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Supplementary Materials for

Kilogram-scale prexasertib monolactate monohydrate synthesis under continuous-flow CGMP conditions

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This PDF file includes:

Materials and Methods

For containment purposes, only pyrazines **1**, **10**, and **12** were handled with special precautions. For manipulation of these compounds, solutions or wet solids were preferred and used whenever possible, so that the risk of airborne contamination was reduced. Solids were only manipulated in fume hoods, ventilated balance enclosures, or glove boxes and any container was sealed and wiped clean prior to removal from the enclosure.

- Up to 1 g per day of solid could be weighed out in a standard ventilated balance enclosure or handled in a fume hood while using normal PPE.
- For manipulation of dry solids up to ~20 g, additional engineering controls and PPE were utilized including 10× respiratory protection.
- For quantities >20 g full body protection with supplied air was utilized, and in conjunction with engineering controls such as fume hood, glove bag or glove box containment; the exact PPE selection for each circumstance was quantity and task dependent.

HPLC Method Details

HPLC data was collected on an Agilent 1260 instrument.
HPLC Method A:
Waters Cortecs C18 column, 3.0 x 100 mm, 2.7 µm particle size, 47 °C temperature, 294 nm.
Solvent A = 10 mM ammonium formate in 95/5 (v/v) water/acetonitrile
Solvent B = 10 mM ammonium formate in 10/90 (v/v) water/acetonitrile

Time (min)	% Solvent A
0.0	81
8.0	34
10.5	0
11.5	0
11.6	81
14.0	81

HPLC Method B:
Waters Xbridge BEH column, 3.0 x 100 mm, 2.5 µm particle size, 25 °C temperature, 274 nm.
Solvent A = 0.1% (v/v) TFA in water
Solvent B = 0.1% (v/v) TFA in acetonitrile

Time (min)	% Solvent A
0	90
8.5	20
8.51	90
11	90

Description of cGMP Equipment Qualification

cGMP equipment qualification for the continuous reactors and continuous separations unit operations were done the same way, using the same procedures, as for typical new batch equipment. The required ranges of pressures, temperatures, liquid levels, and mass flow rates were demonstrated and documented using standard cGMP protocols. The volume for each of the three coiled tube reactors was not directly measured, but was calculated from the known tubing length and inside diameter. The residence time distribution (RTD), mixing rates, and heat transfer rates for the cGMP qualified coiled tube reactors were not measured in the reactors themselves. Instead, these parameters were measured using identical reactors in development labs prior to constructing the cGMP units. A benefit of SVC is that the same size reactors can be used in research as those used in manufacturing; therefore, many parameters can be measured in the development labs beforehand. The RTD was characterized by quantifying axial dispersion through experimental measurements during start up and shutdown transitions with the actual chemistry running, and then numerically modeling the data. In the manufacturing campaign, the startup and shutdown transitions were measured using a refractive index probe for information only (non-cGMP data collection), therefore the RTD in the manufacturing plant equipment was quantified, but this was not done as part of equipment qualification. The heat transfer rates in the high temperature coiled tube reactor and in the countercurrent heat exchangers were measured and numerically modeled during the development experiments by inserting thermocouples at the inlet and outlet of the shell and tube side of each of the heat exchangers and inserting thermocouples along the length of the PFR near the inlet. The mixing of the two reagents at the inlet to the thermal tube reactor and the S_NAr (Step 2) reactor were confirmed to be sufficient for the chemistry by comparing reaction rates and impurity profiles for well mixed batch reactors. Additionally, the Step 2 coupling reaction was afforded extra residence time (3 hours) over what was required for high conversion (2 hours was sufficient) to ensure that heat up time was not a factor. Numerical modeling showed that heatup time from room temperature to 70 °C was 125 seconds in the step 2 PFR. A different type of PFR such as a micro reactor could have achieved a much faster heatup rate, but it was not needed. It was more adventageous to keep the reactor inexpensive and disposable because of the high potency of the compound. The PFA tube reactor only cost $1371 and used as a consumable item. Ultimately, all key equipment parameters were known and confirmed at manufacturing scale before the start of the cGMP manufacturing run.

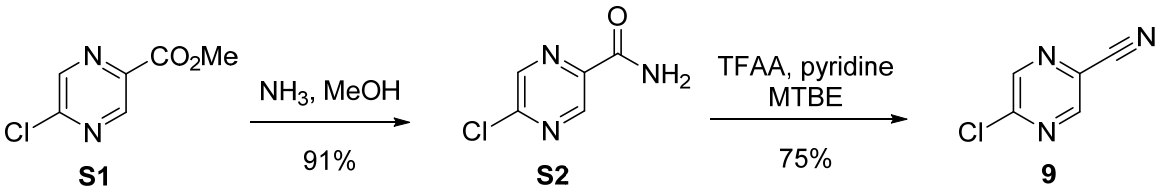
Discussion of Capital and Operational Expenditures

The total capital cost for this production campaign was approximately €1,000,000 and was deliberately kept low because this was a proof of concept manufacturing campaign. Roughly one half the capital was used for the mobile skids, which included the reactors, constant temperature baths, oven, pumps, liquid-liquid extractors, evaporator, continuous crystallizers, dual filters and instrumentation. The other half was for the infrastructure to automate the portable skids by fieldbus connections and the continuous plant automation. The same engineering standards were used for the portable continuous skids that are used for the rest of the manufacturing plant including the 2000 gallon plant modules. A sufficient number of laboratory fume hoods adjacent to the 50 gallon batch plant module already existed to run the continuous campaign in three individual segments. However, for future capability to run the entire continuous train with all the steps simultaneously, additional capital would need to be spent on a facility designed with a larger number of fume hoods as well as supporting vessels for feeding, collecting, and surge. An additional evaporator skid would need to be purchased because the same evaporator was used on two different steps.

The level of operating staff for this effort was comparable to batch production mode. Normal batch plant operating personnel were cross-trained and ran this continuous process. Similar to batch production mode, two operators covered the dayshift and two operators covered the night shift for the continuous production. Additionally, a technical operations person (engineer) covered both shifts, because the continuous processing and all of the continuous reactors and unit operations were new to the manufacturing plant. In the future, around the clock technical operations coverage is not expected to be necessary.

The capital cost for the new SVC facility is €35,000,000 (*37*). This is about the same as the capital cost for a new 250 gallon batch facility with three main process vessels. We believe that the productivity of the SVC facility will be higher than the productivity of a 250 gallon batch facility because the continuous process runs three or four steps at a time, while the batch facility only runs one step at a time. The SVC facility is expected to use three or four operators at a time on day shift and night shift. In comparison, a batch facility uses two operators at a time on both shifts. However, the overall production campaign time is shorter for the continuous facility because it can conduct three to four synthetic route steps at once.

Method for Preparation of chloride **9:**



5-chloropyrazine-2-carboxamide (**S2**) (*38*):

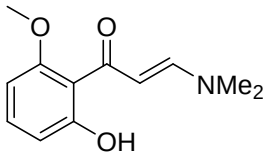
To a 1000 L reactor was charged methanol (170 kg) and methyl 5-chloropyrazine-2-carboxylate (**S1**) (59.0 kg, 341.9 mol) with stirring. Additional methanol (92 kg) was added, and the slurry was cooled to 0 °C. A solution of 30 kg of ammonia in 170 kg of methanol was then added over 2 h to the slurry. The reaction slurry was stirred at 0 °C for 6 h. The slurry was then filtered and the solids were washed with methanol. The solids were dried under vacuum at 50 °C to afford 5-chloropyrazine-2-carboxamide (**S2**) as a tan solid (48.8 kg, 309.7 mol, 91%).

5-chloropyrazine-2-carbonitrile (**9**) (*39*):

Caution: It was observed during development that direct contact with 5-chloropyrazine-2-carbonitrile (**9**) caused skin irritation and all possible precautions should be taken to avoid contact with the dust or vapor, as **9** is a low melting solid and has an appreciable vapor pressure at ambient conditions. This material should be handled in a properly ventilated enclosure and impenetrable PPE should be used by operations personnel.

To a 2000 L reactor was charged MTBE (220 kg) along with amide **S2** (48.8 kg, 309.7 mol) and pyridine (74.2 kg, 938 mol, 3 equiv). The mixture was cooled to 5 °C with stirring. A mixture of trifluoroacetic anhydride (TFAA, 99.4 kg, 473.3 mol) in MTBE (77.2 kg) was then added over 140 min while the reaction temperature was maintained below 15 °C. After the TFAA addition was complete, the reaction mixture was stirred an additional 5 h at 5 °C, after which time HPLC analysis showed the reaction to be complete. Water (96 kg) was added over 1 h while the temperature was maintained below 5 °C. The quenched mixture was warmed to 20 °C and stirred for 0.5 h. The layers were allowed to settle and the lower aqueous layer was removed. The aqueous layer was back extracted with MTBE (181 kg) and the organic layers were combined. To the combined organic layers was charged water (94 kg) and the mixture was stirred at 20 °C for 0.5 h. The layers were allowed to settle and the lower aqueous layer was removed. The wash procedure was repeated one additional time. After layer separation, saturated aqueous NaCl was added (94 kg) and the mixture stirred at 20 °C. The brine layer was removed, and a second, identical brine wash was conducted. After removal of the final brine layer, the organic layer was transferred to a 1000 L reactor and concentrated to ~50 L using vacuum distillation while the temperature was maintained below 20 °C. After concentration, *n*-heptane (102 kg) was added slowly over 12 h at 20 °C. The product crystallized, and a slurry formed. After the heptane addition, the slurry was cooled to 0 °C over 2 h and stirred an additional 5 h. The slurry was then cooled to -10 °C over 2 h

and then held with stirring for 5 h. The solids were then isolated by filtration and the product cake was washed with heptane (40 kg) and dried at ambient temperature and light vacuum to afford nitrile **9** as an off-white solid (32.4 kg, 232.2 mol, 75%).



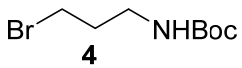
3

(*E*)-3-(dimethylamino)-1-(2-hydroxy-6-methoxyphenyl)prop-2-en-1-one (**3)**

A 500 mL flask was equipped with overhead stirring, a thermocouple, heating mantle, and nitrogen protection. DMF (100 mL) was added, followed by acetophenone **2** (50.0 g, 0.301 mol) and DMF-DMA (45.0 g, 95%, 0.359 mol, 1.19 equiv). With stirring, the mixture was heated to 90 °C for 12 h. The solution was cooled to ambient temperature and used directly in the next step as the solution in DMF.

Bright yellow crystals; DSC = 83.9 °C; HPLC T_R (Method A, min) = 2.03;
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (brs, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 6.44 (d, *J* = 19.6 Hz, 1H), 6.42 (d, *J* = 19.2 Hz, 1H), 6.08 (brs, 1H), 3.81 (s, 3H), 3.16 (brs, 3H), 2.89 (brs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 188.9, 163.2, 159.4, 155.2, 132.5, 111.7, 109.9, 101.5, 96.6, 55.6, 44.7, 37.1; HRMS calc'd for $C_{12}H_{16}NO_3^+$ ($M+H^+$) 222.1125, found 222.1121, δ = 1.8 ppm; IR (ATR, cm^{-1}) 1615 (vs), 1581 (m), 1548 (m), 1467 (s), 1454 (s), 1433 (s), 1407 (s).

See Fig. S5 and S6 for the NMR spectra.

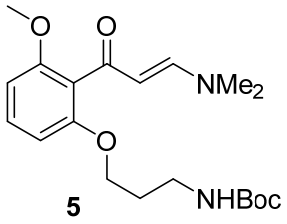


4

tert-butyl (3-bromopropyl)carbamate (**4**)

To a 250 mL flask with magnetic stirring was charged water (50 mL) and solid NaOH (10.08 g, 0.252 mol, 1.1 equiv). The mixture was stirred at ambient temperature until the solids dissolved. In a 1 L flask with overhead stirring and nitrogen protection, 2-MeTHF (150 mL) was charged, followed by Boc_2O (50.0 g, 0.229 mol, 1.0 equiv), and the solution was cooled with stirring to 10–15 °C using an ice/water bath. Next, 3-bromopropylamine hydrobromide (55.17 g, 0.252 mol, 1.1 equiv) was added, followed by water (50 mL). Stirring was continued while the NaOH solution was slowly added over 1 h to the liquid/liquid biphasic mixture of Boc_2O and the amine and the temperature was allowed to come to ambient and stirred overnight. Agitation was stopped to allow the layers to settle, and the aqueous layer was removed. 120 g of 2.5% citric acid in brine was then added and the mixture was stirred for 30 min. The aqueous layer was removed and 7% (w/w) aq. $NaHCO_3$ was added until the pH reached 7–8. After stirring 30 min, the agitation was stopped and layer separation took place. The aqueous layer was removed and saturated aq. NaCl (75 mL) was added with stirring for 30 min. The brine layer was removed and the organic layer was concentrated to below 150 mL volume using vacuum at <35 °C. DMF (50 mL) was then charged to the reactor, and the solution was sparged with N_2 for >8 h to inert and

remove some of the residual 2-MeTHF. NMR assay returned 51.7 g of product (0.217 mol, 95% yield) which was held with refrigeration as the solution until use in the next step.



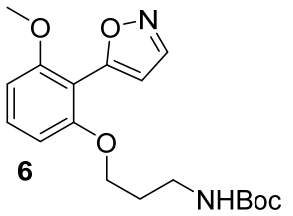
5

tert-butyl (*E*)-(3-(2-(3-(dimethylamino)acryloyl)-3-methoxyphenoxy)propyl)carbamate (**5**)

To the crude solution of **3** was added anhydrous K_3PO_4 (82.5 g, 0.389 mol, 1.29 equiv) at ambient temperature, followed by bromide **4** (82.5 g, 0.346 mol, 1.15 equiv), and the mixture was stirred overnight at ambient temperature. The solids were then filtered off and to the filtrate was set aside. To the solids was added MTBE (350 mL), and the slurry was stirred for 30 min. The solids were filtered off and the filtrate was added to the initial filtrate. This process was repeated a second time to wash the solids using an additional 250 mL of MTBE, and the final waste cake was washed again with 100 mL MTBE. The combined filtrates were charged to a 2 L reactor with bottom outlet along with water (100 mL) and 300 mL of 25% aq. NaCl, and stirred at ambient temperature for 15 min. The stirring was stopped to allow for layer separation, and the aqueous layer was removed. The aqueous layer was back extracted with 250 mL of MTBE, and this layer was combined with the main organic fraction. The combined organic layers were then heated to 35 °C and were washed with a mixture of 350 mL of 25% aq. NaCl and water (40 mL). The aqueous layer was removed and the organic layer was concentrated under vacuum to <750 mL. Water (250 mL) was added dropwise at 35 °C, which caused a slurry to form (solids + 2 liquid layers), and the mixture was stirred for 1 h. The mixture was the cooled to 20 °C and stirred overnight. Filtration of the slurry afforded a solid, which was washed with MTBE (150 mL) and dried in vacuum to afford ketone **5** as a light brown solid that contained 27% water by mass (134.0 g, assay = 65.2%, yield = 87.4 g, 0.231 mol, 76.7% over 2 steps).

Tan glassy solid; DSC = 61.8 °C; HPLC T_R (Method B, min) = 5.52;
^{1}H NMR (500 MHz, DMSO-d_6, 85 °C acquisition temperature) δ 7.19 (t, *J* = 8.3 Hz, 1H), 7.01 (d, J = 12.9 Hz, 1H), 6.64 (d, *J* = 8.3 Hz, 1H), 6.63 (d, *J* = 8.3 Hz, 1H), 6.37 (brs, 1H), 5.07 (d, *J* = 12.9 Hz, 1H), 3.94 (t, *J* = 6.5 Hz, 2H), 3.68 (d, *J* = 1.0 Hz, 3H), 3.03 (q, *J* = 6.5 Hz, 2H), 2.85 (s, 6H), 1.74 (pent, *J* = 6.5 Hz, 2H), 1.38 (d, J = 1.0 Hz, 9H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C acquisition temperature) δ 187.9, 156.5, 155.5, 155.1, 153.5, 128.5, 121.7, 105.8, 104.7, 99.3, 77.0, 66.2, 55.5, 39.6 (broad), 36.9, 28.9, 27.8 (3C); HRMS calc'd for $C_{20}H_{31}N_2O_5^+$ ($M+H^+$) 379.2228, found 379.2222, δ = 1.6 ppm; IR (ATR, cm^{-1}) 3335 (br), 2933 (w), 1704 (m), 1629 (m), 1590 (vs), 1464 (m), 1436 (m), 1400 (w).

