq.) in water (5 L) is charged while maintaining the batch >80 °C. The resulting mixture is heated to 95-100 °C and stirred for 6 h. Following complete conversion, the batch is cooled to 85-90 °C and treated with a slurry of **3** seeds (5 g) in water (100 mL).The resulting mixture is stirred for 3 h at 85-90 °C, during which time a thick slurry is formed. The batch is cooled to 20 °C over 3 h, after which the solid is collected by filtration and washed with water (25 L). The product sulfone **3** is obtained as a light orange solid (6.6 kg, 72%).

Data for nitrile **6**: m.p. = 70-73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 5.3, 1H), 7.20 (d, J = 1.5, 1H), 7.09 (dd, J_1 = 5.3, J_2 = 5.3 Hz, 1H), 1.92 (dd, J_1 = 13.7, J_2 = 2.8 Hz, 2H), 1.55 (dd, J_1

= 13.7, J_2 = 2.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 150.1, 149.0, 120.3, 120.1, 118.4, 20.3, 13.5; HRMS: calcd for $C_9H_8N_2Cl$ [M + H]: 179.0371. Found: 179.0381.

Data for acid **7**: m.p. = 160-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.7 (bs, 1H), 8.32 (d, J = 5.1, 1H), 7.49, (s, 1H), 7.39 (dd, J_1 = 6.1, J_2 = 4.1 Hz, 1H), 1.50 (dd, J_1 = 11.4, J_2 = 3.0 Hz, 2H), 1.28 (dd, J_1 = 11.4, J_2 = 3.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 153.0, 150.6, 149.9, 125.8, 125.2, 28.1, 16.5; HRMS: calcd for $C_9H_9ClNO_2$ [M + H]: 198.0316. Found: 198.0320.

Data for acid **3**: m.p. = 175-178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, J = 5.0, 1H), 7.99 (s, 1H), 7.70 (dd, J_1 = 5.0, J_2 = 1.6 Hz, 1H), 3.29 (s, 3H), 1.58 (dd, J_1 = 11.4, J_2 = 2.9 Hz, 2H), 1.34 (dd, J_1 = 11.4, J_2 = 2.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ173.9, 157.9, 152.2, 150.5, 129.3, 122.3, 40.3, 28.5, 16.7; HRMS: calcd for $C_{10}H_{12}NO_4S$ [M + H]: 242.0482. Found: 242.0486.



***tert*-pentyl (1-(2-(methylsulfonyl)pyridin-4-yl)cyclopropyl)carbamate 8.** To a 1 L reactor fitted with a mechanical stirrer, N_2 inlet and bubbler, and reflux condensor was added acid **3** (101.7 g, 382.7 mmol, 1.0 eq.), NEt_3 (79.58 mL, 574.1 mmol, 1.5 eq.), *t*-AmOH (83.3 mL, 765.5 mmol, 2 eq.) and toluene (712 mL) at 25 °C. The resulting mixture is heated to 100 °C. DPPA (78.8 mL, 363.6 mmol, 0.95 eq.) is added slowly over 15 min via syringe, and the resulting mixture is allowed to stir at 100 °C for 1 h and monitored by HPLC. After reaction completion, the mixture is then heated to 110 °C in order to remove excess *t*-AmOH (1:1 with toluene) by distillation. The batch is then cooled to 70 °C, treated with water (711.9 mL), and further cooled to 20 °C. The resulting biphasic slurry is filtered and washed with water (300 mL) and heptane (300 mL). Carbamate **8** is obtained as an off-white solid (76.7 g, 61% yield). m.p. = 87-93 °C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.62 (m, 1H), 7.96-7.63 (m, 2H), 7.32 (m, 1H), 3.26 (s, 3H), 4.52-4.45 (m,

1 H), 4.16-4.11 (m, 2 H), 2.47 (dd, J_1 = 10.3, J_2 = 1.8 Hz, 1 H), 1.96 (t, J = 9.2 Hz, 1 H), 1.77-1.48 (m, 2H), 1.40-1.26 (m, 10H), 0.89-0.55 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers) δ 158.1, 155.9, 150.4, 122.7, 116.5, 81.1, 40.2, 34.8, 33.3, 26.2, 25.7, 21.2, 8.6; HRMS: calcd for $C_{15}H_{23}N_2O_4S$ [M + H]: 327.1373. Found: 327.1383.

Data for **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 5.0 Hz, 1H), 8.63 (d, J = 5.1 Hz, 1H), 8.51 (s, 1H), 7.90 (s, 1H), 7.68 (dd, J_1 = 4.9, J_2 = 1.4 Hz, 1H), 7.63 (s, 1H), 7.36 (dd, J_1 = 4.9, J_2 = 1.4 Hz, 1H), 3.27 (s, 6H), 1.53 (dd, J_1 = 11.4, J_2 = 2.4 Hz, 2H), 1.42 (m, 2H), 1.33 (m, 2H), 1.28 (dd, J_1 = 11.4, J_2 = 2.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 158.2 (2), 157.1, 152.7, 150.7, 150.5, 128.4, 123.2, 121.3, 116.3, 40.5, 40.2, 34.8, 20.8, 15.8; HRMS: calcd for $C_{19}H_{22}N_3O_5S_2$ [M + H]: 436.0995. Found: 436.1000.

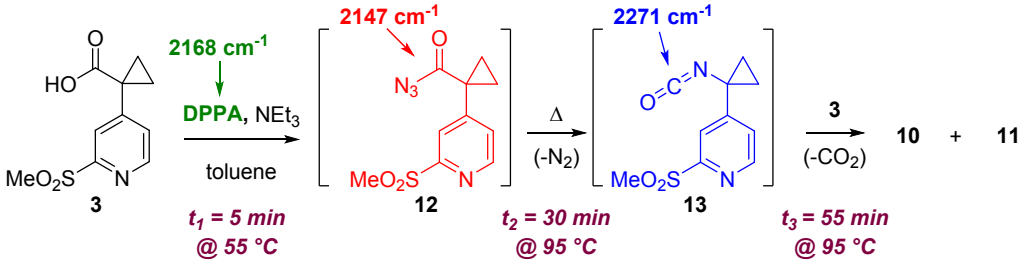
Data for **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 5.2 Hz, 2H), 7.74 (s, 2H), 7.42 (d, J = 4.2 Hz, 2H), 7.26 (s, 2H), 3.29 (s, 6H), 1.39 (d, J = 12.6 Hz, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 158.2, 157.9, 150.3, 123.2, 116.3, 40.2, 34.7, 21.8; HRMS: calcd for $C_{19}H_{23}N_2O_5S_2$ [M + H]: 451.1104. Found: 451.1110.

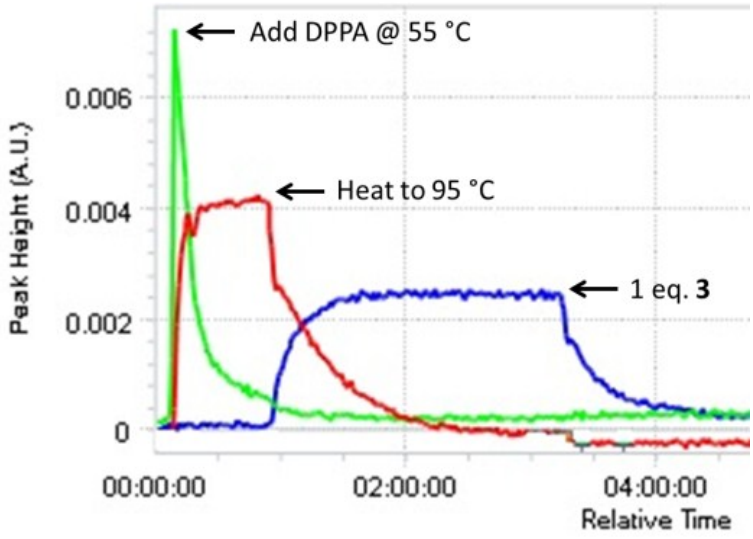
1-(2-(methylsulfonyl)pyridin-4-yl)cyclopropan-1-amine hydrochloride 2. A suspension of carbamate **8** (1.23 kg, 3.69 mmol, 1.0 eq.) in *n*-PrOH (6.14 L) is treated with conc HCl (923 mL, 11.0 mol, 3.0 eq.). The slurry is heated to 65 °C and stirred for 2 h, after which the solution became homogeneous and CO_2 gas evolution is observed. The resulting mixture is then cooled to 20-25 °C and stirred for 1 h, after which it is filtered and washed with cold *n*-PrOH (2.4 L). The product HCl salt **2** is obtained as an-off-white solid (840 g, 90%). m.p. = 198-202 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (bs, 3H), 8.77 (d, J = 5.2 Hz, 1H), 8.00 (d, J = 1.3 Hz, 1H), 7.67 (dd, J_1 = 5.2 Hz, J_2 = 1.6 Hz 1H), 3.31 (s, 3H), 1.68 (dd, J_1 = 13.4 Hz, J_2 = 7.1 Hz, 2H), 1.47 (dd, J_1 = 13.4 Hz, J_2 = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 151.4, 150.7, 124.2, 117.4, 40.4, 35.3, 15.9; HRMS: calcd for $C_9H_{13}N_2O_2S$ [M + H^+]: 213.0692. Found: 213.0696.

1-(4-fluorophenyl)-N-(1-(2-(methylsulfonyl)pyridin-4-yl)cyclopropyl)-1H-pyrazolo[3,4-c]pyridine-4-carboxamide (1) via traditional amide coupling. To a suspension of acid **9**[1] (1 kg, 3.89 mol, 1.0 eq.) and amine HCl salt **2** (1.06 kg, 4.28 mmol, 1.1 eq.) in NMP (2 L) is added NEt_3 (2.8 L, 19.4 mol, 5.0 eq.). After stirring for 15 min, the resulting slurry is treated with T3P (2.86 L, 4.86 mmol, 1.07 eq., 50 wt% in EtOAc) while maintaining the batch temperature <40 °C. After addition, the batch is heated to 65 °C over 30 min and stirred for 2 h. Water (2 L) is added over 30 min while maintaining the batch >60 °C. A slurry of amide **1** seeds (1 g) in water (100 mL) is added, after which water (4-6 L) is added over 30 min while maintaining the batch >60 °C. After holding for 30 min, the batch is cooled to 25 °C over 2 h. The solids were collected by filtration and washed with 1:4 NMP/water (2 L) and water (2 L). The product amide **1** was isolated as an off-white solid (1.71 kg, 95%). m.p. = 140-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 9.43 (s, 1H), 8.95 (s, 1H), 8.70 (s, 1H), 8.68 (d, J = 5.2 Hz, 1H), 7.93 (s, J_1 = 8.8 Hz, J_2 = 4.7 Hz, 1H), 7.82 (s, 1H), 7.54 (d, J = 4.1 Hz, 1H), 7.49 (t, J = 8.7 Hz, 1H), 3.29 (s, 3H), 1.61 (bs, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 162.7, 160.3, 158.4, 156.9, 150.6, 139.2, 138.2, 135.8, 135.6, 125.4 (d, J_{C-F} = 8.8 Hz), 123.3, 121.9, 117.2 (d, J_{C-F} = 23.1 Hz), 116.4, 40.2, 34.9, 20.9; HRMS: calcd for $C_{22}H_{19}FN_5O_3S$ [M + H^+]: 452.1187. Found: 452.1189.