See Fig. S7 and S8 for the NMR spectra.



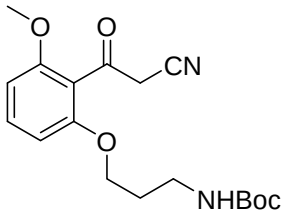
6

tert-butyl (3-(2-(isoxazol-5-yl)-3-methoxyphenoxy)propyl)carbamate

A 1 L reactor was equipped with overhead stirring and nitrogen protection. Ethanol (250 mL) was charged, followed by the crude ketone **5** (134.0 g gross, assay = 65.2%, 87.4 g, 0.231 mol) and additional ethanol was used to wash the ketone into the reactor (175 mL). The mixture was stirred at ambient temperature until a clear solution formed. Hydroxylamine hydrochloride (18.0 g, 0.259 mol, 1.12 equiv) was then added, and the solution was heated to 40 °C for 6 h. HPLC showed consumption of the starting material, and the solution was concentrated under vacuum to <150 mL. MTBE (250 mL) was added, and the solution was distilled under vacuum to <150 mL. A second portion of MTBE (250 mL) was added, and the mixture was again concentrated to <150 mL under vacuum. MTBE (500 mL) was then added along with water (250 mL) and 50 mL of 25% aq. NaCl solution. The biphasic mixture was stirred at ambient temperature and the aqueous phase was removed. The brine wash was repeated two additional times. The MTBE layer was then concentrated to <150 mL under vacuum and ethanol (250 mL) was added. The solution was then concentrated to <150 mL under vacuum and the crude solution of isoxazole **6** was used directly in the next step.

Colorless crystals; DSC = 63.0 °C; HPLC T_R (Method B, min) = 7.29;
^{1}H NMR (400 MHz, CD_3CN) δ 8.37 (t, *J* = 2.0 Hz, 1H), 7.41 (t, *J* = 8.8 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.52 (brs, 1H), 5.31 (brs, 1H), 4.02 (t, *J* = 6.0 Hz, 2H), 3.79 (s, 3H), 3.11 (q, *J* = 6.8 Hz, 2H), 1.81 (q, *J* = 6.4 Hz, 2H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, CD_3CN) δ 165.0, 159.6, 158.8, 156.8, 151.1, 133.1, 106.7, 106.1, 105.7, 105.2, 79.0, 67.4, 56.6, 38.1, 30.2, 28.5 (3C); HRMS calc'd for $C_{18}H_{25}N_2O_5^+$ ($M+H^+$) 349.1758, found 349.1749, δ = 2.6 ppm; IR (ATR, cm^{-1}) 3359 (s), 2979 (w), 2945 (w), 2922 (w), 2877 (w), 1681 (vs), 1602 (m), 1591 (m), 1532 (s), 1465 (m).

See Fig. S9 and S10 for the NMR spectra.



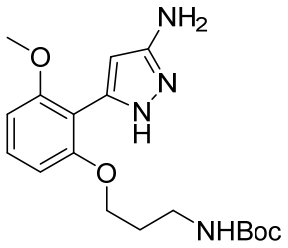
7

tert-butyl (3-(2-(2-cyanoacetyl)-3-methoxyphenoxy)propyl)carbamate (**7**)

To the concentrated solution of **6** was added ethanol (100 mL) and water (100 mL). KOH pellets were then slowly added to the solution (18 g, 85%, 0.273 mol, 1.18 equiv), and were washed in with 50 mL of additional ethanol. The pellets dissolved, and the solution was heated to 50 °C under nitrogen protection. After 6 h, HPLC analysis showed the reaction to be complete. The solution was concentrated by distillation under vacuum to <150 mL and water (100 mL) was added. Acetic acid was then added in a dropwise manner until the solution pH was 10–12. Next, ethyl acetate (500 mL) was added, and more acetic acid was added in order to adjust the solution pH to 5–7. 50 mL of 25% aq. NaCl solution was then added at 30 °C, and the mixture was stirred. The aqueous layer was then removed. 50 mL of 25% aq. NaCl solution was then added, along with water (250 mL) and the 30 °C mixture was stirred. The aqueous layer was removed and the brine/water wash was repeated once more. Next, the organic layer was concentrated to <300 mL under vacuum and heated to 55 °C. Heptane (400 mL) was added dropwise and a slurry formed at 55 °C. The slurry was slowly cooled to ambient temperature and stirred overnight. The solids were isolated by filtration and washed with 2:1 EtOAc/heptane (100 mL). The solids were then dried under vacuum at 50 °C to afford nitrile **7** (71.0 g, assay = 98.0%, 0.200 mol, 86.6% for 2 steps) as a pale yellow solid.

Pale yellow powder; DSC = 104.4 °C; HPLC T_R (Method B, min) = 6.92;
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, *J* = 8.4 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 6.56 (d, *J* = 8.8 Hz, 1H), 4.90 (brs, 1H), 4.04 (t, *J* = 6.0 Hz, 1H), 3.87 (s, 2H), 3.83 (s, 3H), 3.26 (t, *J* = 6.4 Hz, 2H), 1.94 (q, *J* = 6.0 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 157.8, 157.0, 156.2, 133.0, 116.7, 114.5, 105.2, 104.2, 79.3, 66.8, 56.1, 37.9, 33.9, 29.5, 28.5 (3C); HRMS calc'd for $C_{18}H_{25}N_2O_5^+$ ($M+H^+$) 349.1758, found 349.1751, δ = 2.0 ppm; IR (ATR, cm^{-1}) 3373 (m), 2984 (w), 2946 (w), 1713 (m), 1676 (vs), 1595 (m), 1591 (m), 1517 (m), 1466 (m).

See Fig. S11 and S12 for the NMR spectra.



8

tert-butyl (3-(2-(3-amino-1H-pyrazol-5-yl)-3-methoxyphenoxy)propyl)carbamate (**8**)

Reaction

Nitrile **7** (28.3 kg, 81.2 mol) was dissolved in THF (101.6 kg) with agitation under nitrogen to form Feed A solution. Feed B solution was prepared by combining methanol (47.3 kg), acetic acid (5.1 kg, 85.4 mol), hydrazine (35% by mass in water, 11.7 kg, 128.0 mol) and water (30 kg) with agitation under nitrogen protection. The two feeds were pumped using two Lewa® MAH micro diaphragm pumps and combined prior to entering a 300 mL mixing chamber. The mixed solution flowed through a counter current heat exchanger (1/8" o.d. 0.069" i.d. tube and 1/4" o.d. 0.18" i.d. shell) and into the 1.4 L PFR. The heat exchanger simultaneously heated the feed with the reactor effluent, and cooled the effluent with the reagent feed. This made the high temperature PFR process highly energy efficient. Feed A was fed at 12.7 mL/min and the hydrazine solution was pumped at 8.8 mL/min. The PFR was 300 feet of 0.25" o.d. 0.18" i.d. stainless steel 316L tubing coiled into an elliptical shape and was contained in an electrically heated GC oven heated to 130 °C. Nominal residence time (V/q) = 70 min. Actual mean residence time in the reactor was less because of thermal expansion of the solvents. The PFR was maintained under 300 psig of backpressure provided by an Equilibar dome loaded diaphragm style back pressure regulator. The reactor effluent passed through the heat exchanger, was depressurized, and automatically sampled by for HPLC analysis. The product stream continuously flowed into the extraction phase.

Extraction

The ambient temperature extraction set up consisted of 3 identical glass agitated round bottom vessels (5 L) and 3 identical static settling vessels. The next figure shows a schematic diagram of one of the three mixer-settler stages.

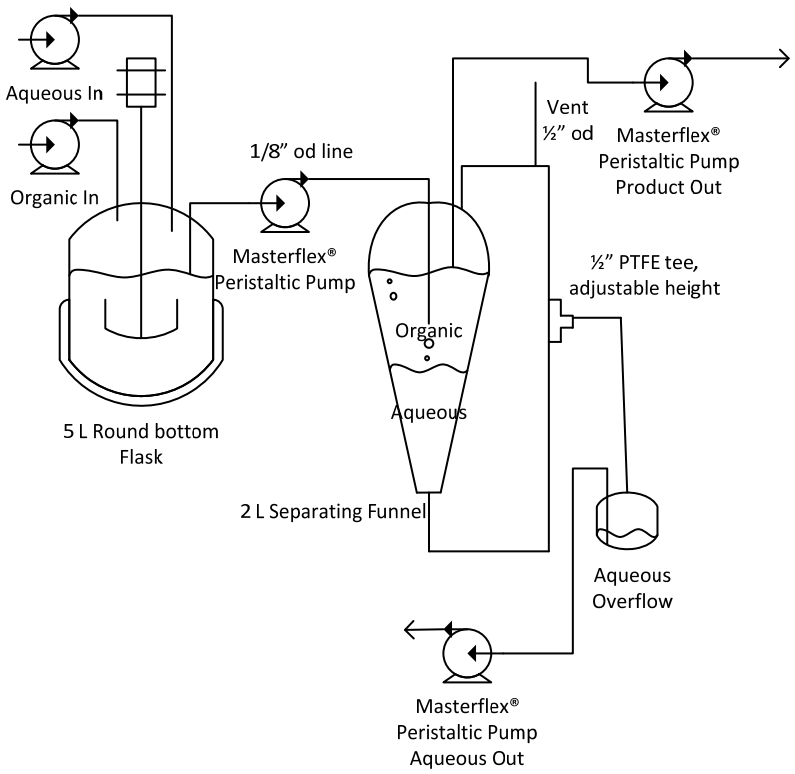


Figure S1. Single stage of continuous countercurrent extraction operation.

Fluid from the agitated biphasic vessels was pumped into the settling vessels at the same rate as the entering fluid streams using Masterflex peristaltic 100 RPM pumps with STAPure Size 16 tubing. Liquid level was maintained in the vessels by positioning the outlet dip tube at desired liquid level and setting out outlet pump flow rate higher than the combined flows into the vessel. There is no cavitation problems with these pumps therefore the pumps can operate with gas pockets and maintain a liquid level in the vessels. Each of the separated layers in the settling vessels was removed with a similar technique. The interface was maintained via an overflow leg out of the bottom of the settler which using gravity was set at a height to produce a desirable interface dependent on the solution densities. In other words, the aqueous overflow Tee was positioned at a height intermediate to the organic layer surface and the aqueous/organic interface. The organic layer was pumped out of the settlers at a rate so as to maintain a constant level in each vessel while the aqueous overflow vessel was maintained at minimum liquid level by pumping out faster than the aqueous flowed in. The reaction stream entered Mixer 1 at 21.5 mL/min along with toluene (10.3 mL/min) and aqueous sodium carbonate (9.2 wt%, 8.2 mL/min). The overflow from Mixer 1 entered Settler 1. The aqueous layer from Settler 1 was sent to waste and the organic layer was continuously pumped to Mixer 2. Mixer 2 also received the aqueous layer from Settler 3 in order to back extract the product. The mixed liquid from Mixer 2 continuously pumped to Settler 2. The aqueous layer from Settler 2 was sent to waste, while the organic layer was continuously pumped to Mixer 3, which also received purified water (2.6 mL/min). From Mixer 3, the

mixed liquid was continuously pumped to Settler 3, the aqueous layer of which was sent to Mixer 2 and the organic layer was sent to the distillation operation.
The table below shows the desired volumes in the each mixer and settler in the system to give 45 min residence time in each stage, based upon 4 kg per day of **8**. The interface height in the settlers is set by manually raising or lowering a lab jack, which positions the overflow tee to set the overflow height of the heavy phase. Lowering this tee lowers the interface height, raising the tee increases the interface height.

Table S1. Operating volumes for continuous extraction system designed for a 45 min residence time in each stage with throughput of 4 kg/day of **8**.

<table>
<tr><th></th><th>Mixer 1</th><th>Settler 1</th><th>Mixer 2</th><th>Settler 2</th><th>Mixer 3</th><th>Settler 3</th></tr>
<tr><td>Organic Volume (mL)</td><td rowspan="2">1900</td><td>1000</td><td rowspan="2">1100</td><td>1000</td><td rowspan="2">1100</td><td>1000</td></tr>
<tr><td>Aqueous Volume (mL)</td><td>1000</td><td>150</td><td>150</td></tr>
<tr><td>Total Volume (mL)</td><td>1900</td><td>2000</td><td>1100</td><td>1150</td><td>1100</td><td>1150</td></tr>
</table>

Concentration

A 20 L Buchi rotary evaporator was equipped with a custom automated system for controlling intermittent flows in and out. The system was capable of accurately charging product solution and fresh solvent, and it had a PFA diptube in the concentration flask capable of discharging the finished product solution for use in the next step. The evaporator bath was maintained at 60 °C through the concentration cycle, and the evaporator flask was rotated at 88 RPM. The automated, repeating concentration cycle consisted of charging approximately 4.8 kg of product solution from the extraction to the Buchi flask. This was evaporated under partial vacuum (130 → 80 → 40 torr) to remove THF, water and toluene. This yielded an oil. DMSO (0.8 kg) was then added, and the solution was further concentrated under full vacuum (15–25 torr) to remove any residual toluene. At the conclusion of this step, additinal DMSO (0.8 kg) was charged to the evaporator flask and the product was emptied via the diptube in the flask into the product collection vessel. Each combined day's worth of **8** product solution was transferred to a storage vessel for assay and release as the solution. The seven steps in the automated evaporator sequence are shown in the next table, along with the time duration for each step.

Table S2. Automated steps for each turnover of the rotary evaporator conditions for concentration of **8**.

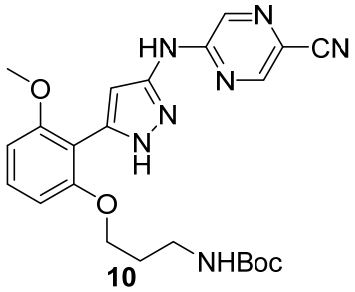
Step	Time (sec)	Absolute Pressure (torr)	Comments
1	1200	130	First concentration point, avoids bumping.
2	1200	80	Second concentration point, pulls off residual THF.
3	900	40	Third concentration point, pulls to an oil
4	120	760	Empty distillate
5	120	400	Charge 0.5 vol of DMSO
6	1800	25	"Full Vacuum"
7	120	400	Charge 2 volumes of DMSO

A more detailed example of how the automated rotary evaporator system operated is given later in the supplementary materials in the section on formic acid stripping.

In total, 112.8 kg of product solution in DMSO was collected, with assay of 23.35% for a yield of 26.4 kg of pyrazole **8** (72.7 mol, 89.6% yield).

Tan powder; DSC = 107.8 °C; HPLC T_R (Method B, min) = 5.59;
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (brs, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 6.92 (brt, *J* = 5.2 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 5.82 (brs, 1H), 4.40 (brs, 2H), 3.98 (t, *J* = 6.0 Hz, 2H), 3.77 (s, 3H), 3.07 (brq, *J* = 6.0 Hz, 2H), 1.82 (brq, *J* = 6.4 Hz, 2H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.4, 156.6, 155.7, 154.4, 134.4, 128.9, 108.0, 105.2, 104.2, 94.2, 77.5, 65.6, 55.6, 36.7, 29.1, 28.2 (3C); HRMS calc'd for $C_{18}H_{27}N_4O_4^+$ ($M+H^+$) 363.2027, found 363.2023, δ = 1.1 ppm; IR (ATR, cm^{-1}) 3452 (m), 3379 (w), 3290 (br), 2975 (w), 1687 (vs), 1585 (w), 1510 (m), 1486 (m).

See Fig. S13 and S14 for the NMR spectra.



10

Reaction

Feed solution A was prepared by mixing 110.9 kg DMSO solution of **8** (assay from the previous step was 23.35%, 25.9 kg, 71.5 mol) with *N*-ethylmorpholine (10.1 kg, 87.7 mol) and additional DMSO (0.5 kg). This produced 122.4 kg of DMSO solution with assay of 20.44% for pyrazole **8** (25.0 kg, 68.5 mol). Feed solution B was prepared by dissolving pyrazine **9** (12.3 kg, 88.1 mol) in DMSO (60.9 kg). Feed solution A was pumped into the 2.8 L PFR at 10.2 mL/min and Feed solution B was pumped at 5.4 mL/min. The PFR was immersed in a heated water bath controlled at 80 °C with a residence time of 180 min. It was constructed from PFA tubing 91.4 m long and 6.4 mm ID, coiled so that it would fit inside a constant temperature bath.

Crystallization, Filtration, and Dissolve-Off

The first mixed suspension mixed product removal (MSMPR) crystallizer was prepared by charging MeOH (1.05 kg), DMSO (0.45 kg) and seed crystals of **10** (94 g). The reaction product stream was automatically sampled for on-line HPLC and continuously flowed directly into MSMPR1. Methanol antisolvent was continuously pumped into MSMPR1 at a rate of 42 mL/min. Both MSMPRs were controlled at 20 °C. The slurry volume in each crystallizer was 3.75 L. The mean residence time in MSMPR1 was 1 hour. Slurry aliquots were transferred every 3 minutes from MSMPR1 to MSMPR2 via an automated transfer zone. The transfer zone consisted of 4 sequenced automated block valves, and it pulled slurry from MSMPR1 by vacuum and then pushed the slurry to MSMPR2 by nitrogen pressure. Mean residence time in MSMPR2 was also 1 hour. Aliquots of slurry were transferred from MSMPR2 onto one of the automated filters every 6 min. The parallel filters were fully automated so that while one filtered the other was deliquored with nitrogen pressure, rinsed with MeOH (0.23 kg), washed with MTBE (0.21 kg), blown dry with nitrogen, and then formic acid was added to re-dissolve the product. The filters operated in alternating fashion to collect 9 aliquots of slurry per cycle. When formic acid (99%, 1.14 kg) was added, the agitator was turned on. After several minutes, the cake had fully dissolved, and the system pushed the product solution to the surge vessel maintained at 0–5 °C. Additional formic acid (0.23 kg) was charged to the filter to rinse out the product completely, and this was also collected in the surge vessel. The filter was then cleaned with MeOH (0.26 kg), which was pushed to waste, and the filter was dried with nitrogen pressure and considered ready for use.
A schematic diagram of the dual filter automated unit operation is shown in the next figure.

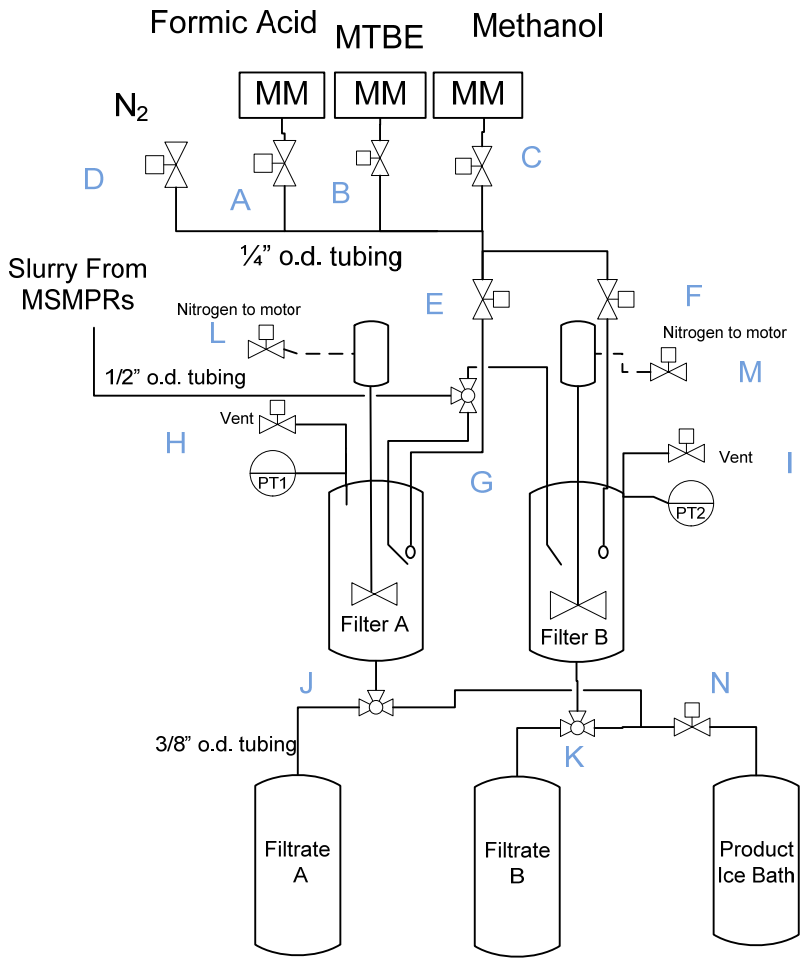


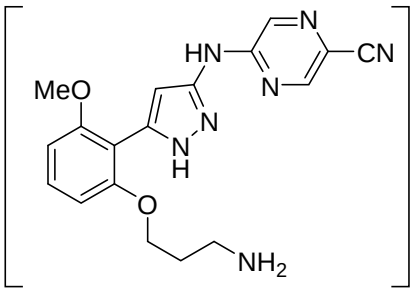
Figure S2. Schematic for dual automated filtration system.

Referring to the dual filter figure and the valve labels, the following describes the detailed automated procedure for a half cycle. This is the half cycle where the slurry is filtered and collected on Filter A, while the wash and dissolve off is done on Filter B:
The DCS automation system did the following:

- *Open Valve G to Filter A (Left side)*
- *Open valve K to Filtrate Receiver*
- *Open valve I to vent filter B*
- *When pressure on PT2 reaches 0, close valve I.*
- *Charge 350 mL methanol via valve C, F and flow meter (MM) 1.*
- *Close valve C.*
- *Open valve D to apply Nitrogen pressure to blow through cake and push wash to Filtrate B*
- *After 5 minutes, close valve D*
- *When pressure reaches pressure setpoint 2, open valve I to vent filter.*
- *Close valve I when pressure reaches 0.*

- *Open valve B to charge 350 mL MTBE to filter B via flow meter (MM) 2.*
- *Close valve B.*
- *Open valve D to apply Nitrogen pressure to cake and push wash to Filtrate B*
- *After 20 minutes (user input), close valve D*
- *When pressure reaches pressure setpoint 2 (8 psig,) open valve I to vent filter.*
- *Switch valve K to the product side (Right)*
- *Charge 80% of the formic acid (1191 mL) to filter B via valve A and flow meter (MM) 3.*
- *Close valve A*
- *Turn on agitation by opening valve M.*
- *After user input (10 minutes) close valve I. Open valves N and D to push the solution into the product receiver can for user specified time (3 min).*
- *Close valves D, M, and N.*
- *Open valve I to vent filter*
- *When PT reads <0.5 psig close valve I.*
- *Open valve A to charge the remaining formic acid (298 mL).*
- *Close valve A*
- *Wait user specified time (1 min)*
- *Open valves D and N to push remaining material into product receiver.*
- *Close valves D and N.*
- *Open valve I to vent the filter.*
- *Switch valve K to the filtrate receiver.*
- *Open valve C to charge 350 mL of MeOH to filter B via flow meter (MM) 1.*
- *Close valves C, I.*
- *Open valve D to blow nitrogen through the filter for 3 minutes.*
- *Close valve D and open I to vent the filter.*
- *Close valves F and I.*
- *Now dissolve off is complete. Wait until total time is 1 hour and then switch filters and repeat the mirror of the above sequence. Continue in alternating fashion.*

tert-butyl (3-(2-(3-((5-cyanopyrazin-2-yl)amino)-1H-pyrazol-5-yl)-3-methoxyphenoxy)propyl)carbamate (**10**)
tan powder; DSC = 222.5 °C; HPLC T_R (Method B, min) = 7.18;
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H), 10.69 (s, 1H), 8.61 (s, 1H), 8.53 (brs, 1H), 7.30 (t, *J* = 8.4 Hz, 1H), 6.95 (brs, 1H), 6.88 (brt, *J* = 4.8 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 4.02 (t, *J* = 6.0 Hz, 2H), 3.82 (s, 3H), 3.11 (brq, *J* = 6.4 Hz, 2H), 1.86 (brq, *J* = 6.0 Hz, 2H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.4, 156.7, 155.6, 151.9, 147.8, 146.3, 135.2, 134.7, 129.7, 117.7, 115.9, 107.0, 105.2, 104.1, 98.4, 77.5, 65.9, 55.7, 36.8, 29.0, 28.1 (3C); HRMS calc'd for $C_{23}H_{28}N_7O_4^+$ ($M+H^+$) = 466.2197, found 466.2188, δ = 1.9 ppm; IR (ATR, cm^{-1}) 3439 (m), 3356 (m), 2978 (w), 2951 (w), 2877 (w), 1681 (vs), 1633 (m), 1519 (m).
See Fig. S15 and S16 for the NMR spectra.



1
Solution in Formic Acid

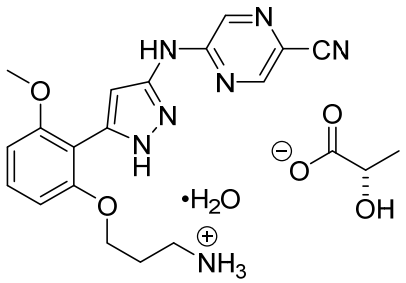
Deprotection Reaction

From the surge vessel, the solution of **1** in formic acid was pumped with a peristaltic pump into the 5.8 L gas-liquid vertical coiled PFR at 24.3 mL/min along with nitrogen gas (30 psig). The PFR was contained in a water bath maintained at 25–30 °C. A peristaltic pump operating at a flow rate of 97.2 mL/min served to regulate the flow of gas and liquid out of the reactor, and reduced surging in the reactor. The mean residence time in the PFR was 240 min. After the reactor, the solution continuously blended with water from a peristaltic pump (6.8 mL/min) and collected in a drum at room temperature. After filling, each drum was transported to refrigerated storage. The drums were changed about every 12 hours.

Over the course of the campaign, a total of 15 product drums were collected, 13 of which were combined and 2 remained segregated. All the material was used for downstream workup and API Isolation Phase.

Table S3. Yield data for API deprotection.

Batch	kgs	Assay (%)	kgs **1**	Mols **1**	Yield	
1	337	5.68	19.15	52.4	76.5%	
2	27.6	5.51	1.52	4.2	6.1%	
3	27.4	5.62	1.54	4.2	6.2%	
			22.21	60.8	88.7%	Totals



12

(2*S*)-2-hydroxypropionic acid-5-({3-[2-(3-aminopropoxy)-6-methoxyphenyl]-1*H*-pyrazol-5-yl}amino) pyrazine-2-carbonitrile monohydrate (**12**)
pale yellow powder; DSC = 161.3 and 245.0 °C; HPLC T_R (Method B, min) = 4.55;
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.61 (brs, 1H), 7.31 (t, *J* = 8.4 Hz, 1H), 6.85 (brs, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 4.11 (t, *J* = 6.0 Hz, 2H), 3.81 (s, 3H), 3.69 (q, *J* = 6.4 Hz, 1H), 2.96 (t, *J* = 7.2 Hz, 2H), 2.02 (q, *J* = 6.8 Hz, 2H), 1.12 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.5, 157.5, 156.5, 151.9, 148.0, 146.3, 135.2, 134.8, 129.8, 117.7, 116.0, 107.1, 105.2, 104.3, 98.2, 66.9, 65.3, 55.8, 36.1, 27.3, 21.3; HRMS calc'd for $C_{18}H_{20}N_7O_2^+$ ($M+H^+$) 366.1673, found 366.1666, δ = 1.9 ppm; IR (ATR, cm^{-1}) 3407 (vs), 3239 (w), 3081 (br), 2970 (m), 1611 (vs), 1563 (m), 1542 (m), 1496 (s), 1465 (m).

See Fig. S17 and S18 for the NMR spectra.

Concentration and Crystallization
The text below describes one of the 5 batches that was manufactured and is considered representative.

Thirteen volume turnovers of the automated evaporator were collected to make the feed material for one large crystallization batch. Each automated cycle of the intermittent evaporator started by charging formic acid solution of **1** (5.68% w/w, ~6.4 kg, ~0.36 kg, ~0.99 mol of **1**) via a polish filter (0.45 µm) into the rotary evaporator distillation flask. A stream of 30% aqueous lactic acid (~2.4 kg, 720 g of lactic acid, ~7.99 mol) was similarly polish filtered into the evaporator before the automated evaporation sequence started. The solution was then concentrated under vacuum with water bath temperature of 60 °C. Evaporation progress was monitored by total process time and distillate temperature. The concentration proceeded by slowly reducing the pressure in the system to prevent bumping until full vacuum (15–25 torr) was achieved. The contents were held under full vacuum at 60 °C for 100 min to remove formic acid. Purified water (1.5 kg) was added and the contents held under full vacuum for 80 min. When the evaporation cycle was complete, a mixture of filtered THF/water (1:3, v/v, 0.78 kg) was added to thin the product solution and the solution was transferred to a portable holding tank for storage at 5 °C. The rotary evaporator was rinsed with a second portion of THF/water (1:3, v/v, 0.18 kg) and this was also added to the holding tank. The holding tank was emptied to the 200 L crystallizer twice to comprise a large crystallization batch (containing 13 total evaporation cycles). For a single batch isolation of **11**, a total of 84.1 kg of **1** in formic acid was processed and 4.88 kg (13.35 mol) of **1** was concentrated in this manner.

Table S4. Automated steps for each turnover of the rotary evaporator conditions for concentration of **1**. This cycle time totals 3.7 hours of operations, but the feed charges, distillate draining, product draining, and automation programming were delayed so that operationally the sequence was 5 hours.