Kinetic analysis of Curtius rearrangement (sequential azide and isocyanate formation):

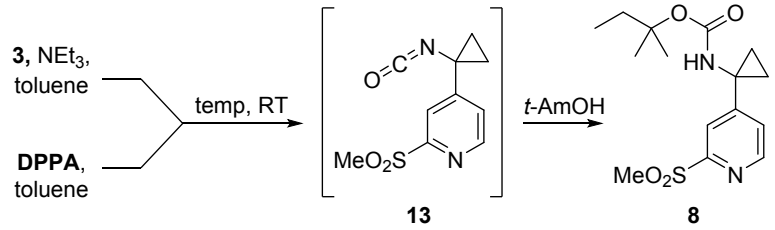
An EasyMax reactor was fitted with a silicon FT-IR probe connected to a Mettler Toledo IC10 FT-IR spectrometer. Acid **3** (20 mmol) was charged, followed by toluene (0.5 M) and NEt_3 (30 mmol). The reactor jacket was set for 55 °C, and DPPA (20 mmol) was added in one portion (green line in graph). As DPPA concentration decreases, concentration of acyl azide **12** (red) increases, with completion achieved after 5 minutes. The reactor jacket was then set for 95 °C. The resulting increase in batch temperature induces Curtius rearrangement, corresponding to a decrease in concentration of **12** and increase in concentration of isocyanate **13** (blue). Rearrangement was found to be complete after 30 min at 95 °C. Acid **3** (20 mmol) is added in one portion, resulting in disappearance of isocyanate **13** and synthesis of a mixture of amide **10** and urea **11**.





CSTR synthesis of Acyl Azide 12 and semi-continuous synthesis of carbamate 8. A stock solution of acid **3** (1.2 kg, 4.78 mol, 1 eq.), NEt_3 (998.4 mL, 7.16 mol, 1.5 eq.), and toluene (6 L) is prepared. A second stock solution containing DPPA (1.033 L, 4.78 mol, 1 eq.) in toluene (2 L) is also prepared. The two stock solutions are pumped via polypropylene tubes and combined in an equimolar ratio in a continuously stirred tank reactor (CSTR) jacketed at 50 °C at a rate to maintain a total residence time (RT) of 10 minutes, and the resulting homogeneous stream of azide **12** is allowed to overflow into a receiving tank containing *t*-AmOH (1.039 L, 9.54 mol, 1 eq.) in toluene (500 mL) stirred at 100 °C. After the flow of isocyanate **12** is complete, the resulting mixture in the receiving tank is stirred for 1 h at 100 °C. The batch is then cooled to 70 °C, treated with water

(7 L), and further cooled to 20 °C. The resulting biphasic slurry is filtered and washed with water (2 L) and heptane (2 L). Carbamate **8** is obtained as an off-white solid (1.53 kg, 75% yield).



Lab Development:
250 mL CSTR, 1 L Tank
73–75% yield

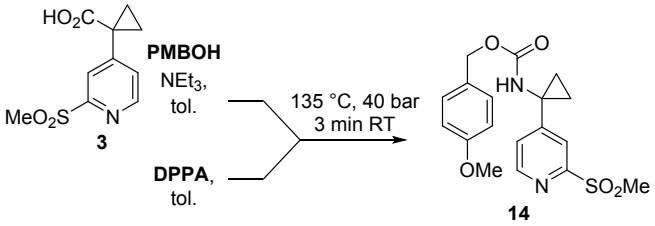
Campaign #2:
500 mL CSTR, 10 L Tank
1.2 kg *t*-Am Carbamate
75–78% yield

Campaign #3:
3 L CSTR, 50 L Tank
8 kg *t*-Am Carbamate
80% yield

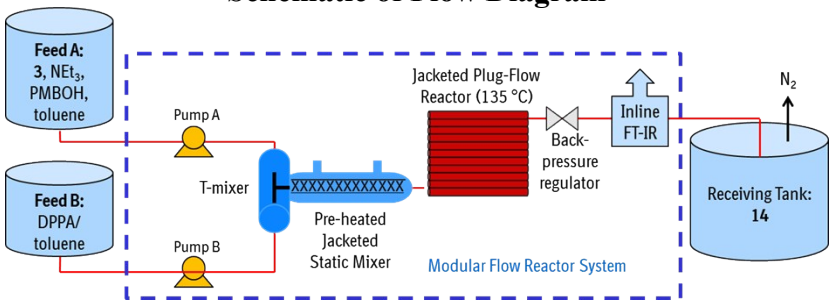
Flow synthesis of Isocyanate 13 and semi-continuous synthesis of carbamate 8. A stock solution of acid **3** (600 g, 2.39 mol, 1 eq.), NEt_3 (499.2 mL, 3.58 mol, 1.5 eq.), and toluene (3 L) is prepared. A second stock solution containing DPPA (516.9 mL, 2.39 mol, 1 eq.) in toluene (1 L) is also prepared. The two stock solutions are pumped via polypropylene tubes and combined in an equimolar ratio via T-mixer and jacketed static mixer, and the resulting homogeneous stream is allowed to undergo Curtius rearrangement in a jacketed tube-in-tube reactor at 135 °C with 3 min residence time (RT) under a back-pressure of 10 bar. An in-line FTIR probe was utilized to ensure complete conversion to isocyanate (no remaining acyl azide present). After exiting the tube-in-tube reactor, the resulting solution of isocyanate **13** is allowed to flow into a receiving tank containing *t*-AmOH (519.6 mL, 4.77 mol, 1 eq.) in toluene (250 mL) stirred at 100 °C. After the flow of isocyanate **13** is complete, the resulting mixture in the receiving tank is stirred for 1 h at 100 °C. The batch is then cooled to 70 °C, treated with water (3.5 L), and further cooled to 20 °C. The resulting biphasic slurry is filtered and washed with water (1 L) and heptane (1 L). Carbamate **8** is obtained as an off-white solid (564 g, 72% yield). A second crop 84.52 g (9%) was isolated from the mother liquor.

Flow synthesis of carbamate 14. A stock solution of acid **3** (10 kg, 39.84 mol, 1 eq.), NEt_3 (5.83 L, 41.03 mol, 1.01 eq.), PMBOH (7.27 kg, 52.62 mol), and toluene (20 L) is prepared. A second

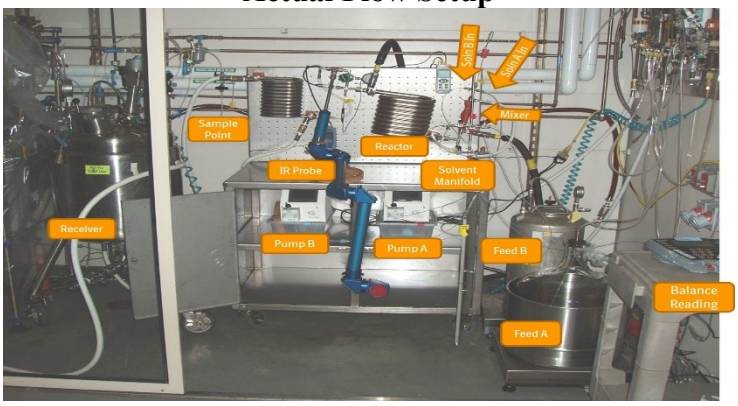
stock solution containing DPPA (8.98 L, 32.65 mol, 1 eq.) in toluene (10 L) is also prepared. The two stock solutions are pumped via polypropylene tubes and combined in an equimolar ratio via T-mixer and jacketed static mixer, and the resulting homogeneous stream is allowed to undergo Curtius rearrangement in a jacketed tube-in-tube reactor at 135 °C with 3 min residence time (RT) under a back-pressure of 10 bar. An in-line FTIR probe was utilized to ensure complete conversion to isocyanate (no remaining acyl azide present). After exiting the tube-in-tube reactor, the resulting solution of carbamate **14** is allowed to flow into a receiving tank held at a jacket temperature of 70 °C. After the flow of carbamate **14** is complete, the resulting mixture in the receiving tank is charged with water (6 V) while maintaining the internal temperature at 70 °C. The batch is then cooled to 20 °C over 3 h, and the resulting slurry is filtered and washed with water (3 L) and heptane (3 L). Carbamate **14** is obtained as an off-white solid (12.48 kg, 80% yield). m.p. = 152.5 °C; ^{1}H NMR (400 MHz, d^6-DMSO, mixture of rotamers) δ 8.63 (d, J = 5.20 Hz, 1H), 8.33 (s, 1H), 7.76 (d, J = 1.52 Hz, 1H), 7.38 (dd, J_1 = 5.06, J_2 = 1.38 Hz, 1H), 7.31 (d, J = 8.44 Hz, 1H), 4.99 (s, 2H), 3.74 (s, 3H), 3.27 (s, 3H), 1.35-1.44 (m, 4H); ^{13}C NMR (100 MHz, d^6-DMSO, mixture of rotamers) δ 159.5, 158.3, 157.6, 156.7, 130.1, 129.4, 129.2, 123.1, 116.4, 114.1, 65.9, 55.6, 35.0, 20.98; HRMS: calcd for $C_{15}H_{23}N_2O_4S$ [M + H]: 377.4345. Found: 377.5683.



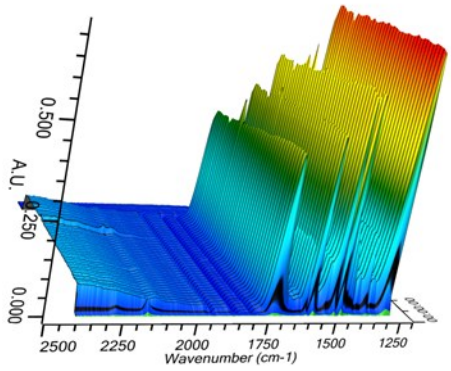
Schematic of Flow Diagram



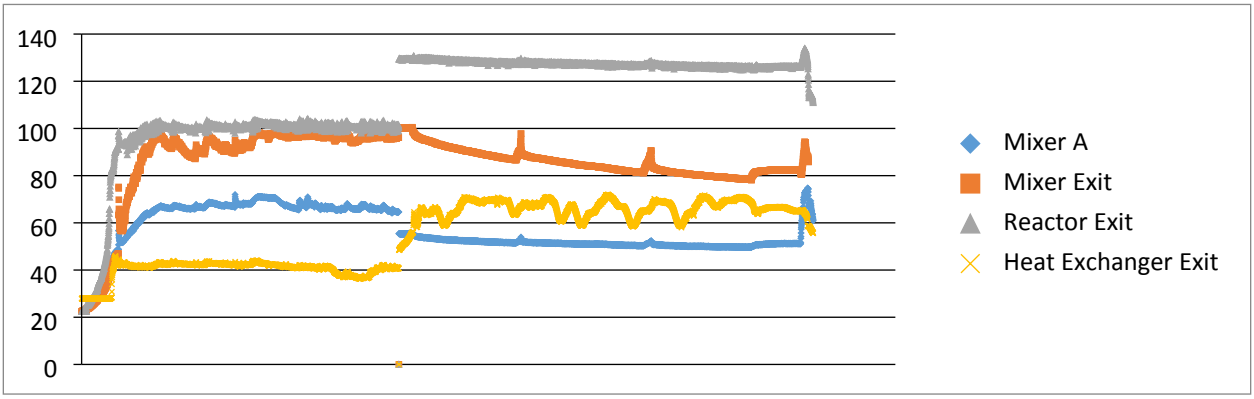
Actual Flow Setup



React IR data: Typical graph showing product at 1724 cm^{-1}, with absence of acyl azide and isocyanate monitored in situ