	Step	Pressure	Duration	Typical Size	Description
1	Charge formic acid solution of **1**	-8.5 psig (300 torr)	5 minutes	6.5 kg	Fill Rotovap with feed solution in formic acid through flow meter into Rotovap
2	Charge LA	-8.5 psig (300 torr)	2 minutes	2.1 kg	Fill Rotovap with lactic acid charge (2.1 kg usually)
3	Evaporation Step 1	-13.5 psig (50 torr)	1 minute	N/A	Any solvents that boil at lower temperature will be stripped (MTBE, MeOH)
4	Evaporation Step 2	-13.8 psig (45 torr)	2 minutes	N/A	Begin evaporation, stop to reduce probability of bumping to distillate tank
5	Evaporation Step 3	-14.0 psig (40 torr)	3 minutes	N/A	Gentle step down to avoid bumping prior to full vacuum
6	Full Vacuum Evaporation	-14.41 psig (~15 torr)	100 minutes	N/A	Complete evaporation to remove formic acid
7	Charge Water	-12.8 psig (100 torr)	2 minutes	1.3 kg	Charge 4 volumes of water to flask
8	Empty Distillate	0 psig (760 torr)	5 minutes	7.8 kg	Empty distillate via automated cart
9	Evaporation Ramp 2	-14.0 psig (50 torr)	7 minutes	N/A	Ramp to get down to full vacuum.
10	Full Vacuum Evaporation 2	-14.41 psig (~15 torr)	80 minutes	N/A	Evaporation to remove the water and formic acid
11	Charge THF/water	-4 psig (550 torr)	3 minutes	550 g	Charge 80% of the THF/water
12	Dissolution Time	0 psig (760 torr)	1 minute	N/A	Allow for THF/water to mix with oil.
13	Empty product oil	0 psig (760 torr)	5 minutes	1.6 kg	Empty flask via diptube
14	Charge THF/water rinse	-4 psig (550 torr)	2 minutes	140 g	Charge remaining THF/ water to rinse the flask
15	Empty Rinse	0 psig (760 torr)	2 minutes	200 g	Empty the flask
16	Empty Distillate 2	0 psig (760 torr)	2 minutes	1.1 kg	Empty distillate from second strip
17	Cycle Wait	N/A	N/A	N/A	N/A

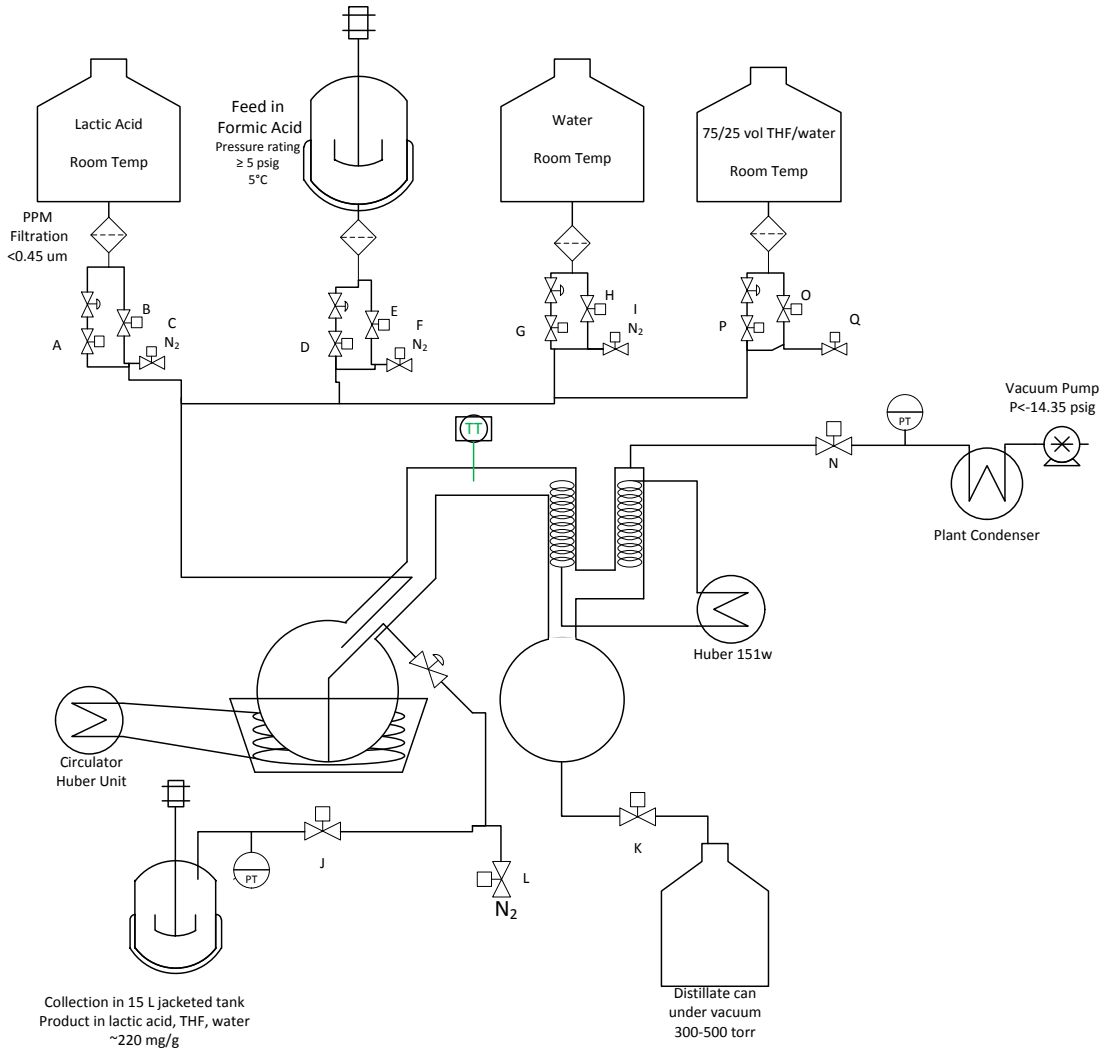


Figure S3. Detailed schematic of the automated intermittent flow rotary evaporator unit operation.

Referring to the valve labels in the figure, the automated sequence for the intermittent flow rotary evaporator cart is described in detail below.

1. *Charge Feed (~6.4 kg)*
   - 1.1. *Open valve N (Pull vacuum on Rotovap 300 torr/ -8.9 psig)*
   - 1.2. *Close valve N (Setpoint achieved)*
   - 1.3. *Open valves D,E*
   - 1.4. *Wait until 95% of mass transfer is achieved, then close valve E.*
   - 1.5. *Wait until total mass in minus deadband is achieved, then close valve D.*
   - 1.6. *Open valve F to blow nitrogen to push liquid from process tubing into Rotovap, 5 seconds*
   - 1.7. *Close valve F*
2. *Charge Lactic Acid (~2.4 kg)*
   - 2.1. *Open valves B, A*

2.2. Wait until 95% of mass transfer is achieved, close valve B.
2.3. Wait until total mass in minus deadband is achieved, then close valve A.
2.4. Open valve C to blow nitrogen to push liquid from process tubing into Rotovap, 5 seconds
2.5. Close valve C

3. *Evaporation step 1*
   3.1. Open valve N
   3.2. Pull until first setpoint reached (50 torr /-13.73 psig), then close valve N. Monitor system if pressure on PT > SP+10 torr then open valve N to pull back to setpoint, monitor for 1 minute
4. *Evaporation step 2*
   4.1. Open valve N to reach setpoint 2
   4.2. Pull until second setpoint achieved (45 torr/ -13.83 psig), close valve N, monitor system if pressure on PT>SP2 + 10 torr then open valve N to achieve setpoint 2, monitor for 2 minutes
5. *Evaporation step 3*
   5.1. Open valve N to achieve setpoint 3
   5.2. Pull until third setpoint achieved (40 torr /-13.93 psig), close valve N, monitor system if pressure on PT>SP2 + 10 torr then open valve N to achieve setpoint 3, monitor for 3 minutes
6. *Full Vacuum*
   6.1. Open valve N to connect to vacuum pump.
   6.2. Pull for 100 minutes, close valve N after 100 minutes. Expected minimum temperature is <20 °C, <22.5°C is OK. Expected pressure is <15 torr (-14.4 psig), <20 torr (-14.3 psig) is OK.
7. *Charge water*
   7.1. Open valve L to add N_2 to the Rotovap and raise the pressure to 100 torr/-12.8 psig
   7.2. Close valve L
   7.3. Open valves G and H
   7.4. Close valve H when 95% of mass transfer is achieved
   7.5. Close valve G when the total mass minus deadband is achieved.
   7.6. Open valve I to blow nitrogen to push liquid from process tubing into Rotovap, 5 seconds
   7.7. Close valve I
8. *Distillate Drain*
   8.1. Open valve L to pressurize Rotovap to atmospheric (760 torr/ 0 psig)
   8.2. Close valve L when Rotovap reaches 760 torr.
   8.3. Check that PT on distillate receiver is <500 torr/-5.0 psig
   8.4. Open valve K to begin distillate transfer
   8.5. Close valve K when the pressure in the Rotovap is <600 torr/-3.1 psig, indicating that the distillate is empty.
9. *Water Evaporation*
   9.1. Open valve N
   9.2. Pull until setpoint achieved (50 torr/-13.73 psig), close valve N, monitor system if pressure on PT > SP+10 torr then open valve N to pull back to setpoint, monitor for 1 minutes
10. *Full Vacuum*
    10.1. Open valve N.

10.2. Pull for 50 minutes, close N valve after 50 minutes. Expected minimum temperature is <20 °C, <22.5°C is OK. Expected pressure is <15 torr (-14.4 psig), <20 torr (-14.3 psig) is OK.

11. *THF/Water addition*
    - *11.1. Open valve L to pressurize Rotovap to 550 torr/ -4.06 psig*
    - *11.2. Close valve L*
    - *11.3. Open valve O and P to transfer material into the Rotovap*
    - *11.4. Close valve O when 95% of material is charged.*
    - *11.5. Close valve P when mass is the setpoint + deadband*
    - *11.6. Open valve Q to blow nitrogen to push liquid from process tubing into Rotovap and clear the line.*
    - *11.7. Close valve Q.*
12. *Transfer Out*
    - *12.1. Allow Rotovap to stir for user setpoint (1 minutes)*
    - *12.2. Open valve L to pressurize Rotovap to 760 torr.*
    - *12.3. Check that vacuum is pulled on product vessel PT on product receiver tank < 500 torr /-5.0 psig*
    - *12.4. Open valve J to transfer product out of the Rotovap*
    - *12.5. Close valve J when Rotovap pressure reaches (600 torr / -3.1 psig)*
13. *THF/water rinse*
    - *13.1. Open valve N to pull Rotovap to 550 torr / -4.06 psig*
    - *13.2. Close valve N*
    - *13.3. Open valve P to transfer material into the Rotovap*
    - *13.4. Close valve P when mass is the setpoint + deadband*
    - *13.5. Open valve Q to blow nitrogen to push liquid from process tubing into Rotovap and clear the line.*
    - *13.6. Close valve Q.*
14. *Transfer Out*
    - *14.1. Open valve L to pressurize Rotovap to 760 torr*
    - *14.2. Check that vacuum is pulled on product vessel PT on receiver tank (<500 torr)*
    - *14.3. Open valve J to transfer product out of the Rotovap*
    - *14.4. Close valve J when Rotovap pressure reaches (600 torr / -3.1 psig)*
15. *Distillate Drain*
    - *15.1. Open valve L to pressurize Rotovap to atmospheric (760 torr / 0 psig)*
    - *15.2. Close valve L when Rotovap at 760 torr*
    - *15.3. Check that PT on receiver tank is <500 torr / -5.0 psig*
    - *15.4. Open valve K to begin distillate transfer*
    - *15.5. Close valve K when the pressure in the Rotovap is <600 torr / -3.1 psig, indicating that the distillate is empty.*
16. *Cycle wait until next transfer*

The following figure shows the process temperature inside the evaporator for 5 total automated cycles. The constant temperature evaporator water bath remained 60 C, but the process temperature in the evaporator operated at low temperatures because of the evaporating solvents. The temperature trends were extremely repeatable from one automated cycle to the next. The signature temperature profile shows when evaporator pressure is increased and decreased, and the temperature profiles during the long extended 100 minute and 50 minute strips at full vacuum.

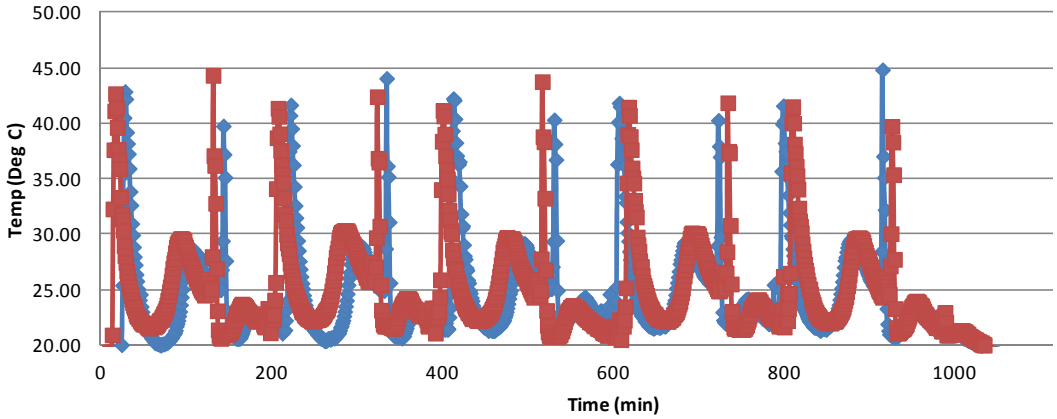


Figure S4. Overlay of rotary evaporator process temperature inside the evaporator for 5 total automated cycles (note 200 minute evaporation cycle used).

The combined concentrated solution in the 200 L vessel was heated to 45 °C with stirring. The headspace was inerted with nitrogen. Filtered THF (21.4 kg) was added at 45 °C, the mixture was cooled to 35 °C, and seed crystals of **12** were added (0.17 kg, 0.36 mol). The seeded mixture was then aged at 35 °C. Additional filtered THF (68.4 kg) was added over 6 hours. The slurry was then cooled to 5 °C over 3.5 h and aged an additional 5 hours prior to filtration at 5 °C.
The slurry was transferred to an agitated filter dryer in portions for filtration. The solids were washed twice with 1% water in THF (v/v, 8.7 kg) and dried under vacuum and with intermittent agitation. After drying, 5.02 kg of solid **12** was obtained (10.60 mol, 79.4% yield).

In total, 5 batches were produced as listed below:

Table S5. Yield data for each API batch

Batch	Input (assay, kg)	Input (moles)	Seed (kg)	Output (kg)	Output - Seed (kg)	Output - Seed (moles)	Batch Yield	Step Yield
1	4.8	13.14	0.17	5.26	5.09	10.75	81.8%	18.3%
2	4.9	13.41	0.17	5.02	4.85	10.24	76.4%	17.4%
3	4.8	13.14	0.17	5.48	5.31	11.21	85.4%	19.0%
4	4.8	13.14	0.17	4.85	4.68	9.88	75.2%	16.8%
5	3.1	8.48	0.17	3.44	3.27	6.91	81.4%	11.9%
Totals	24.05	65.82	0.85	24.05	23.2	49.00	N/A	83.5%

All batches exhibited acceptable quality attributes such as purity, assay, and X-Ray powder pattern.

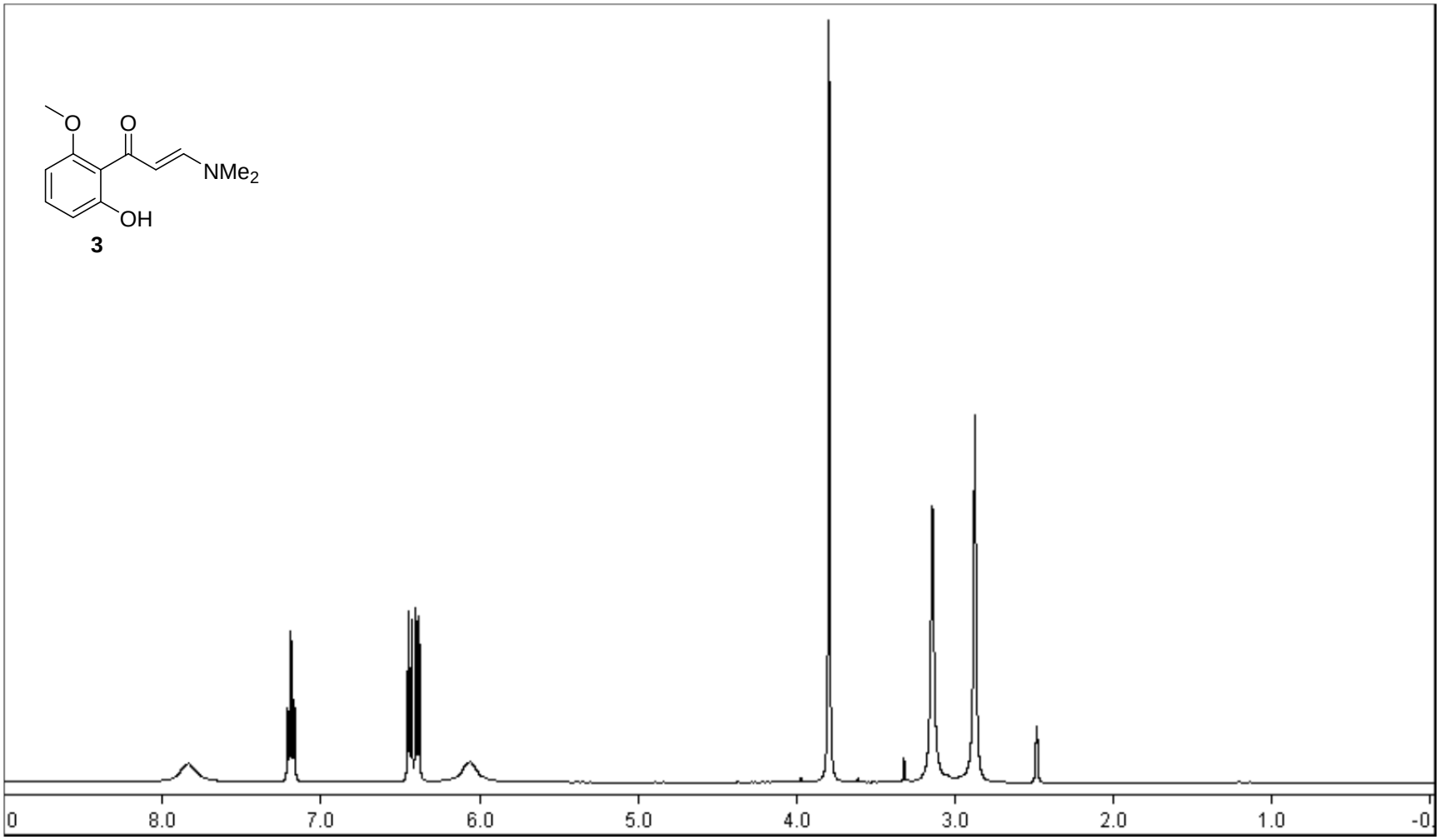


Figure S5. ^{1}H NMR spectrum of **3.**

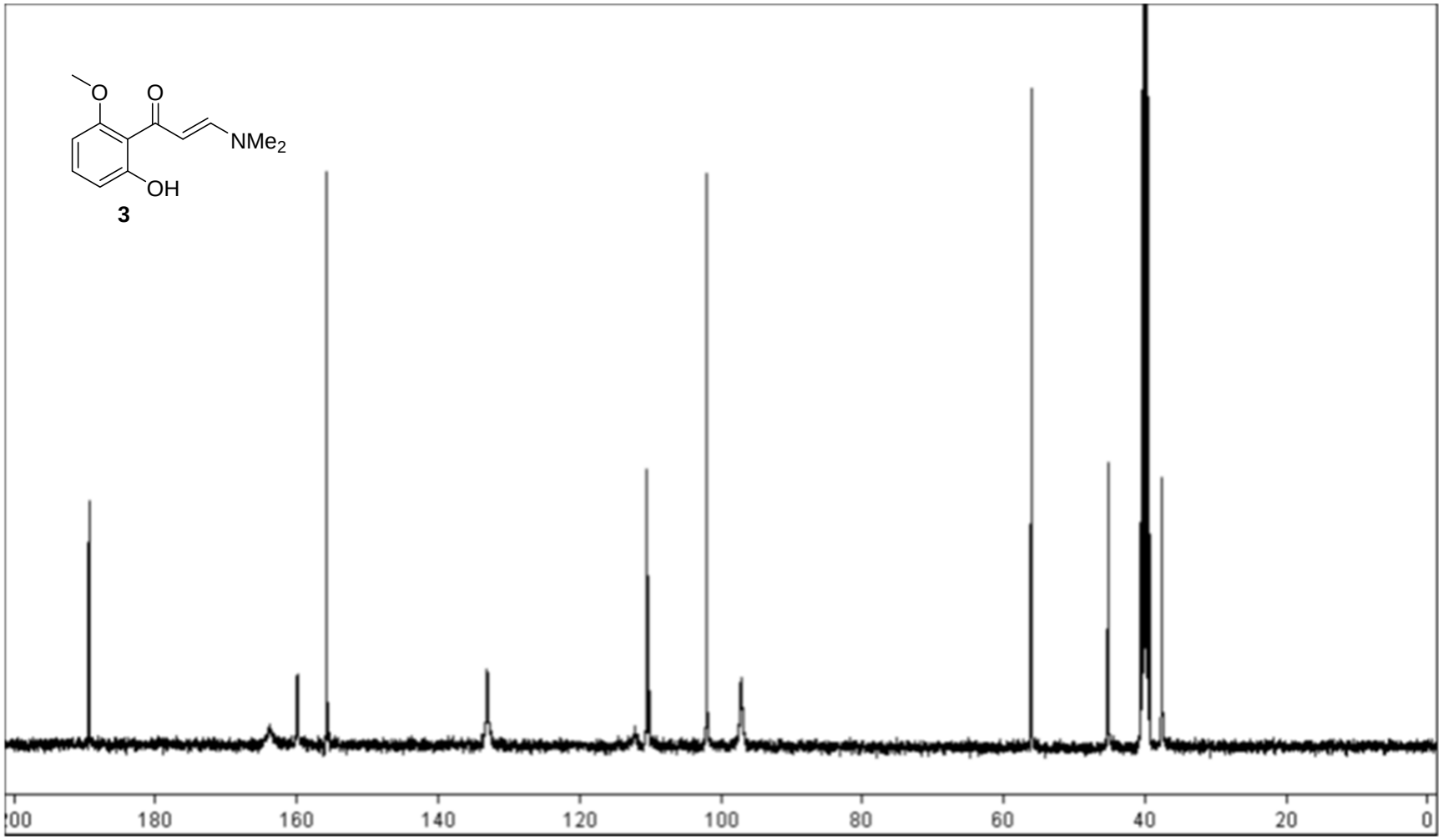


Figure S6. ^{13}C NMR spectrum of **3.**

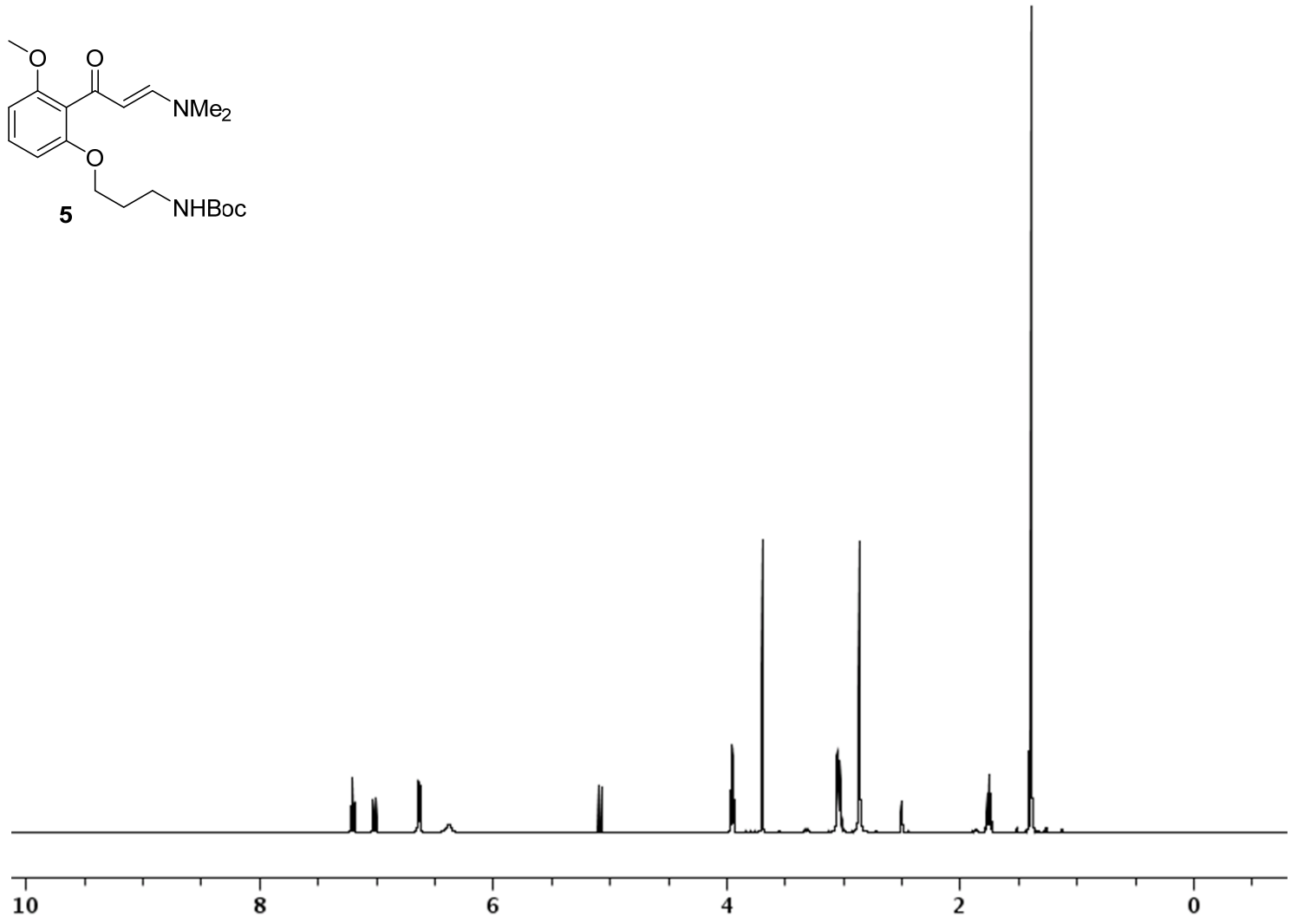


Figure S7. ^{1}H NMR spectrum of **5.**

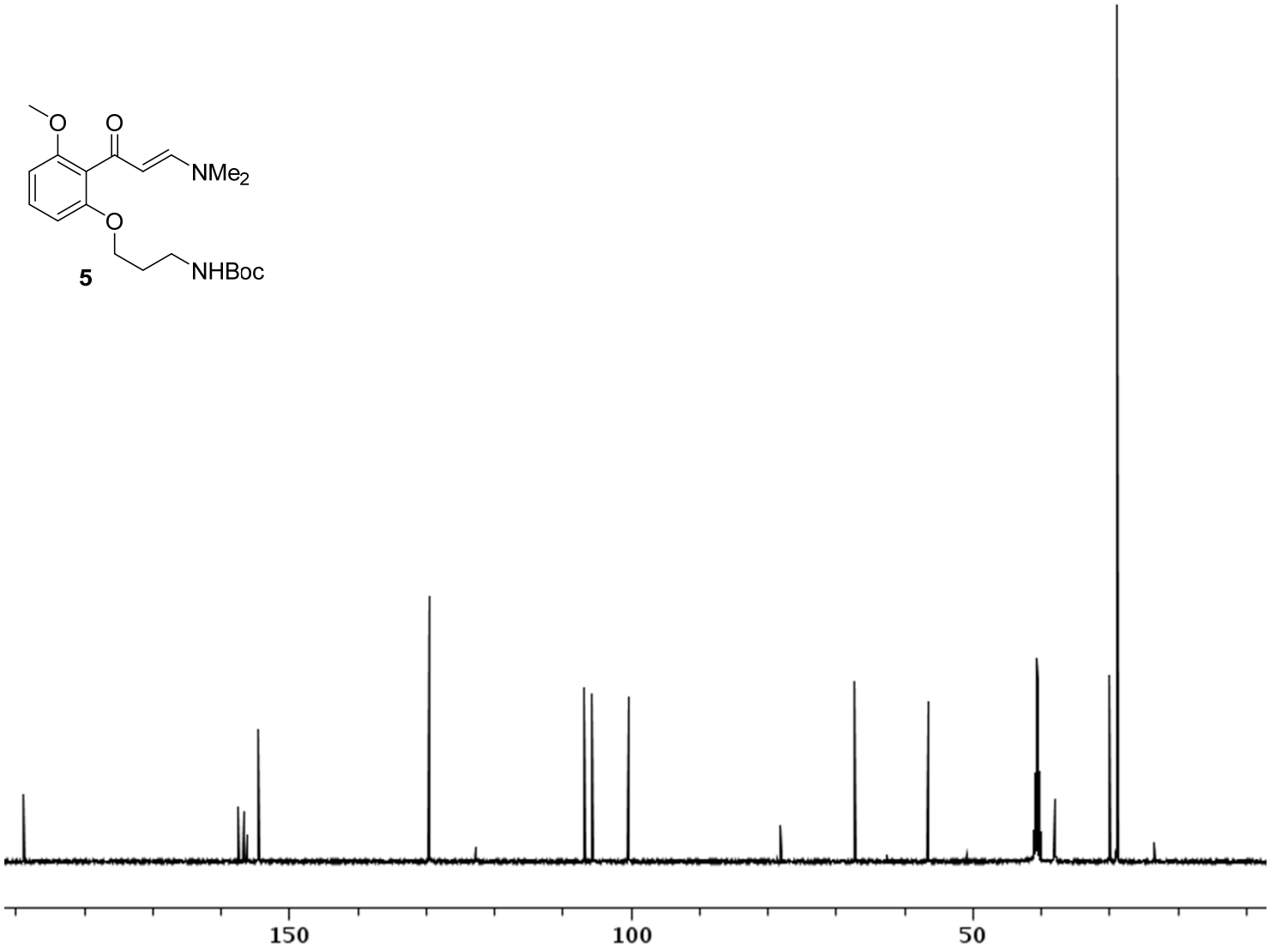


Figure S8. ^{13}C NMR spectrum of **5.**

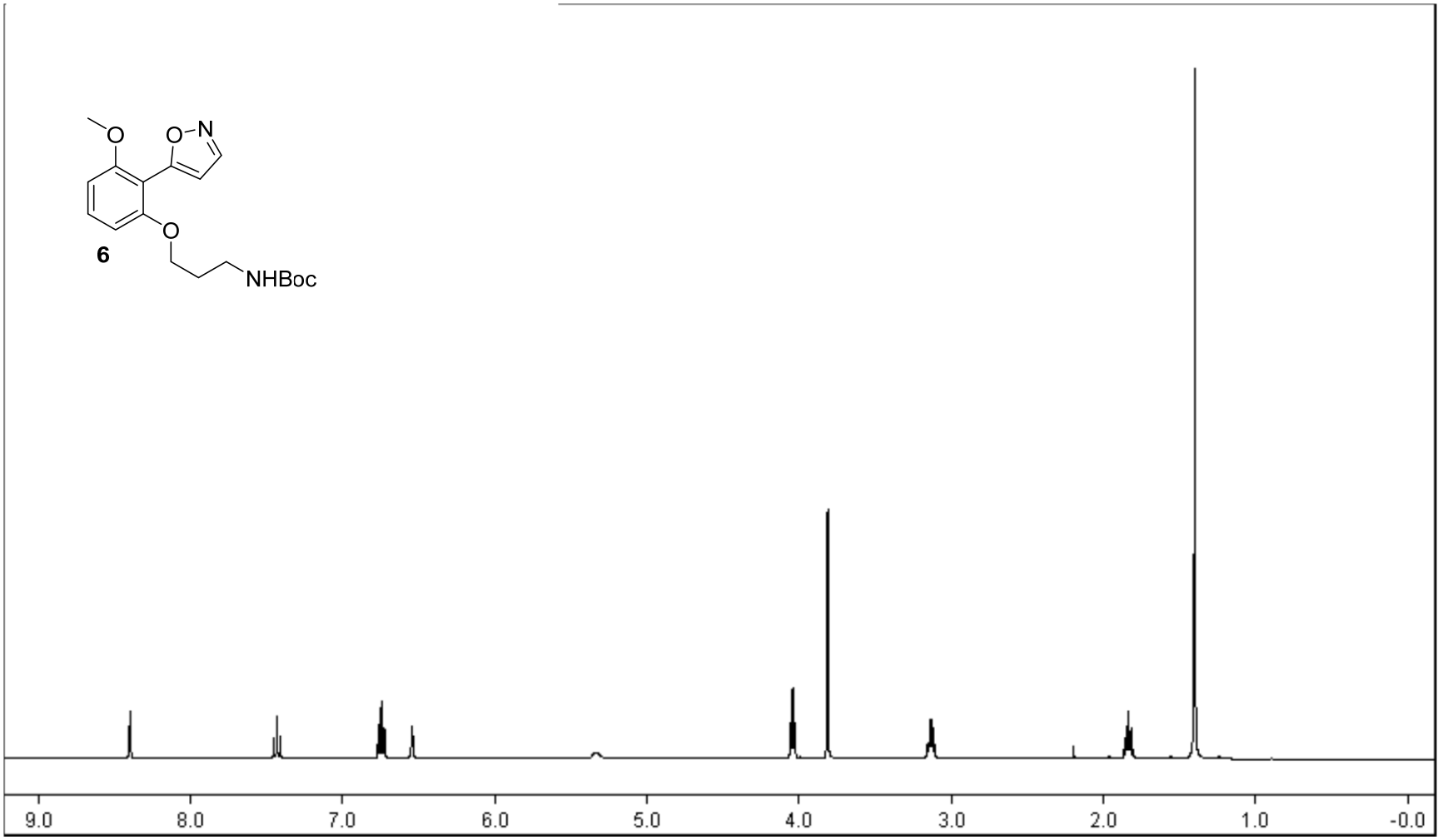


Figure S9. ^{1}H NMR spectrum of **6.**

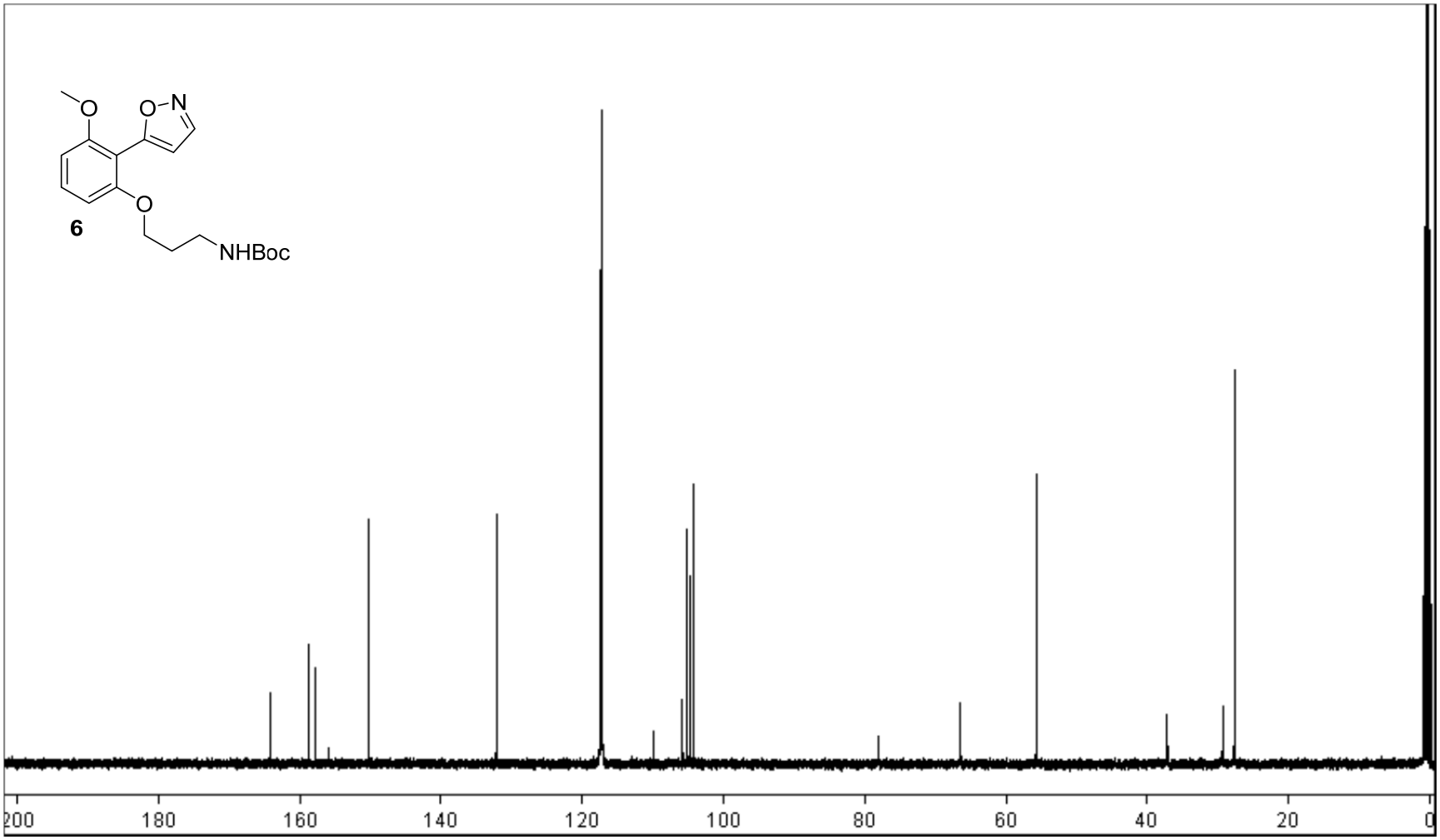


Figure S10. ^{13}C NMR spectrum of **6.**

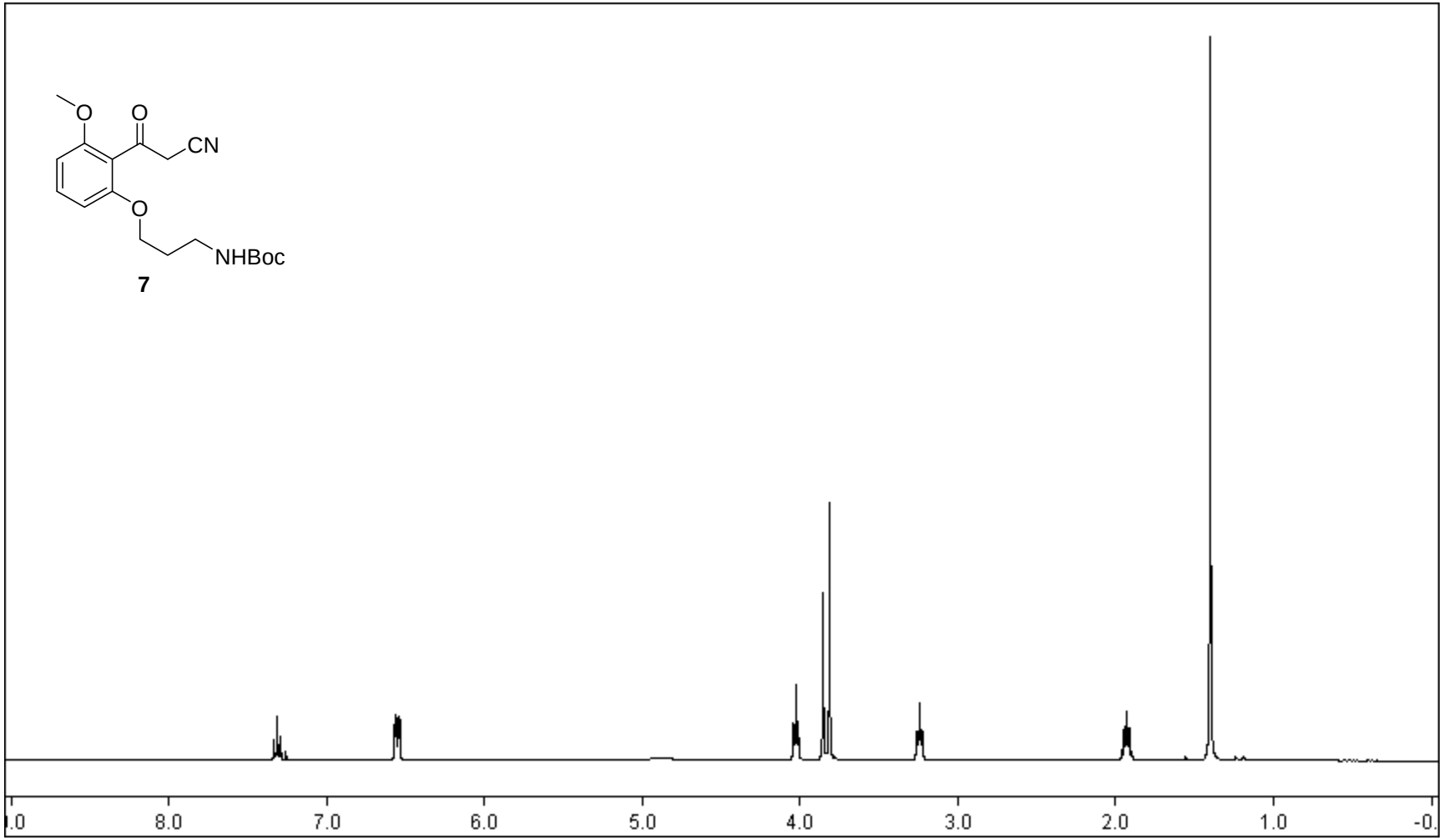


Figure S11. ^{1}H NMR spectrum of **7.**

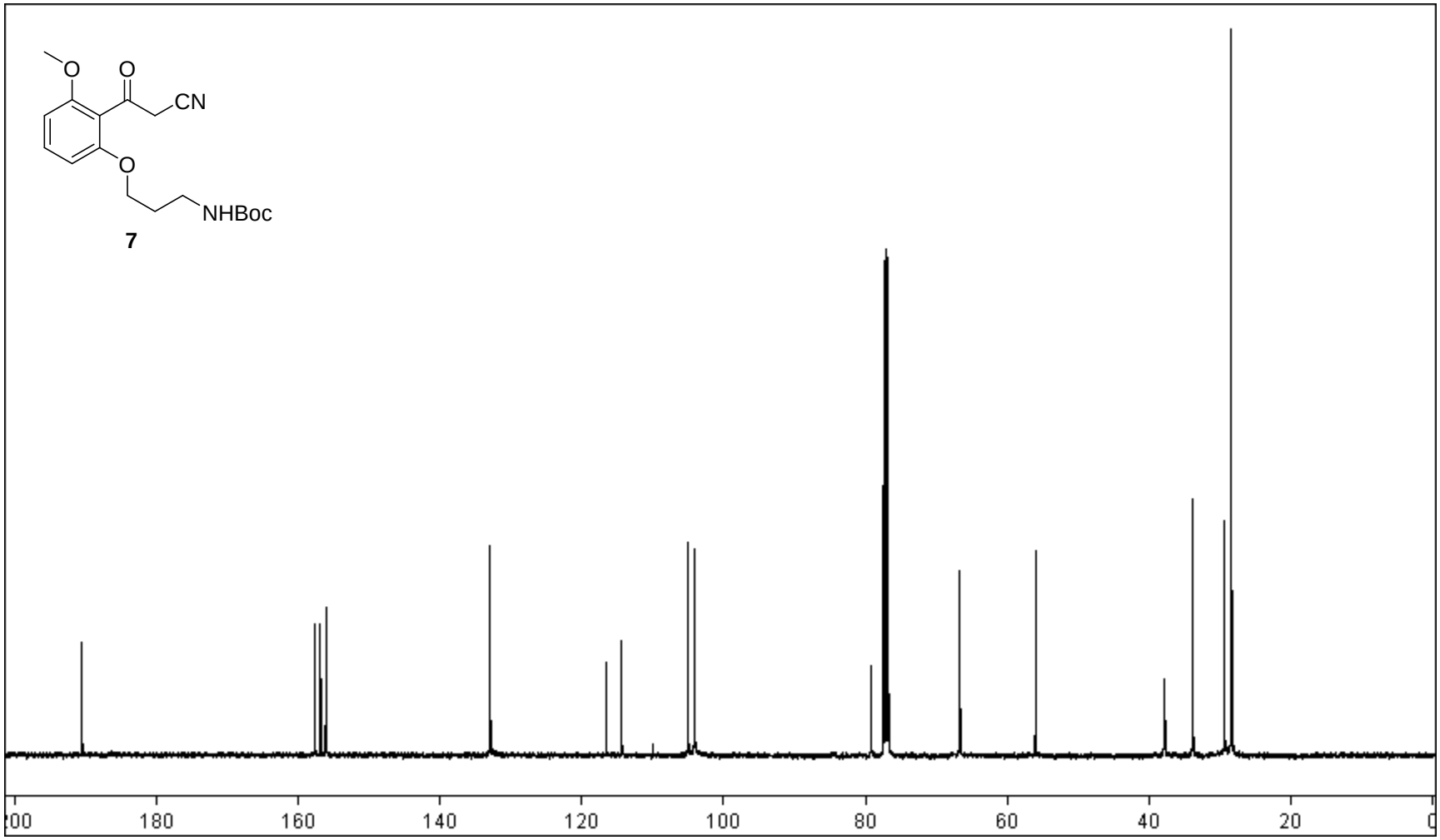


Figure S12. ^{13}C NMR spectrum of **7.**

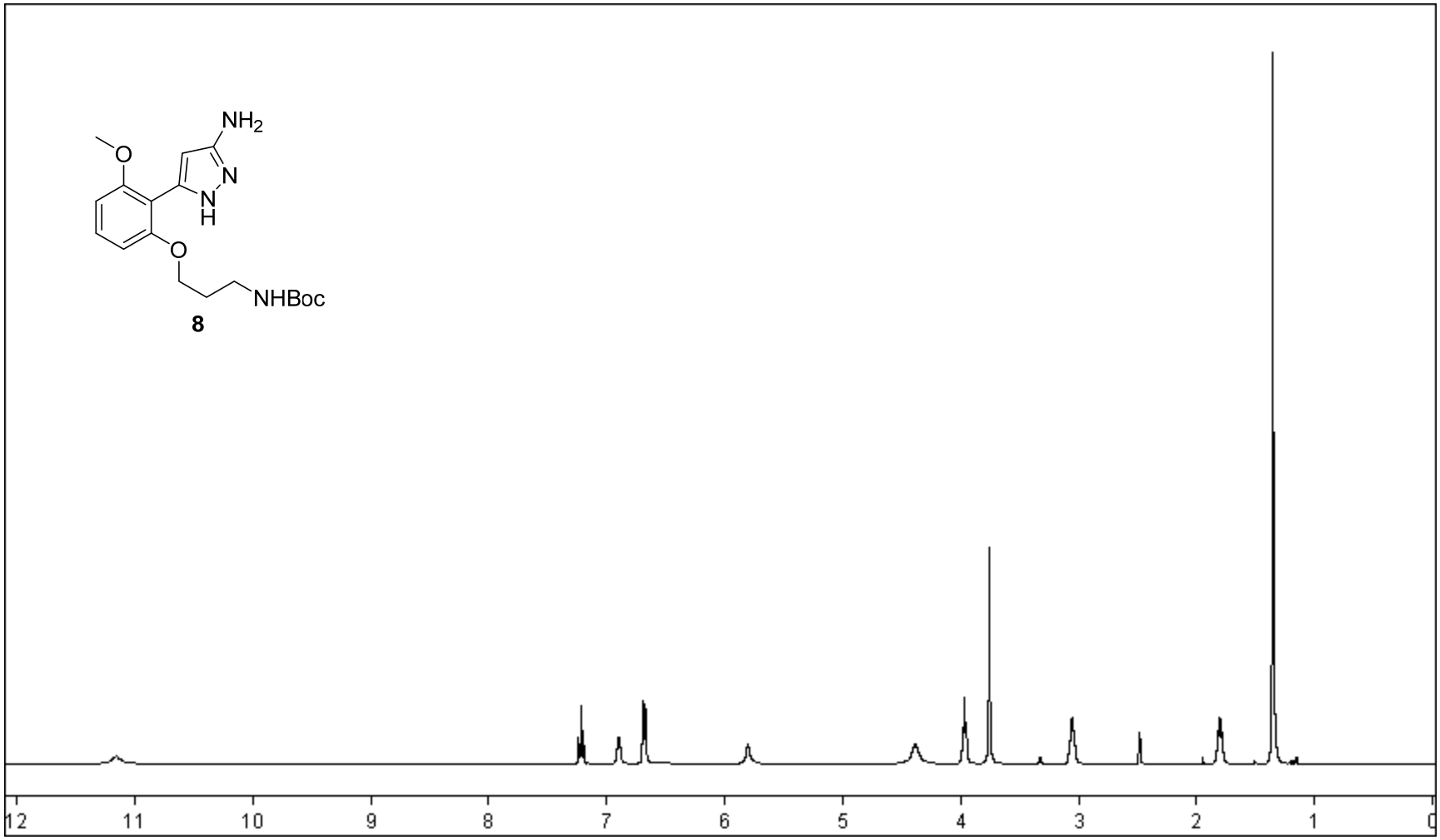


Figure S13. ^{1}H NMR spectrum of **8.**

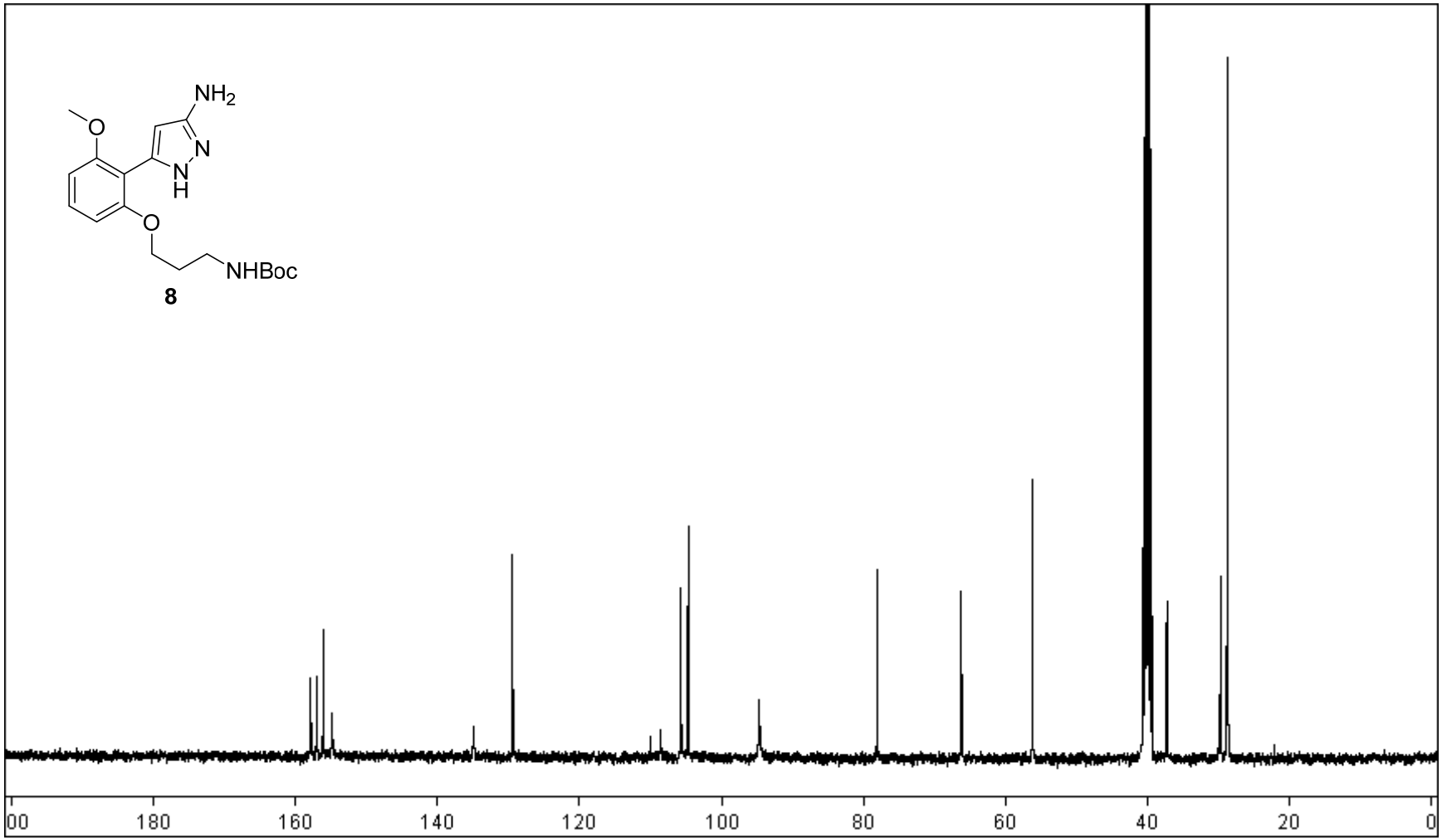


Figure S14. ^{13}C NMR spectrum of **8.**

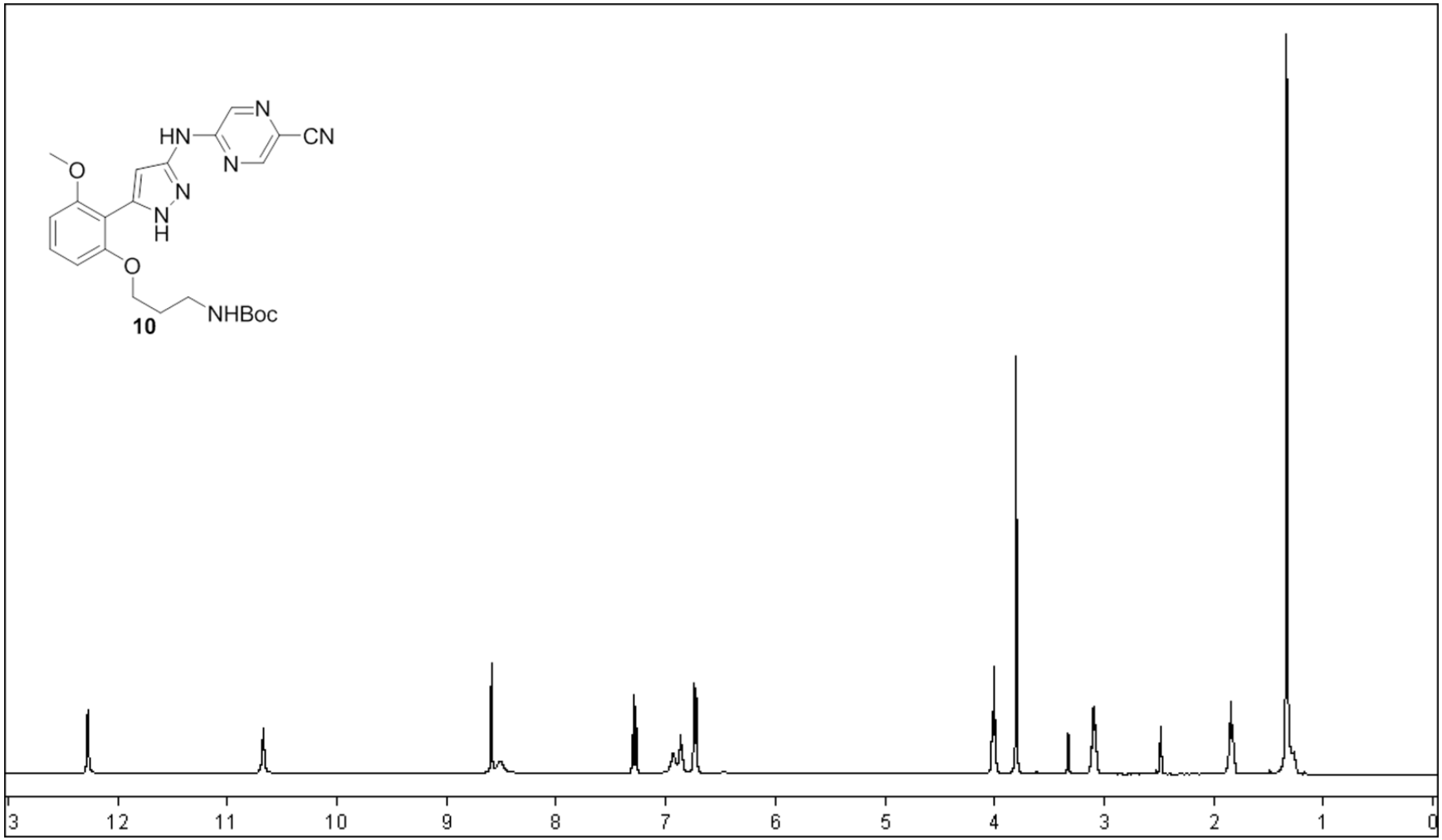


Figure S15. ^{1}H NMR spectrum of **10.**

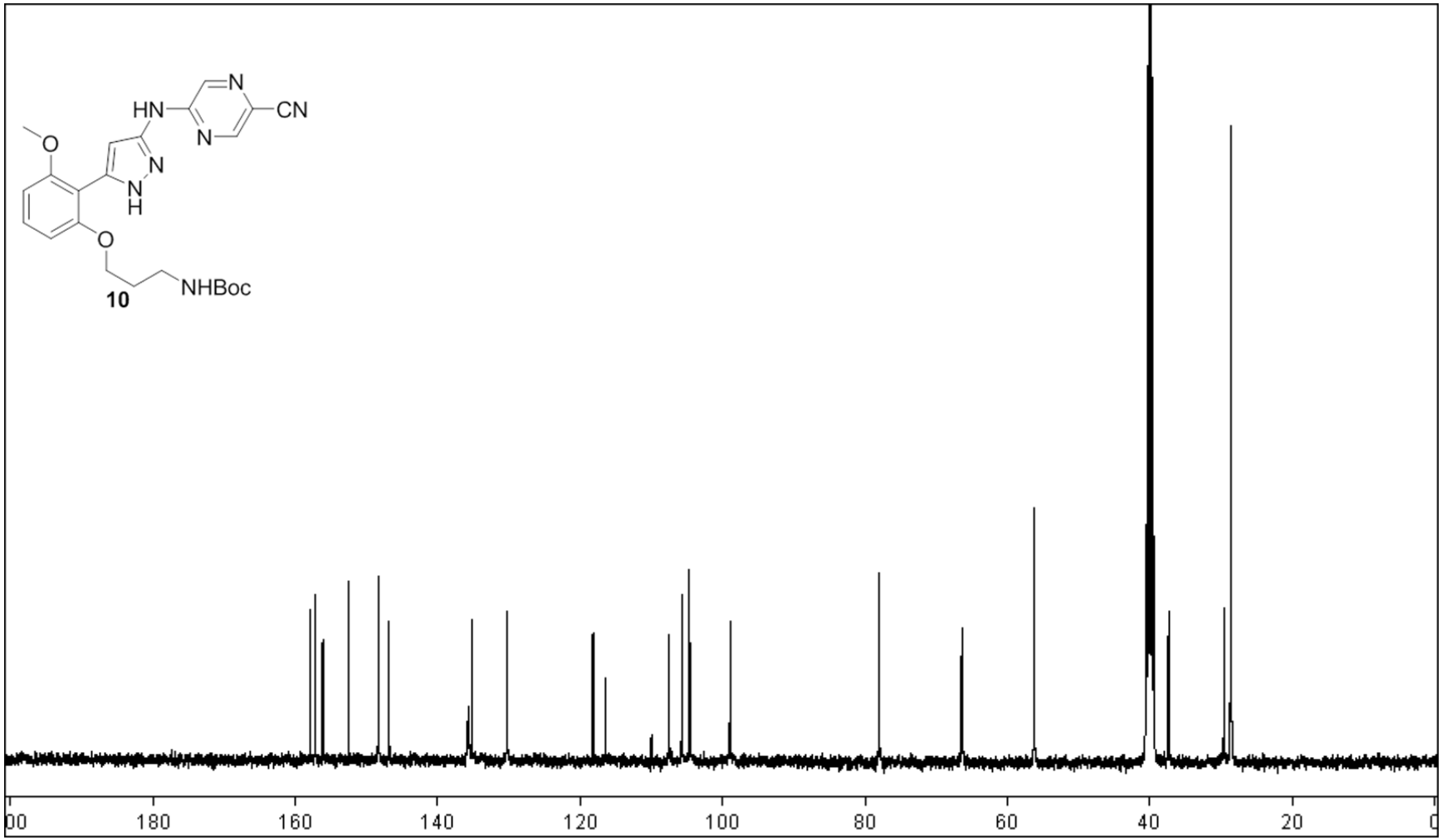


Figure S16. ^{13}C NMR spectrum of **10.**

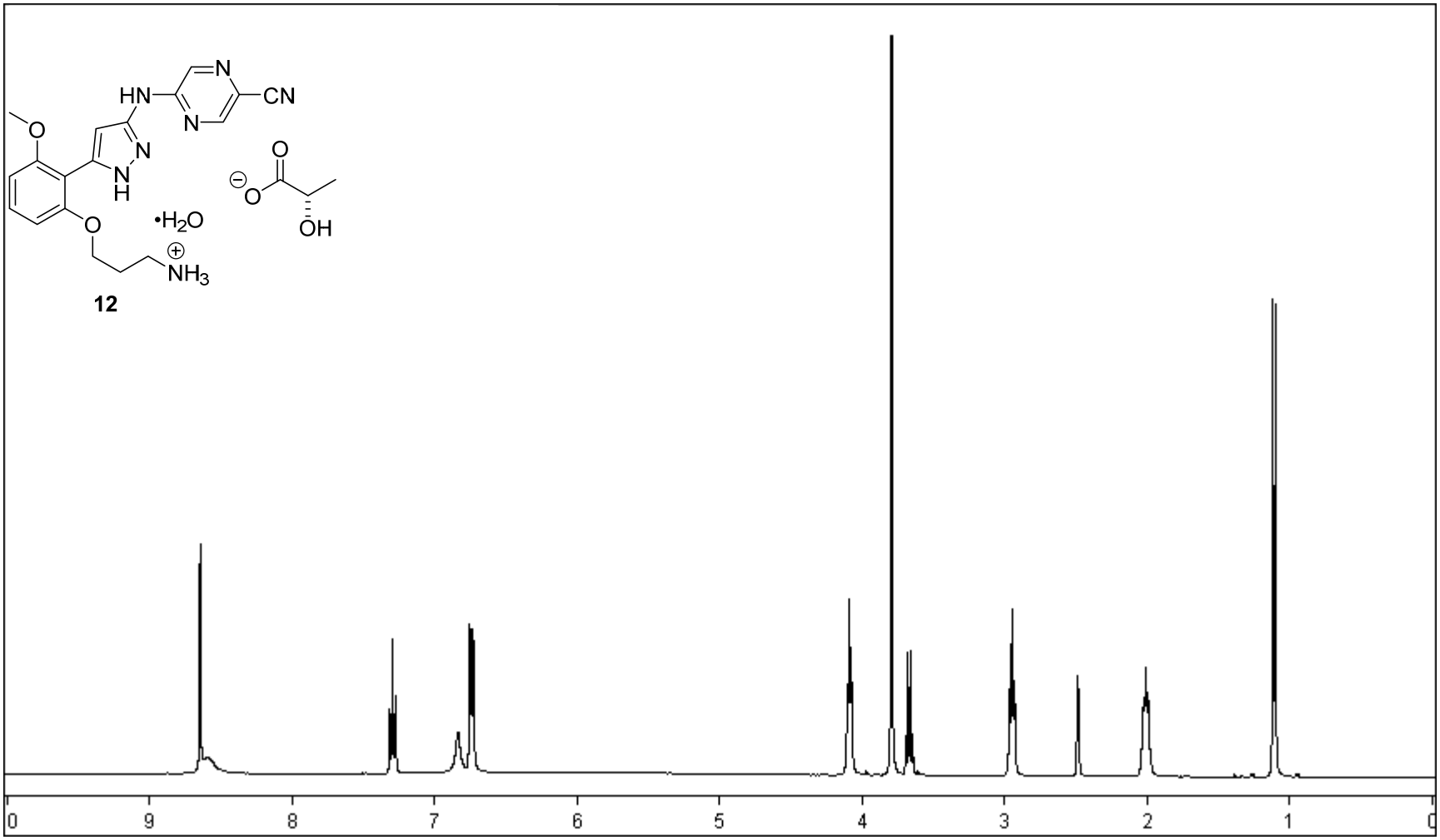


Figure S17. ^{1}H NMR spectrum of **12.**

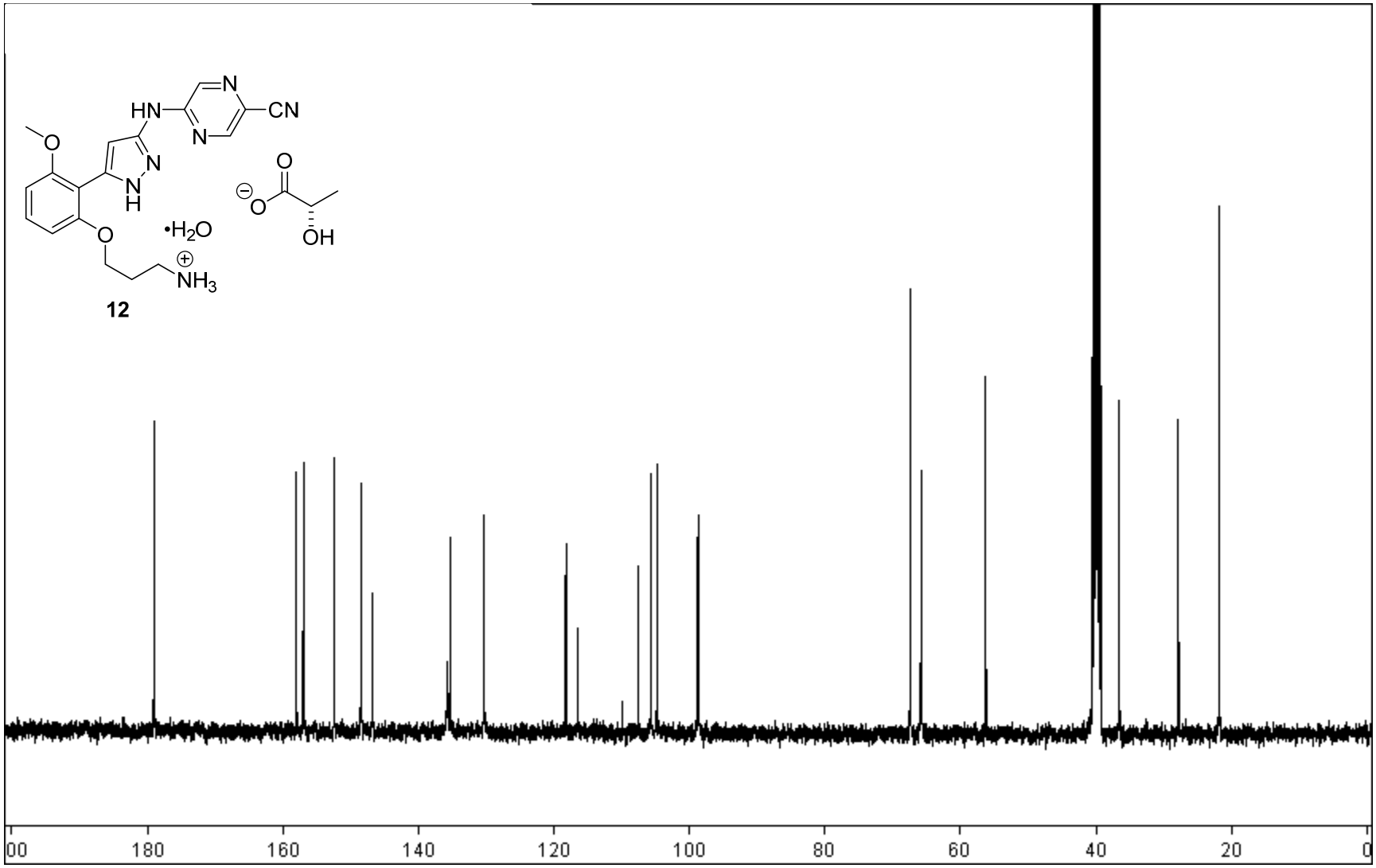


Figure S18. ^{13}C NMR spectrum of **12.**

Residence Time Distribution Model for Stage 2.

This section describes the process model used to calculate breakthrough and push out curves for non-reactive components (e.g. impurities, solvents, etc.) through the entire process train.

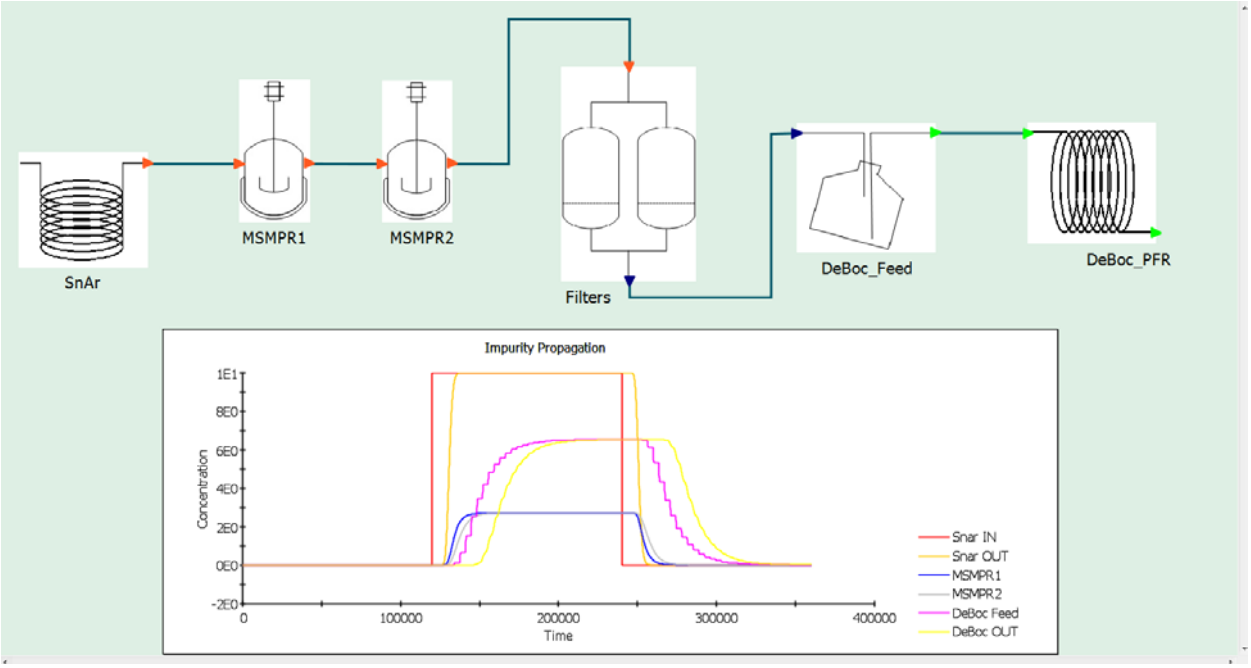


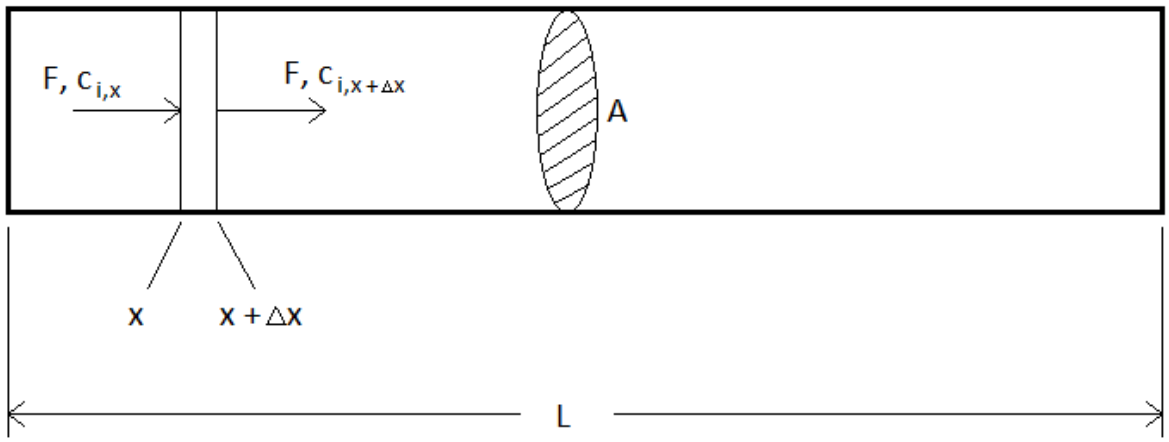
Figure S19. Screenshot of the model flow sheet along with a typical simulation output.

The model is built in gPROMS ModelBuilder 4.0.0, and consists of custom scripted unit operations as follows:

1) A plug flow reactor (PFR) with dispersion.
2) Two constant volume mixed-suspension mixed-product removal (MSMPR) crystallizers.
3) A tandem filter.
4) A feed vessel.
5) An additional PFR with dispersion.

S_NAr Reactor Model