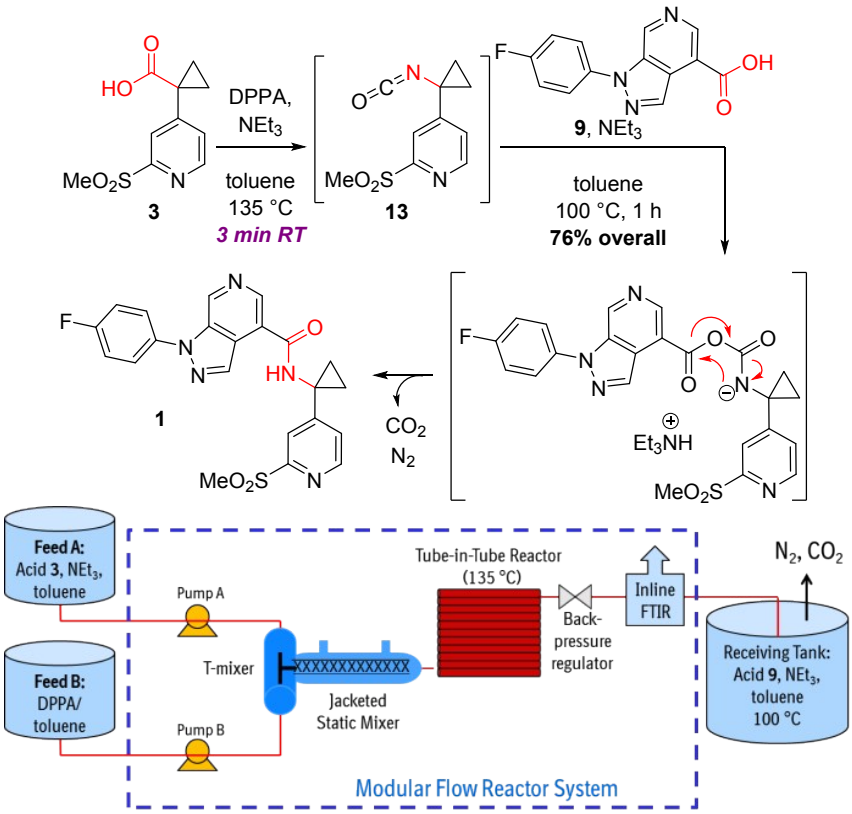


Temperature Monitoring during Typical Run



1-(4-fluorophenyl)-N-(1-(2-(methylsulfonyl)pyridin-4-yl)cyclopropyl)-1H-pyrazolo[3,4-c]pyridine-4-carboxamide (1) via Curtius rearrangement acid-isocyanate coupling. A stock solution of acid **3** (116 g, 480.9 mmol, 1.4 eq.), NEt_3 (81.4 mL, 583.9 mmol, 1.7 eq.), and toluene (621.6 mL) is prepared. A second stock solution containing DPPA (103.4 mL, 477.5 mol, 1.4 eq.) in toluene (300 mL) is also prepared. The two stock solutions are pumped via polypropylene tubes and combined in an equimolar ratio via T-mixer and jacketed static mixer, and the resulting homogeneous stream is allowed to undergo Curtius rearrangement in a jacketed tube-in-tube reactor at 135 °C with 3 min residence time (RT). An in-line FTIR probe was utilized to ensure complete conversion to isocyanate (no remaining acyl azide present). After exiting the tube-in-tube reactor, the resulting solution of isocyanate **13** is allowed to flow into a receiving tank containing acid **9** (88.8 g, 343.5 mmol), NEt_3 (62.2 mL, 449.0 mmol, 1.3 eq.), and toluene (888 mL) stirred at 100 °C. After the flow of isocyanate **13** is complete, the resulting mixture in the receiving tank is stirred for 1 h at 100 °C. The batch is then cooled to 70 °C, treated with water (2

L), and further cooled to 20 °C. The resulting biphasic slurry is filtered and washed with water (1 L) and heptane (1 L). Amide **1** is obtained as an off-white solid (117.9 g, 76% yield).



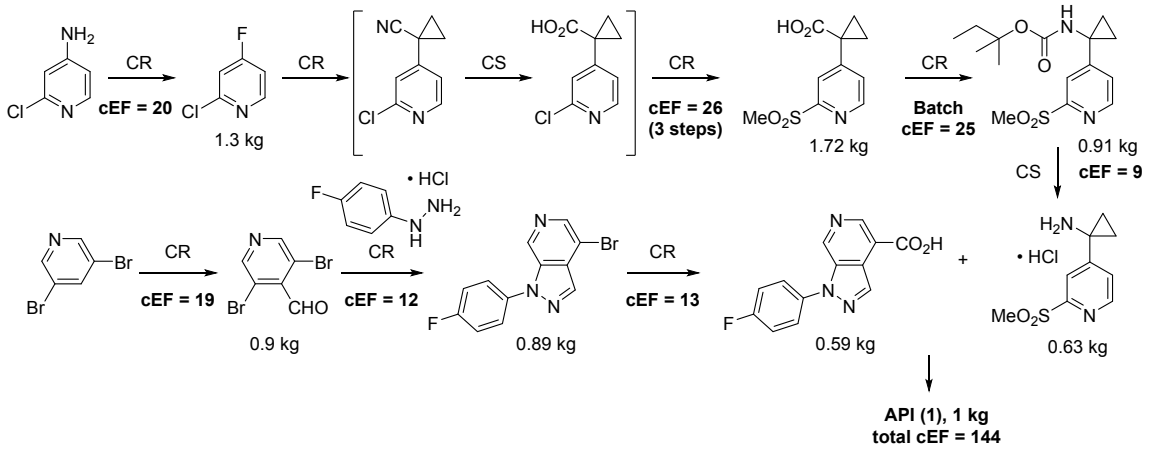
E-factor and GAL calculations:[2]

Definitions:

- cEF = complete E-factor = Σ(raw materials+reagents+solvent+water-product) / product
- Complexity = no. of construction steps (CS) + no. of strategic redox steps (SR)[3]
- CR = construction reaction
- SR = strategic redox reaction
- CS = concession reaction
- %ideality = complexity / total steps
- Complexity = #CR + #SR
- Simplified Literature E factor analysis (outsourced raw materials): cEF (literature) = 37 kg/kg x literature step #
- GAL = Green Aspiration Level = DS Complexity x 26 kg/kg
- RPG = Relative Process Greenness = GAL / cEF x 100%.
- RPI = Relative Process (Greenness) Improvement = RPG (current route) – RPG (initial route)

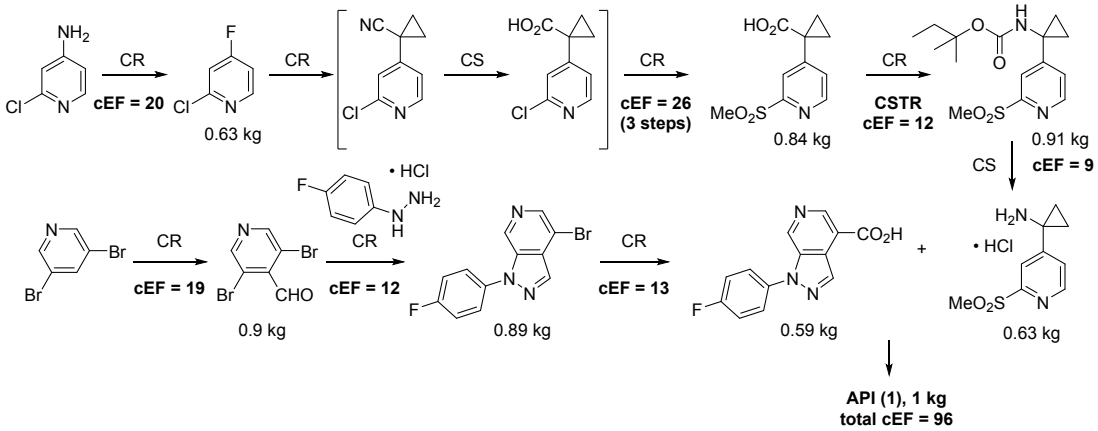
- RCI = Relative Complexity Improvement = 1- [Complexity (current route) / Complexity (initial route)]
- PI = (Overall) Process Improvement = (RPI + RCI) / 2

Route 1 (Batch Curtius Process):



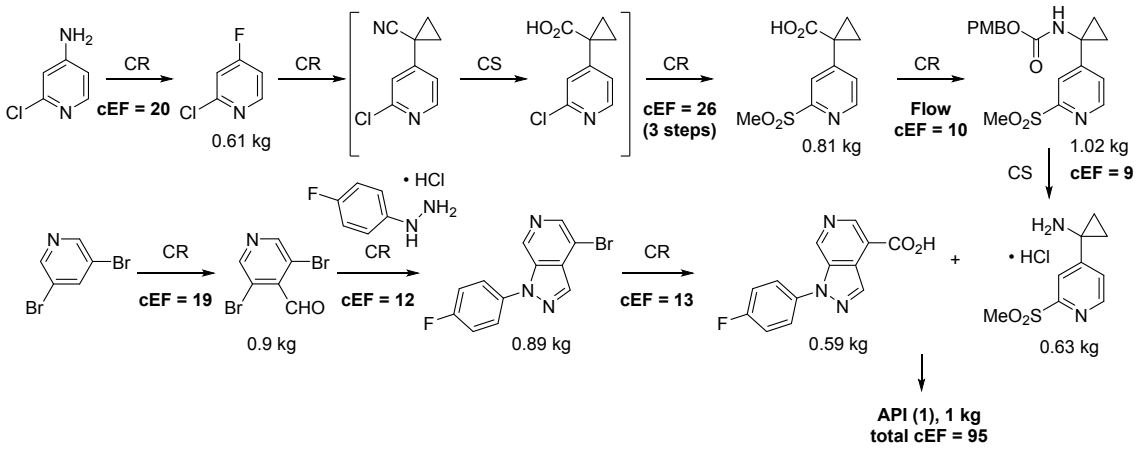
- cEF = **144 kg/kg**
- Complexity = **8**
- Ideality = 8/10 = **80%**
- GAL(cEF/early phase project) = 26 x 8 = **208 kg/kg**
- RPG = (208) / 144 = **144%** (44% better than the industry average).

Route 2 (CSTR Curtius Process):



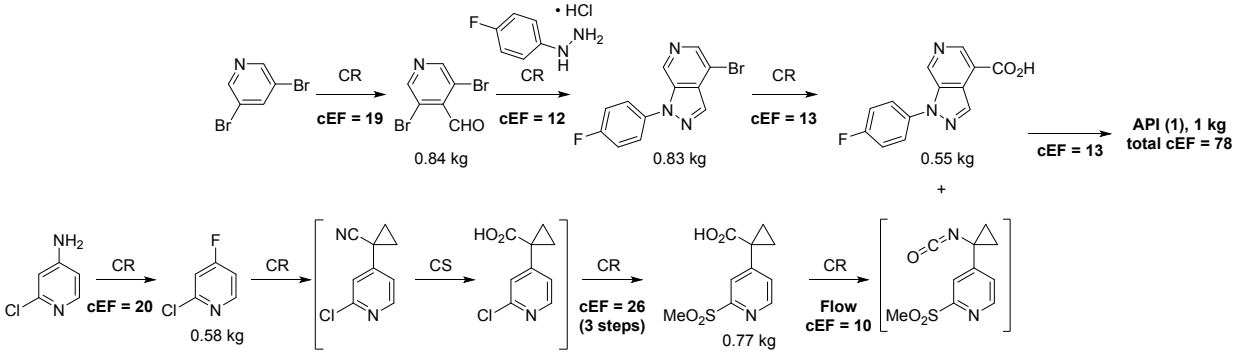
- cEF = **96 kg/kg**
- Complexity = **8**
- Ideality = 8/10 = **80%**
- GAL(cEF/early phase project) = 26 x 8 = **208 kg/kg**
- RPG = (208) / 96 = **216%** (116% better than the industry average).
- RPI = 216-144 = 72%
- RCI = 0
- PI = (72+0)/2 = 36%