The S_NAr reactor is modeled using a shell balance, a technique that considers a tubular reactor (total length L) to be a series of discrete elements of differential length, Δx. A mass balance can be written for a generic segment in this case, considering both convection and axial dispersion. Homogeneity in the radial direction is assumed in this case, and thermal expansion is neglected. No chemical reactions are considered for this case.



$$Accumulation = In - Out$$

$$\frac{\delta n_i}{\delta t} = \frac{\delta(A\Delta x c_i)}{\delta t} = A\Delta x \frac{\delta c_i}{\delta t} = Qc_i|_x - Qc_i|_{x+\Delta x} + DA\frac{\delta c_i}{\delta x}\Big|_{x+\Delta x} - DA\frac{\delta c_i}{\delta x}\Big|_x$$

$$\frac{\delta c_i}{\delta t} = \frac{Q}{A}\frac{-(c_i|_{x+\Delta x} - c_i|_x)}{\Delta x} + D\frac{\left(\frac{\delta c_i}{\delta x}\Big|_{x+\Delta x} - \frac{\delta c_i}{\delta x}\Big|_x\right)}{\Delta x}$$

$$\frac{\delta c_i}{\delta t} = -\frac{Q}{A}\frac{\delta c_i}{\delta x} + D\frac{\delta^2 c_i}{\delta x^2}$$

Figure S20. A diagram of the shell balance with Q as volumetric flow rate (m^3/s), c_i as concentration of component i (mol/m^3), n_i as moles of component i (mol), D as dispersion coefficient (m^2/s), A as cross sectional area (m^2) and L as reactor length (m).

gPROMS is a compiled algebraic and differential equation solver, so the model equations are formulated exactly as written in mathematical form. The software interprets the implicitly written differential equation and in this case, the reactor is discretized into 200 sections and the equations are solved using the fourth order center finite difference method (CFDM). Flow rate, cross sectional area and reactor length are all known and input to the model. The dispersion coefficient is determined from solvent testing. A dispersion curve for a representative reactor is shown below. The curve is an IR measurement of the transition from a toluene filled reactor to DMSO. The transition is not symmetrical, indicating some interaction between DMSO and the tubing. A transition between 2-MeTHF and xylenes is quite symmetrical and a bit sharper (data not shown here). The other curve shown in the figure below is the model generated dispersion curve. The dispersion coefficient was manually adjusted to closely match the more diffuse tail of the transition in order to be conservative. The resulting dispersion coefficient used was 1e-2 m^2/s, giving a D/uL of 0.0127.