Route 3: PMB Flow Route

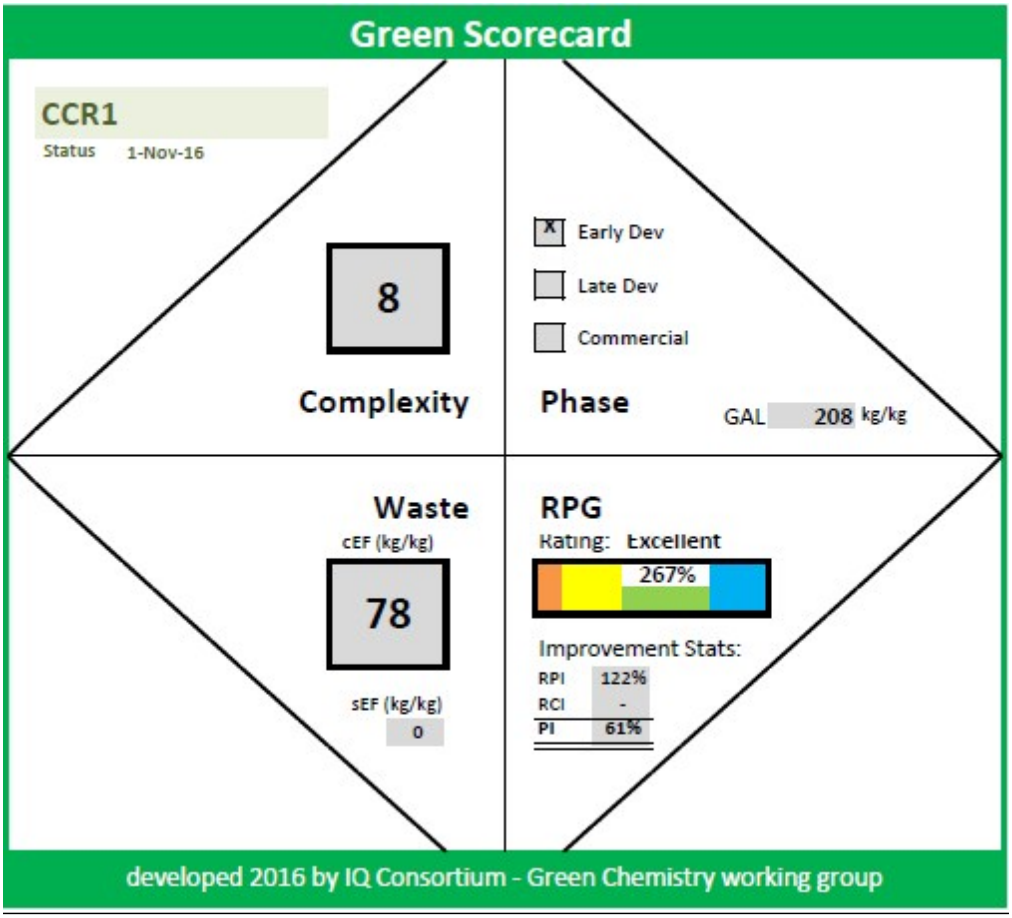


- cEF = **95 kg/kg**
- Complexity = **8**
- Ideality = 8/10 = **80%**
- GAL(cEF/early phase project) = 26 x 8 = **208 kg/kg**
- RPG = (208) / 95 = **218%** (118% better than the industry average).
- RPI = 144-95 = 49
- RPI = 218-144 = 74%
- RCI = 0
- PI = (74+0)/2 = 37%

Route 4: Direct Flow Curtius Amide Coupling:

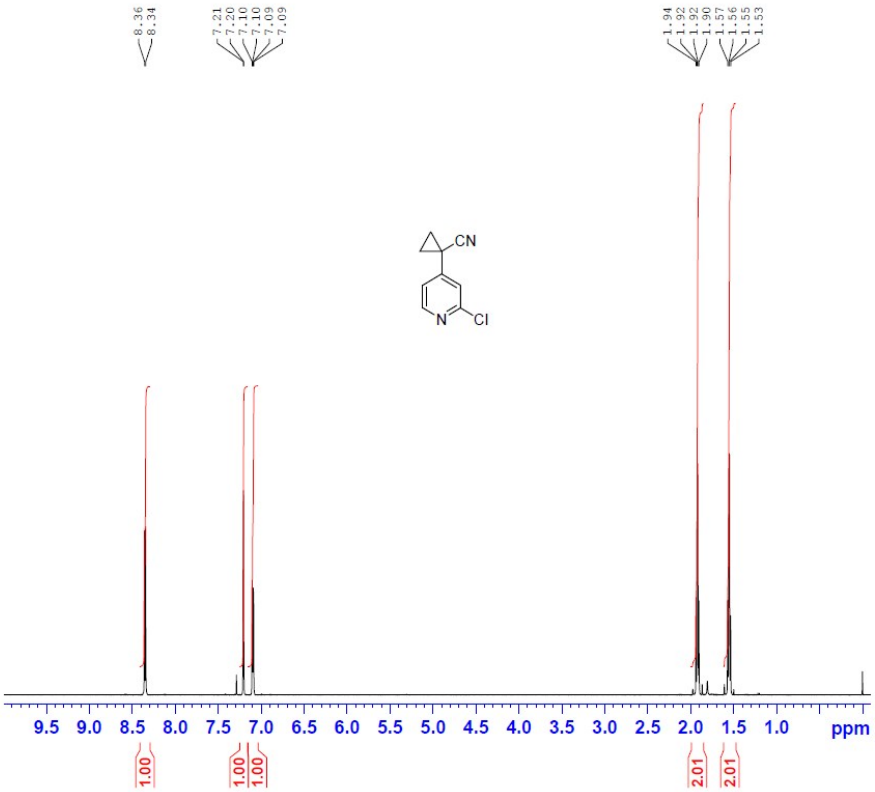


- cEF = **78 kg/kg**
- Complexity = **8**
- Ideality = 9/10 = **80%**
- GAL(cEF/early phase project) = 26 x 8 = **208 kg/kg**
- RPG = (208) / 78 = **266%** (166% better than the industry average).
- RPI = 266-144 = 122%
- RCI = 0
- PI = (122+0)/2 = 61%



^{1}H and ^{13}C NMR spectra for all compounds:

^{1}H NMR spectrum of 6



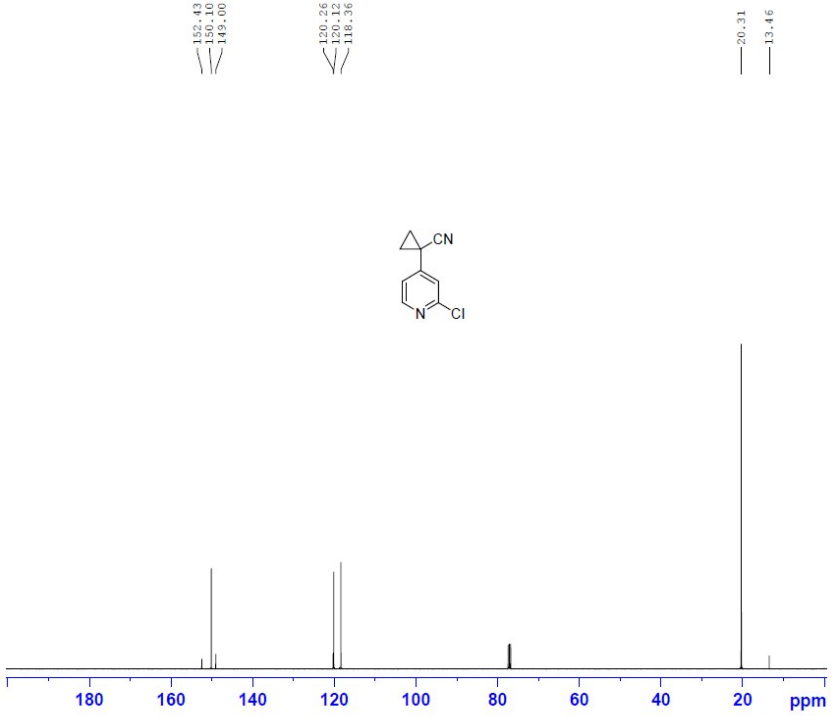
Current Data Parameters
NAME 79220-ccr1
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20151123
Time_ 11.09
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg10
TD 32768
SOLVENT CDCl3
NS 4
DS 4
SWH 5896.227 Hz
FIDRES 0.179939 Hz
AQ 2.7787263 sec
RG 456
DW 84.800 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 400.1327209 MHz
NUC1 1H
P1 15.00 usec
PLW1 10.50000000 W

F2 - Processing parameters
SI 65536
SF 400.1299988 MHz
WDW EM
SSB 0
LB 0.05 Hz
GB 0
PC 1.00

^{13}C NMR spectrum of 6



Current Data Parameters
NAME 79220-ccr1
EXPNO 2
PROCNO 1

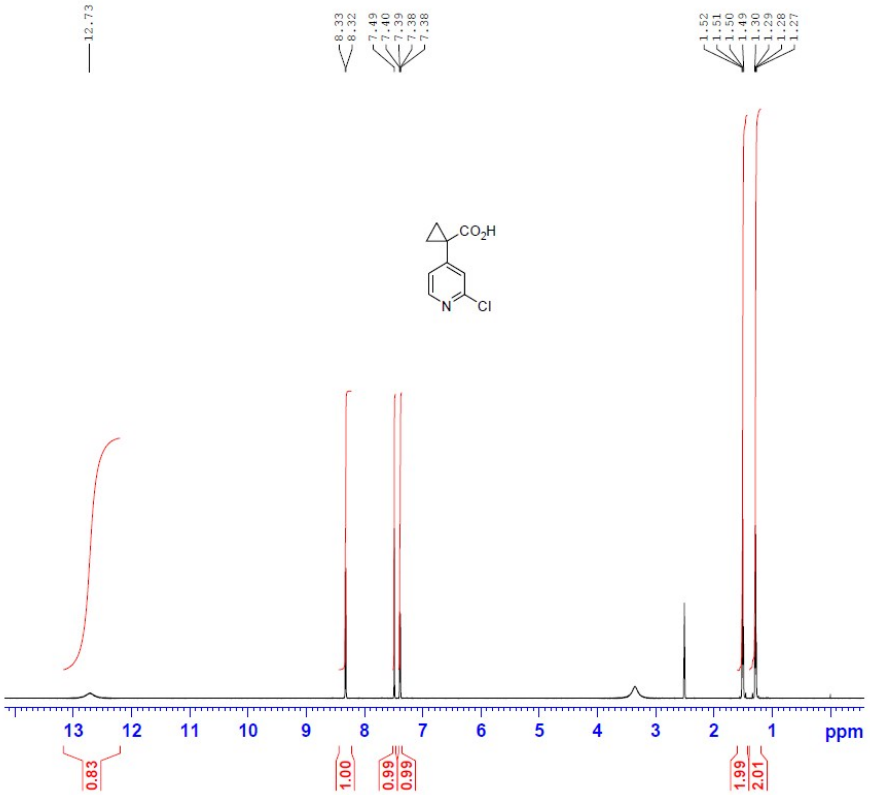
F2 - Acquisition Parameters
Date_ 20151123
Time_ 20.14
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg
TD 32768
SOLVENT CDCl3
NS 1024
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 0.6815744 sec
RG 2050
DW 20.800 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 100.6243395 MHz
NUC1 13C
P1 10.90 usec
PLW1 43.00000000 W

======== CHANNEL f2 ========
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 10.50000000 W
PLW12 0.29166999 W
PLW13 0.14670999 W

F2 - Processing parameters
SI 65536
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