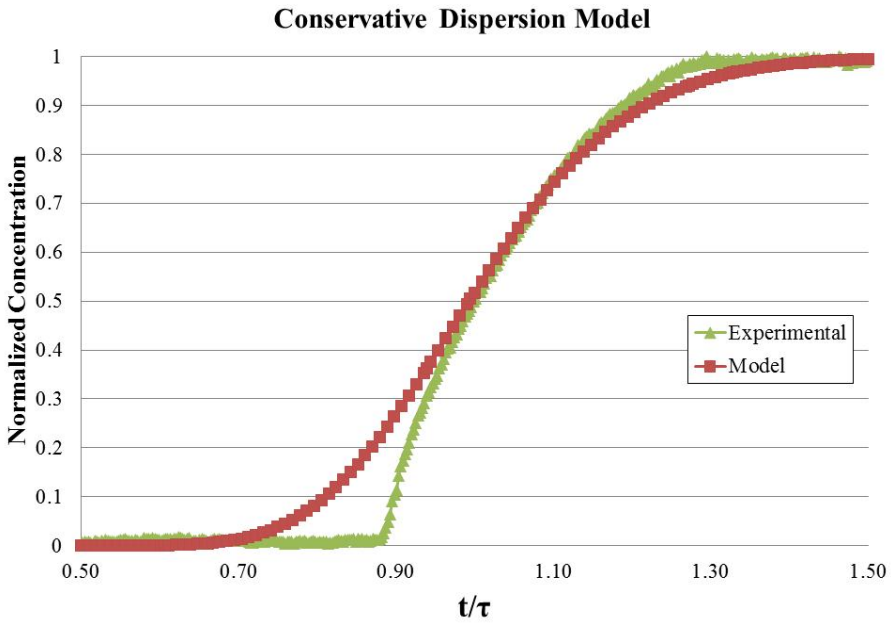


Figure S21. Transition curve showing model vs. experimental for Step 2 PFR.

MSMPR Model

The MSMPRs are modeled assuming constant volume, and in this case phase changes are ignored. The calculated concentrations are simply the composite concentration in the vessel. The equations used to model the MSMPRs are written below with V as the nominal volume (m^3):

$$Accumulation = In - Out$$

$$\frac{dn_i}{dt} = \frac{d(Vc_i)}{dt} = V\frac{dc_i}{dt} = Q_{IN}c_{i,IN} - Q_{OUT}c_i$$

Specifically in this case, MSMPR1 has 2 flows in, the feed from the S_NAr reactor and MeOH anti-solvent, such that:

$$\frac{dc_i}{dt} = \frac{Q_{IN}}{V}c_{i,IN} - \frac{Q_{IN} + Q_{MeOH}}{V}c_i$$

MSMPR2 has equal in and out flow rates, and simplifies to:

$$\frac{dc_i}{dt} = \frac{Q_{IN} + Q_{MeOH}}{V}\left(c_{i,IN} - c_i\right)$$

Filter Model

The filters are modeled by what is known as a state-transition network (STN). This is a system of process states that are governed by a set of rules; each state having its own set of equations. In this case, the filters go through a series of 6 states, the rules which govern them are based only on elapsed

time, such that they are scheduled operations (i.e. duty and standby filters change once an hour). The list of filter states are described below.

Table S6. Listing of automated filter states.

State	Description
F1Active_F2Formic	Filter 1 is the duty filter, while formic acid is charged to filter 2.
F1Active_F2Discharge	Filter 1 is the duty filter, while filter 2 is discharged to DeBoc feed.
F1Active_F2Idle	Filter 1 is the duty filter, while filter 2 sits idle.
F2Active_F1Formic	Filter 2 is the duty filter, while formic acid is charged to filter 1.
F2Active_F1Discharge	Filter 2 is the duty filter, while filter 1 is discharged to DeBoc feed.
F2Active_F1Idle	Filter 2 is the duty filter, while filter 1 sits idle.