^{1}H NMR spectrum of 7



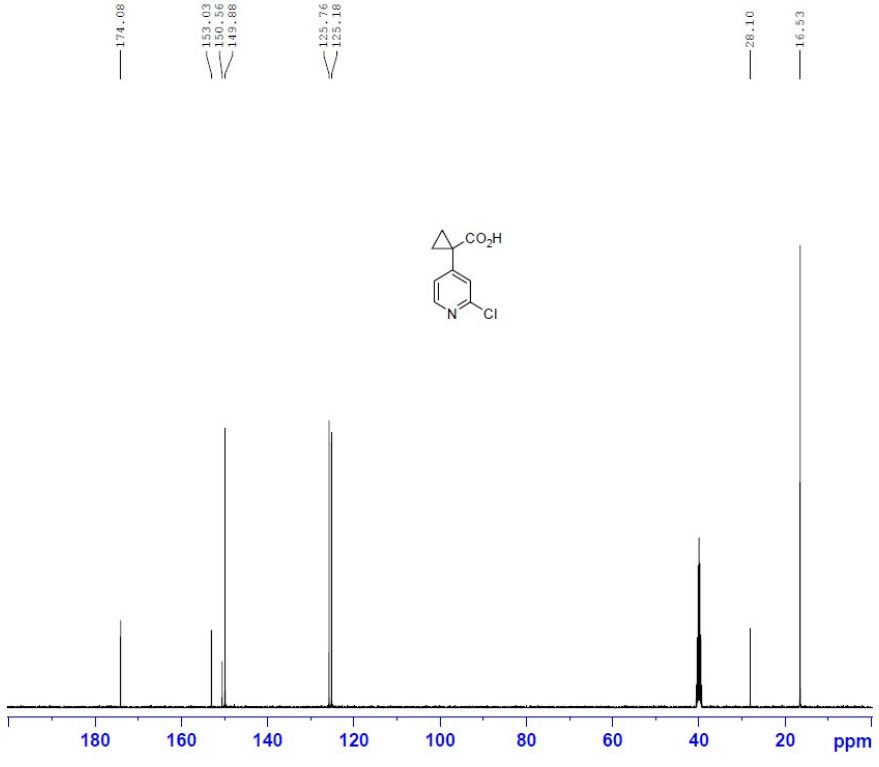
```
Current Data Parameters
NAME            79221-ccr1
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20151123
Time                 11.13
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG              zg10
TD                  32768
SOLVENT              DMSO
NS                       4
DS                       4
SWH              5896.227 Hz
FIDRES           0.179939 Hz
AQ               2.7787263 sec
RG                     575
DW                84.800 usec
DE                 6.50 usec
TE                298.0 K
D1             2.00000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1           400.1327209 MHz
NUC1                   1H
P1                  15.00 usec
PLW1          10.50000000 W

F2 - Processing parameters
SI                   65536
SF             400.1300005 MHz
WDW                    EM
SSB       0
LB                  0.05 Hz
GB        0
PC                  1.00
```

^{13}C NMR spectrum of 7



```
Current Data Parameters
NAME            79221in
EXPNO                 1
PROCNO                1

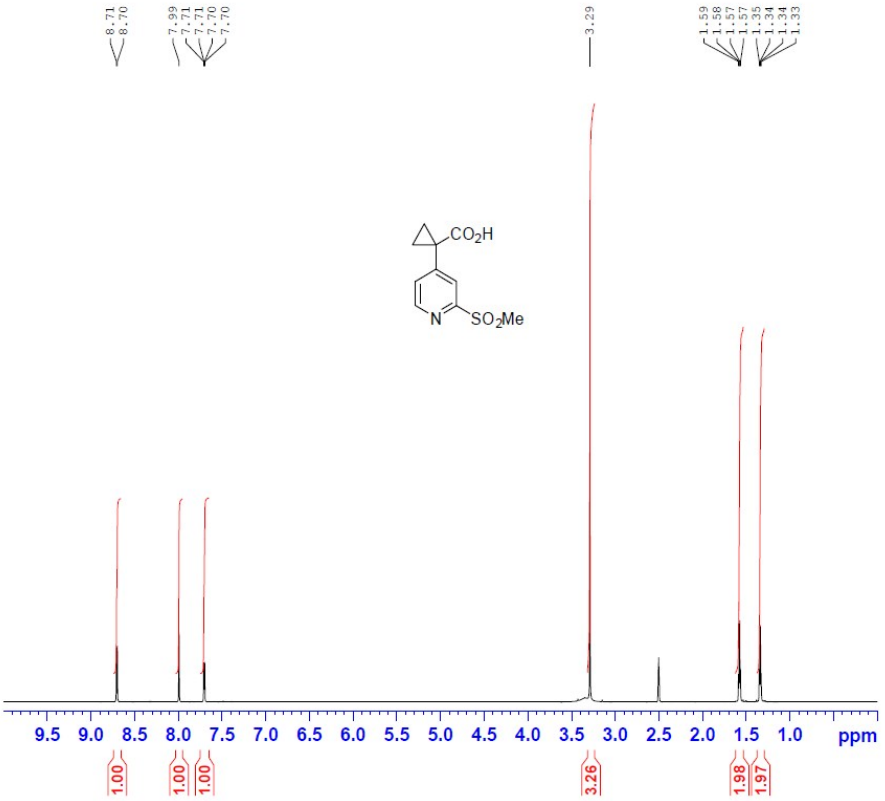
F2 - Acquisition Parameters
Date_          20151207
Time              19.49
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg
TD               32768
SOLVENT           DMSO
NS                 512
DS                   4
SWH          24038.461 Hz
FIDRES        0.733596 Hz
AQ           0.6815744 sec
RG                2050
DW              20.800 usec
DE               6.50 usec
TE              298.0 K
D1          2.00000000 sec
D11         0.03000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1        100.6243395 MHz
NUC1                13C
P1                10.90 usec
PLW1        43.00000000 W

======== CHANNEL f2 ========
SFO2        400.1316005 MHz
NUC2                1H
CPDPRG[2        waltz16
PCPD2             90.00 usec
PLW2        10.50000000 W
PLW12        0.29166999 W
PLW13        0.14670999 W

F2 - Processing parameters
SI                65536
SF          100.6127690 MHz
WDW                 EM
SSB       0
LB               1.00 Hz
GB        0
PC                1.40
```

^{1}H NMR spectrum of 3



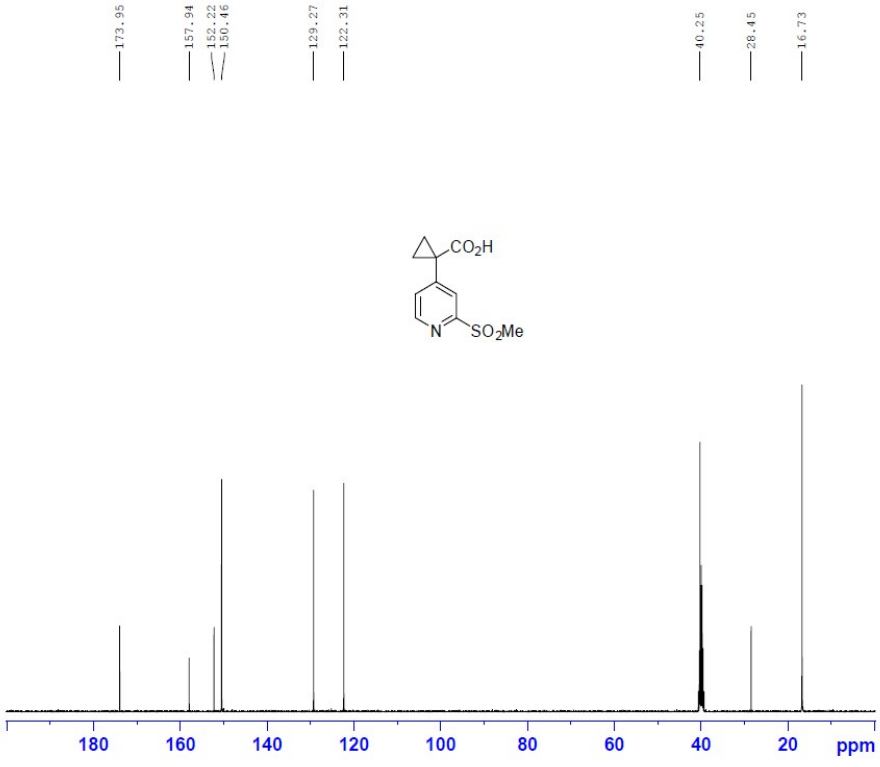
```
Current Data Parameters
NAME          79222-ccr1
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20151124
Time              10.00
INSTRUM           spect
PROBHD   5 mm PABBI 1H-
PULPROG            zg10
TD                32768
SOLVENT            DMSO
NS                   16
DS                    0
SWH            7500.000 Hz
FIDRES         0.228882 Hz
AQ            2.1845334 sec
RG                  362
DW               66.667 usec
DE                6.50 usec
TE               299.0 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 8.00 usec
PL1                3.00 dB
PL1W        14.98121262 W
SFO1        500.1325007 MHz

F2 - Processing parameters
SI                 16384
SF          500.1300050 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

^{13}C NMR spectrum of 3



```
Current Data Parameters
NAME          79222-ccr1
EXPNO                  3
PROCNO                 1

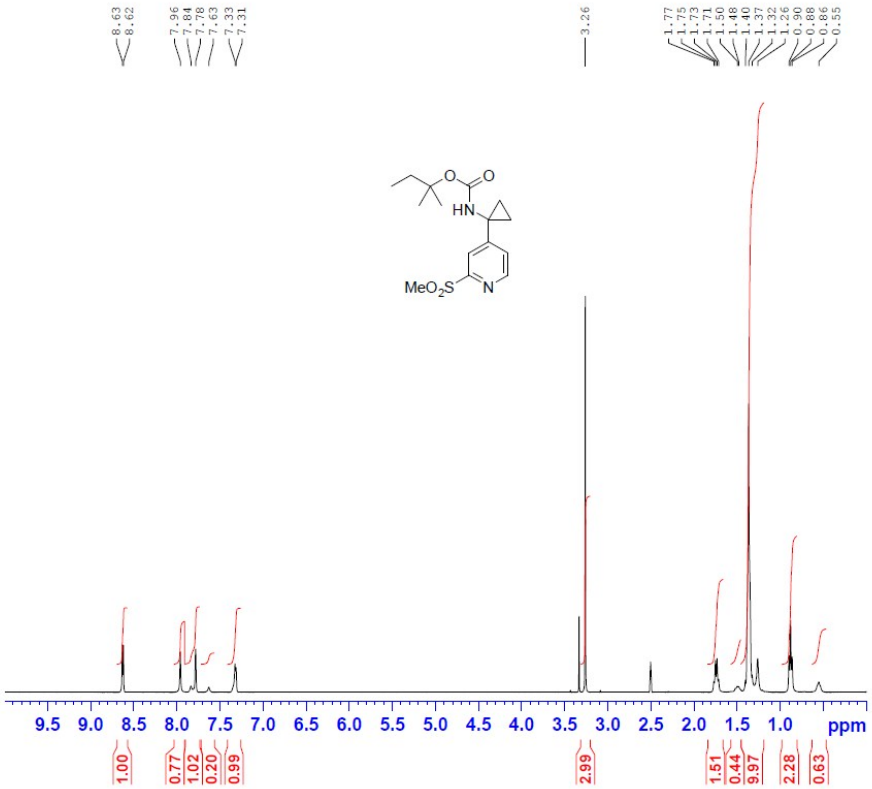
F2 - Acquisition Parameters
Date_           20151124
Time              19.27
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG            zgpg
TD                32768
SOLVENT            DMSO
NS                  512
DS                    4
SWH           24038.461 Hz
FIDRES         0.733596 Hz
AQ            0.6815744 sec
RG                 2050
DW               20.800 usec
DE                6.50 usec
TE               298.0 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1        100.6243395 MHz
NUC1                 13C
P1                10.90 usec
PLW1        43.00000000 W

======== CHANNEL f2 ========
SFO2        400.1316005 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2             90.00 usec
PLW2        10.50000000 W
PLW12        0.29166999 W
PLW13        0.14670999 W

F2 - Processing parameters
SI                 65536
SF          100.6127690 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

^{1}H NMR spectrum of 8



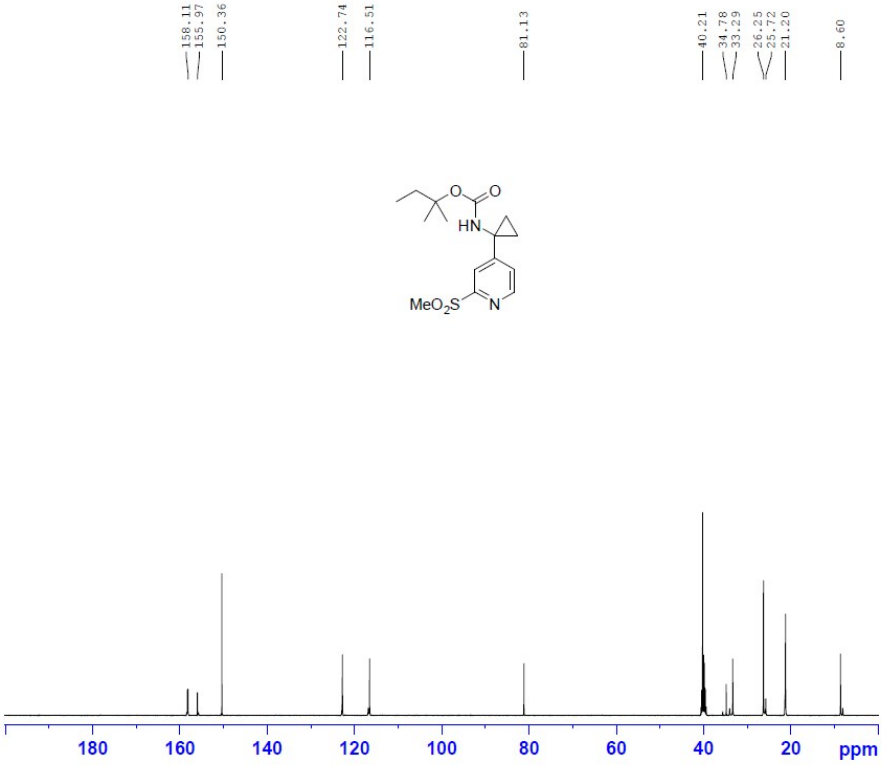
```
Current Data Parameters
NAME                 79271-ccr1
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_               20151123
Time                   11.21
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg10
TD                    32768
SOLVENT                DMSO
NS                        4
DS                        4
SWH                5896.227 Hz
FIDRES            0.179939 Hz
AQ                2.7787263 sec
RG                      203
DW                   84.800 usec
DE                    6.50 usec
TE                   298.0 K
D1                2.00000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1             400.1327209 MHz
NUC1                       1H
P1                      15.00 usec
PLW1            10.50000000 W

F2 - Processing parameters
SI                        65536
SF               400.1300020 MHz
WDW                        EM
SSB          0
LB                     0.05 Hz
GB           0
PC                     1.00
```

^{13}C NMR spectrum of 8



```
Current Data Parameters
NAME                 79271-ccr1
EXPNO                         2
PROCNO                        1

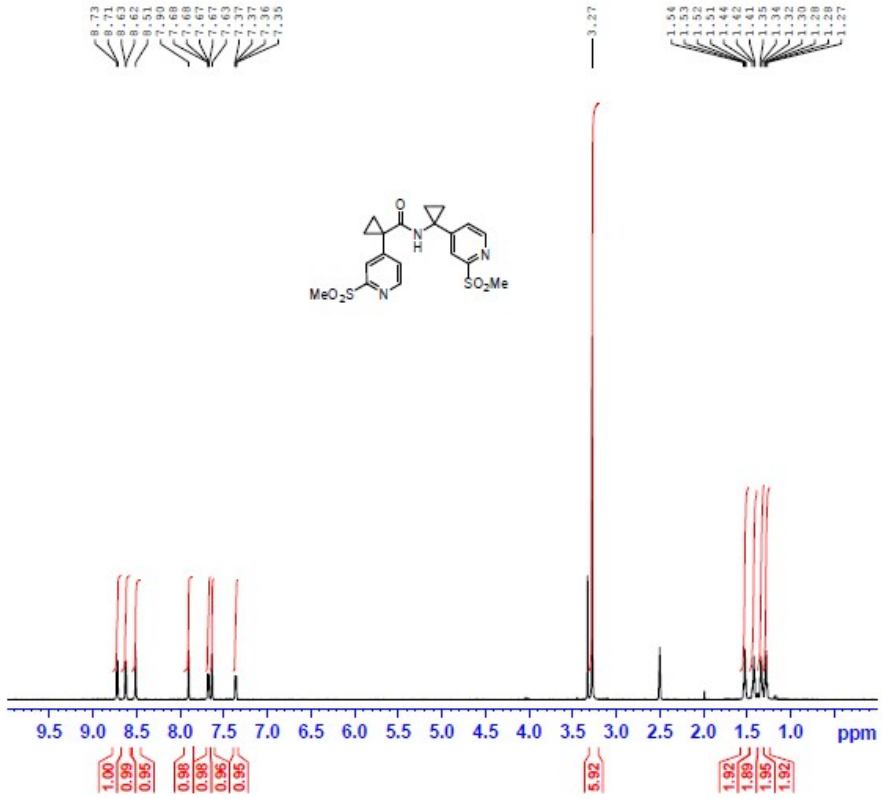
F2 - Acquisition Parameters
Date_               20151123
Time                   22.46
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zgpg
TD                    32768
SOLVENT                DMSO
NS                      1024
DS                        4
SWH               24038.461 Hz
FIDRES            0.733596 Hz
AQ                0.6815744 sec
RG                     2050
DW                   20.800 usec
DE                    6.50 usec
TE                   298.0 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1             100.6243395 MHz
NUC1                      13C
P1                      10.90 usec
PLW1            43.00000000 W

======== CHANNEL f2 ========
SFO2             400.1316005 MHz
NUC2                       1H
CPDPRG[2              waltz16
PCPD2                  90.00 usec
PLW2            10.50000000 W
PLW12            0.29166999 W
PLW13            0.14670999 W

F2 - Processing parameters
SI                        65536
SF               100.6127690 MHz
WDW                        EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```

^{1}H NMR spectrum of 10



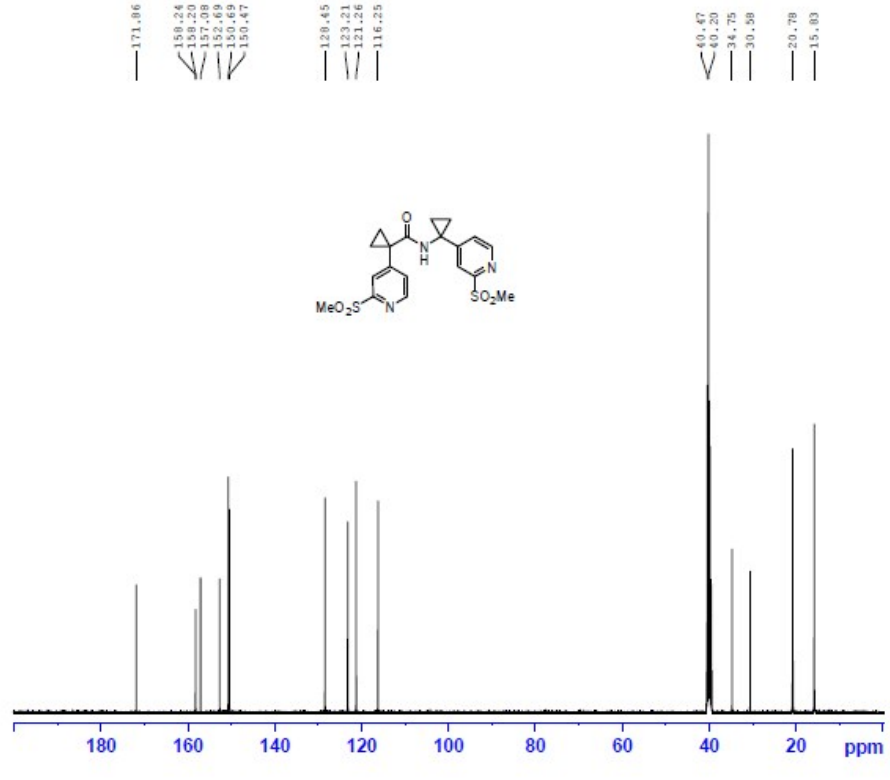
```
Current Data Parameters
NAME                  79274-ccr1
EXPNO                          1
PROCNO                         1

F2 - Acquisition Parameters
Date_                  20151123
Time                      11.40
INSTRUM                   spect
PROBHD    5 mm PABBO BB-
PULPROG                   zg10
TD                       32768
SOLVENT                   DMSO
NS                             4
DS                             4
SWH                    5896.227 Hz
FIDRES                 0.179939 Hz
AQ                     2.7787263 sec
RG                           406
DW                        84.800 usec
DE                         6.50 usec
TE                        298.0 K
D1                     2.00000000 sec
TD0                            1

======== CHANNEL f1 ========
SFO1                 400.1327209 MHz
NUC1                         1H
P1                          15.00 usec
PLW1                10.50000000 W

F2 - Processing parameters
SI                         65536
SF                   400.1300032 MHz
WDW                           EM
SSB                0
LB                            0.05 Hz
GB                 0
PC                            1.00
```

^{13}C NMR spectrum of 10



```
Current Data Parameters
NAME                  79274-ccr1
EXPNO                          2
PROCNO                         1

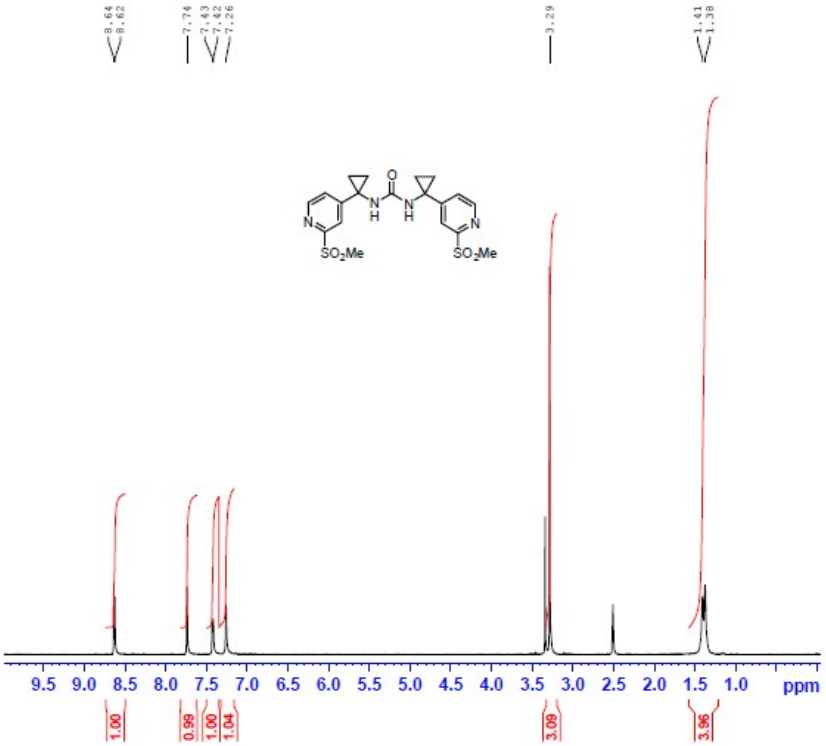
F2 - Acquisition Parameters
Date_                  20151124
Time                       2.59
INSTRUM                   spect
PROBHD    5 mm PABBO BB-
PULPROG                   zgpg
TD                       32768
SOLVENT                   DMSO
NS                         1024
DS                             4
SWH                   24038.461 Hz
FIDRES                 0.733596 Hz
AQ                     0.6815744 sec
RG                          2050
DW                        20.800 usec
DE                         6.50 usec
TE                        298.0 K
D1                     2.00000000 sec
D11                    0.03000000 sec
TD0                            1

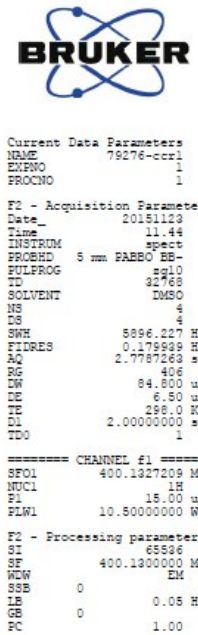
======== CHANNEL f1 ========
SFO1                 100.6243395 MHz
NUC1                         13C
P1                         10.90 usec
PLW1                43.00000000 W

======== CHANNEL f2 ========
SFO2                 400.1316005 MHz
NUC2                         1H
CPDPRG[2                 waltz16
PCPD2                      90.00 usec
PLW2                10.50000000 W
PLW12                0.29166999 W
PLW13                0.14670999 W

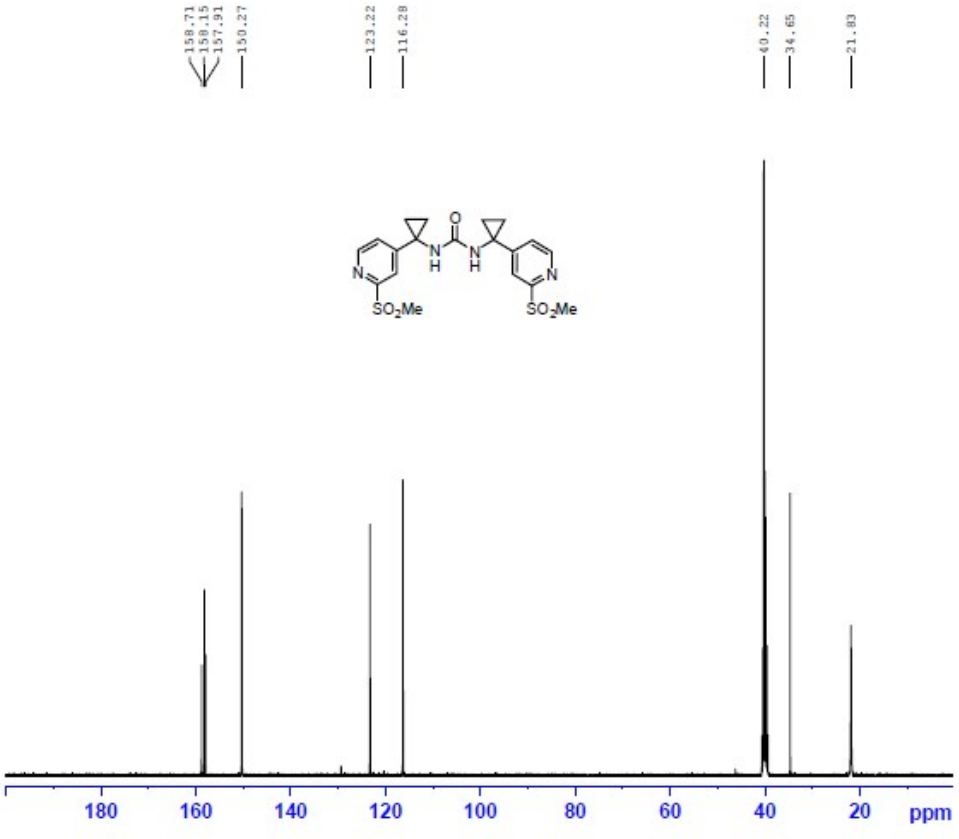
F2 - Processing parameters
SI                         65536
SF                   100.6127690 MHz
WDW                           EM
SSB                0
LB                            1.00 Hz
GB                 0
PC                            1.40
```

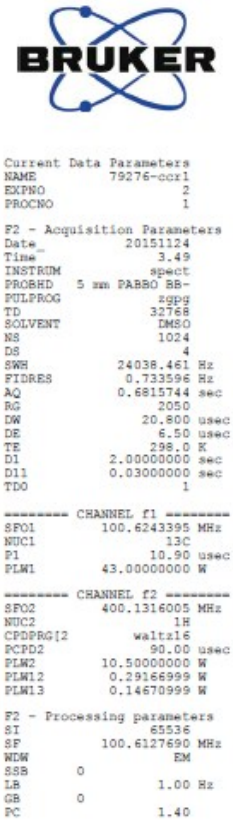
^{1}H NMR spectrum of 11



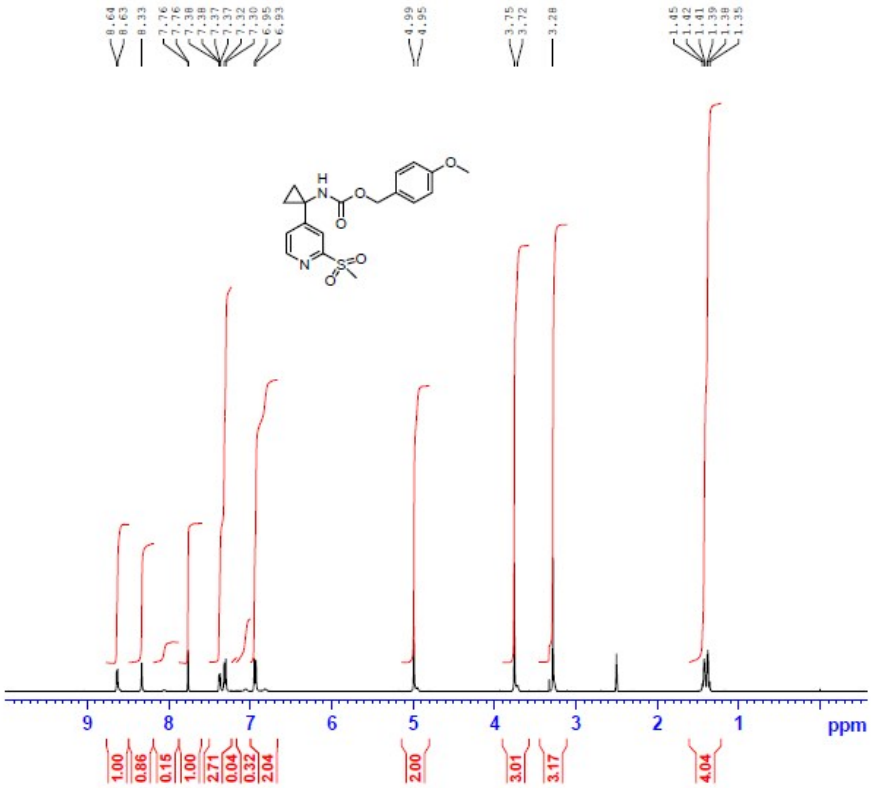


^{13}C NMR spectrum of 11





^{1}H NMR spectrum of 14



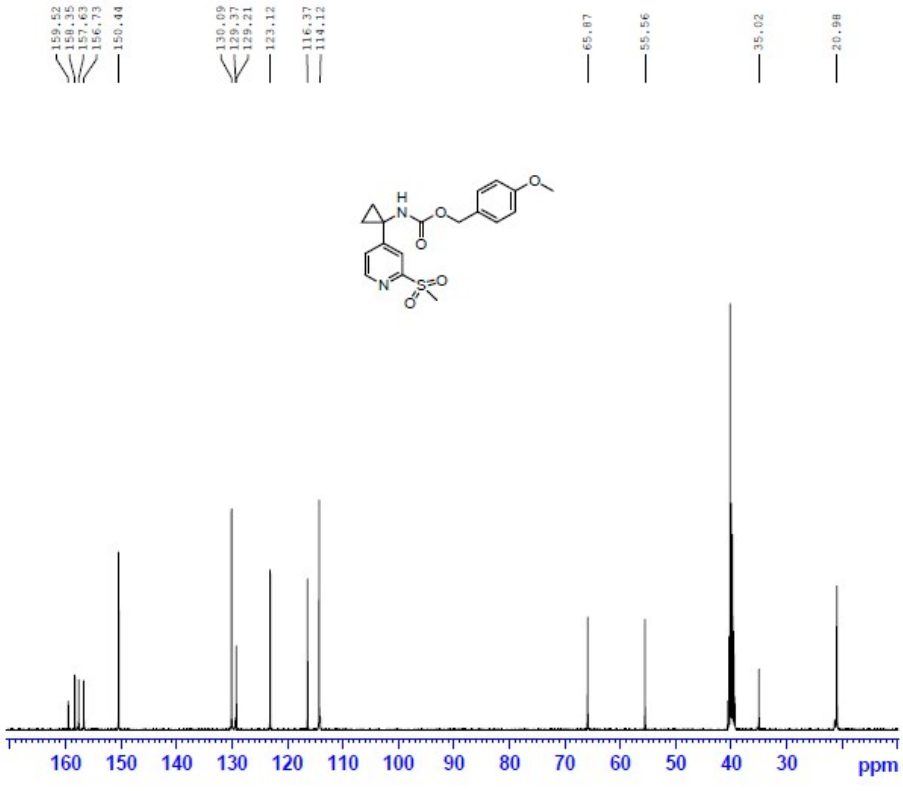
```
Current Data Parameters
NAME                in79303
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20161104
Time                  15.20
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG               zg10
TD                   32768
SOLVENT                DMSO
NS                        4
DS                        4
SWH                5896.227 Hz
FIDRES            0.179939 Hz
AQ                2.7787263 sec
RG                      203
DW                   84.800 usec
DE                    6.50 usec
TE                   298.0 K
D1                2.00000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1             400.1327209 MHz
NUC1                      1H
P1                    15.00 usec
PLW1             10.50000000 W

F2 - Processing parameters
SI                        65536
SF               400.1300031 MHz
WDW                       EM
SSB          0
LB                     0.05 Hz
GB           0
PC                     1.00
```

^{13}C NMR spectrum of 14



```
Current Data Parameters
NAME                in79303
EXPNO                     2
PROCNO                    1

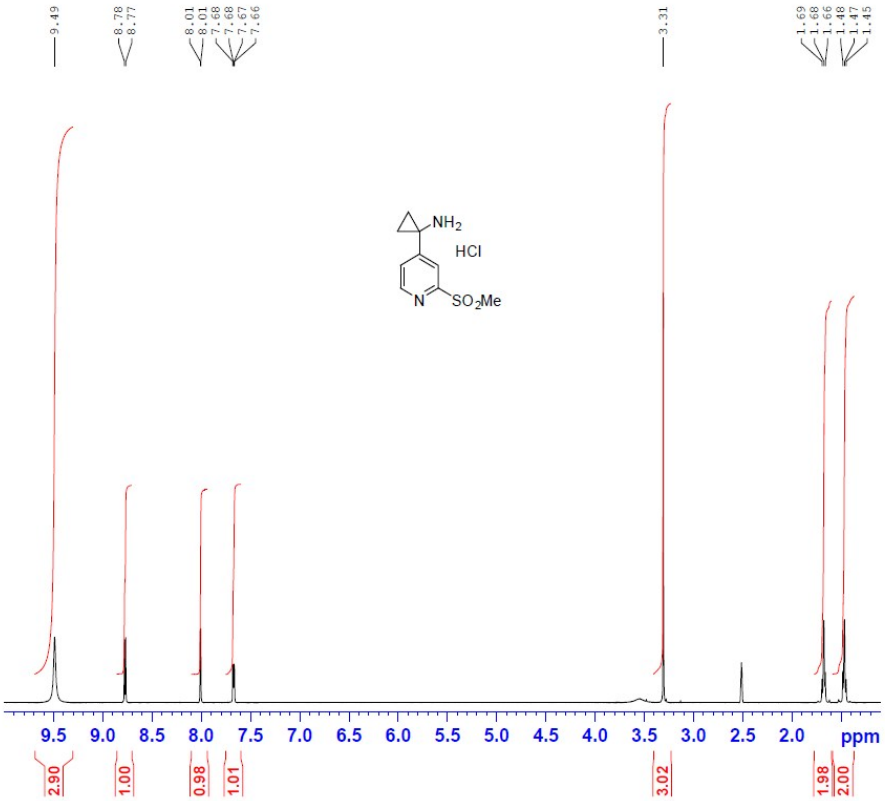
F2 - Acquisition Parameters
Date_              20161104
Time                  20.38
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG             zgpg
TD                   32768
SOLVENT                DMSO
NS                     2056
DS                        4
SWH               24038.461 Hz
FIDRES            0.733596 Hz
AQ                0.6815744 sec
RG                     2050
DW                   20.800 usec
DE                    6.50 usec
TE                   298.0 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1             100.6243395 MHz
NUC1                      13C
P1                    10.90 usec
PLW1             43.00000000 W

======== CHANNEL f2 ========
SFO2             400.1316005 MHz
NUC2                      1H
CPDPRG[2             waltz16
PCPD2                 90.00 usec
PLW2             10.50000000 W
PLW12             0.29166999 W
PLW13             0.14670999 W

F2 - Processing parameters
SI                        65536
SF               100.6127690 MHz
WDW                       EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```

^{1}H NMR spectrum of 2



BRUKER

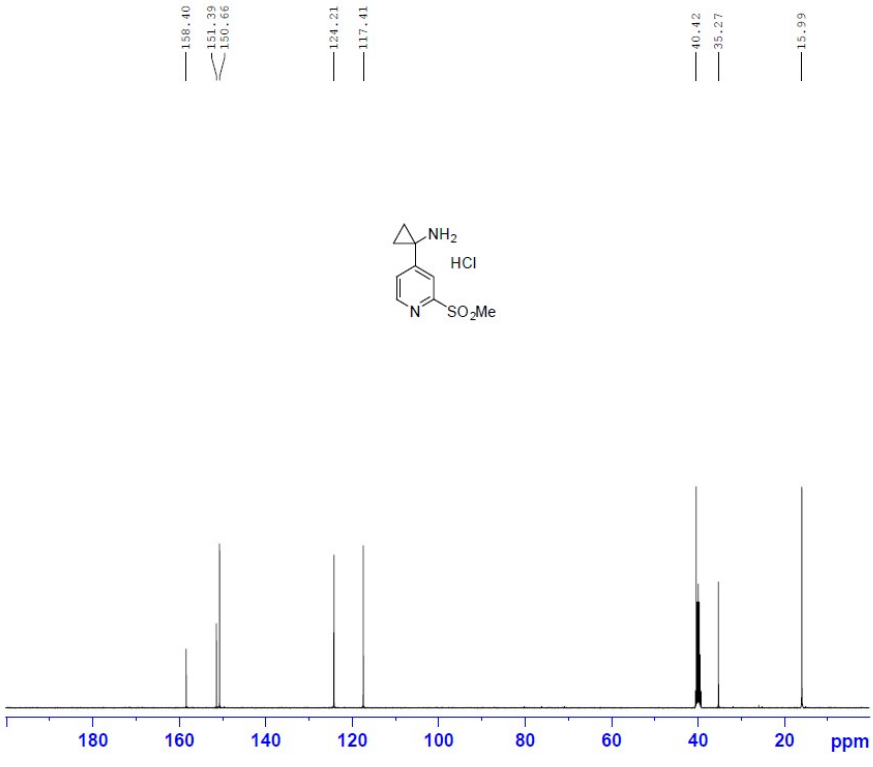
```
Current Data Parameters
NAME          639843-ccr1
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_              20151123
Time                 11.24
INSTRUM              spect
PROBHD    5 mm PABBO BB-
PULPROG              zg10
TD                  32768
SOLVENT               DMSO
NS                       4
DS                       4
SWH               5896.227 Hz
FIDRES           0.179939 Hz
AQ               2.7787263 sec
RG                     362
DW                84.800 usec
DE                 6.50 usec
TE                298.0 K
D1             2.00000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1          400.1327209 MHz
NUC1                    1H
P1                  15.00 usec
PLW1          10.50000000 W

F2 - Processing parameters
SI                   65536
SF            400.1299983 MHz
WDW                     EM
SSB          0
LB                   0.05 Hz
GB           0
PC                   1.00
```

^{13}C NMR spectrum of 2



BRUKER

```
Current Data Parameters
NAME          639843-ccr1
EXPNO                   2
PROCNO                  1

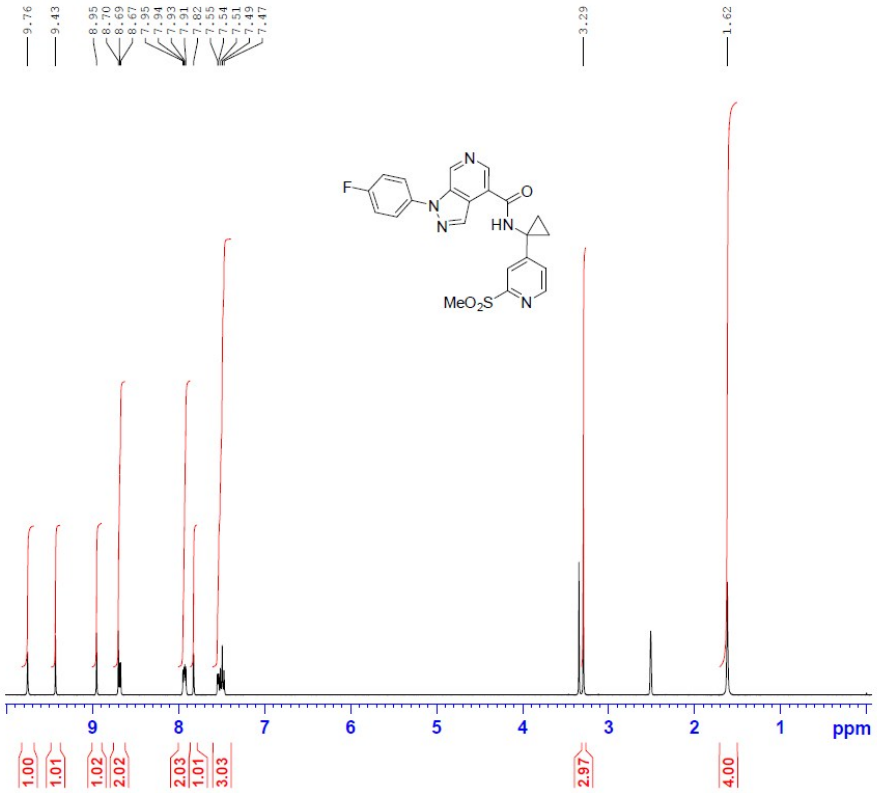
F2 - Acquisition Parameters
Date_              20151123
Time                 23.36
INSTRUM              spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg
TD                  32768
SOLVENT               DMSO
NS                    1024
DS                       4
SWH              24038.461 Hz
FIDRES           0.733596 Hz
AQ               0.6815744 sec
RG                    2050
DW                20.800 usec
DE                 6.50 usec
TE                298.0 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1          100.6243395 MHz
NUC1                   13C
P1                  10.90 usec
PLW1          43.00000000 W

======== CHANNEL f2 ========
SFO2          400.1316005 MHz
NUC2                    1H
CPDPRG[2            waltz16
PCPD2               90.00 usec
PLW2          10.50000000 W
PLW12          0.29166999 W
PLW13          0.14670999 W

F2 - Processing parameters
SI                   65536
SF            100.6127690 MHz
WDW                     EM
SSB          0
LB                   1.00 Hz
GB           0
PC                   1.40
```

^{1}H NMR spectrum of 1

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Current Data Parameters
NAME          639667-ccr1
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
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Time                 11.36
INSTRUM              spect
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PULPROG              zg10
TD                  32768
SOLVENT              DMSO
NS                      4
DS                      4
SWH               5896.227 Hz
FIDRES           0.179939 Hz
AQ               2.7787263 sec
RG                    575
DW                 84.800 usec
DE                  6.50 usec
TE                298.0 K
D1             2.00000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1          400.1327209 MHz
NUC1                   1H
P1                  15.00 usec
PLW1          10.50000000 W

F2 - Processing parameters
SI                  65536
SF            400.1299995 MHz
WDW                    EM
SSB       0
LB                   0.05 Hz
GB        0
PC                   1.00
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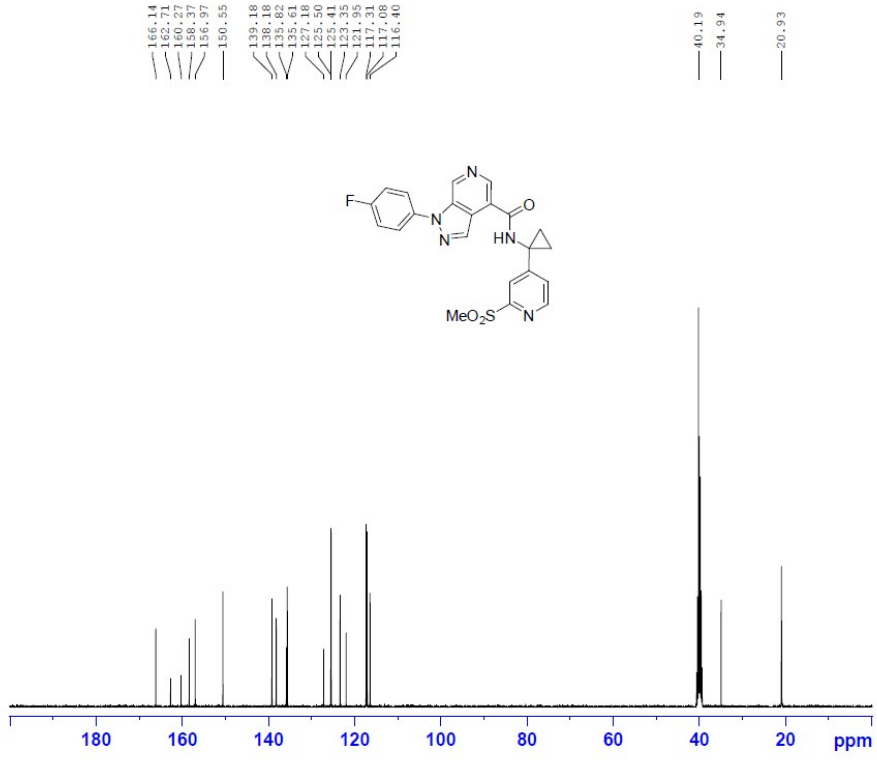
^{13}C NMR spectrum of 1

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Current Data Parameters
NAME          639667-ccr1
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
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Time                  2.09
INSTRUM              spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg
TD                  32768
SOLVENT              DMSO
NS                   1024
DS                      4
SWH              24038.461 Hz
FIDRES           0.733596 Hz
AQ               0.6815744 sec
RG                   2050
DW                 20.800 usec
DE                  6.50 usec
TE                298.0 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1          100.6243395 MHz
NUC1                   13C
P1                  10.90 usec
PLW1          43.00000000 W

======== CHANNEL f2 ========
SFO2          400.1316005 MHz
NUC2                   1H
CPDPRG[2          waltz16
PCPD2               90.00 usec
PLW2          10.50000000 W
PLW12          0.29166999 W
PLW13          0.14670999 W

F2 - Processing parameters
SI                  65536
SF            100.6127690 MHz
WDW                    EM
SSB       0
LB                   1.00 Hz
GB        0
PC                   1.40
```

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