When a filter is in an active state, all of the component of interest entering the filter is accumulated. This is conservative, as some of the component is likely present in solution, and is lost to filtrate. This accumulation is accomplished by the following equation with m_i as mass of component i (kg) and MW_i as molecular weight of component i (kg/mol):

$$\frac{dm_i}{dt} = Q_{IN} c_{i,IN} MW_i$$

Obviously, when a filter is in idle mode, there is no accumulation or loss, so $dm_i/dt = 0$. When the filter is in the formic acid charge state, dm_i/dt is still zero, but now formic acid is allowed to accumulate where $\dot{m}_{FA}$ is the mass flow rate of formic acid onto the filter (kg/s):

$$\frac{dm_{FA}}{dt} = \dot{m}_{FA}$$

This state is controlled by a rule that uses an arbitrary rate of formic acid flow to achieve a target formic acid amount that is equal to what is used in the actual process. At this point, meaningful mass fractions (x_i ,x_{FA}) can be calculated from masses on the filter, and used to calculate the discharge phase (equation shown for component i):

$$\frac{dm_i}{dt} = \dot{m}_{OUT} x_i$$

This state is governed by a rule which enforces the filter is empty, thus the outlet flow rate is chosen arbitrarily.

DeBoc Feed Bottle Model

The DeBoc feed bottle is modeled as a well-mixed tank with variable volume. The model simply calculates the component mass balances (including solvent). In this case, the outlet flow rate is held constant as the feed to the DeBoc PFR, but the inlet feed rate is variable and is scheduled by the outlet of the filter. The component mass balance is written below:

$$\frac{dm_i}{dt} = \dot{m}_{IN} x_{i,IN} - \dot{m}_{OUT} x_i$$

The feed bottle is set such that the operating volume is nominally 5 L.

DeBoc PFR Model

The same model is used for the DeBoc PFR as is used for the S_NAr PFR. The difference being the dispersion coefficient is fit from data representative of the DeBoc reactor. Below is the resulting fit which was done as a parameter estimation run within gPROMS. This fit resulted in a dispersion coefficient of 1.12e-4 m^2/s, and a D/uL of 0.0018.

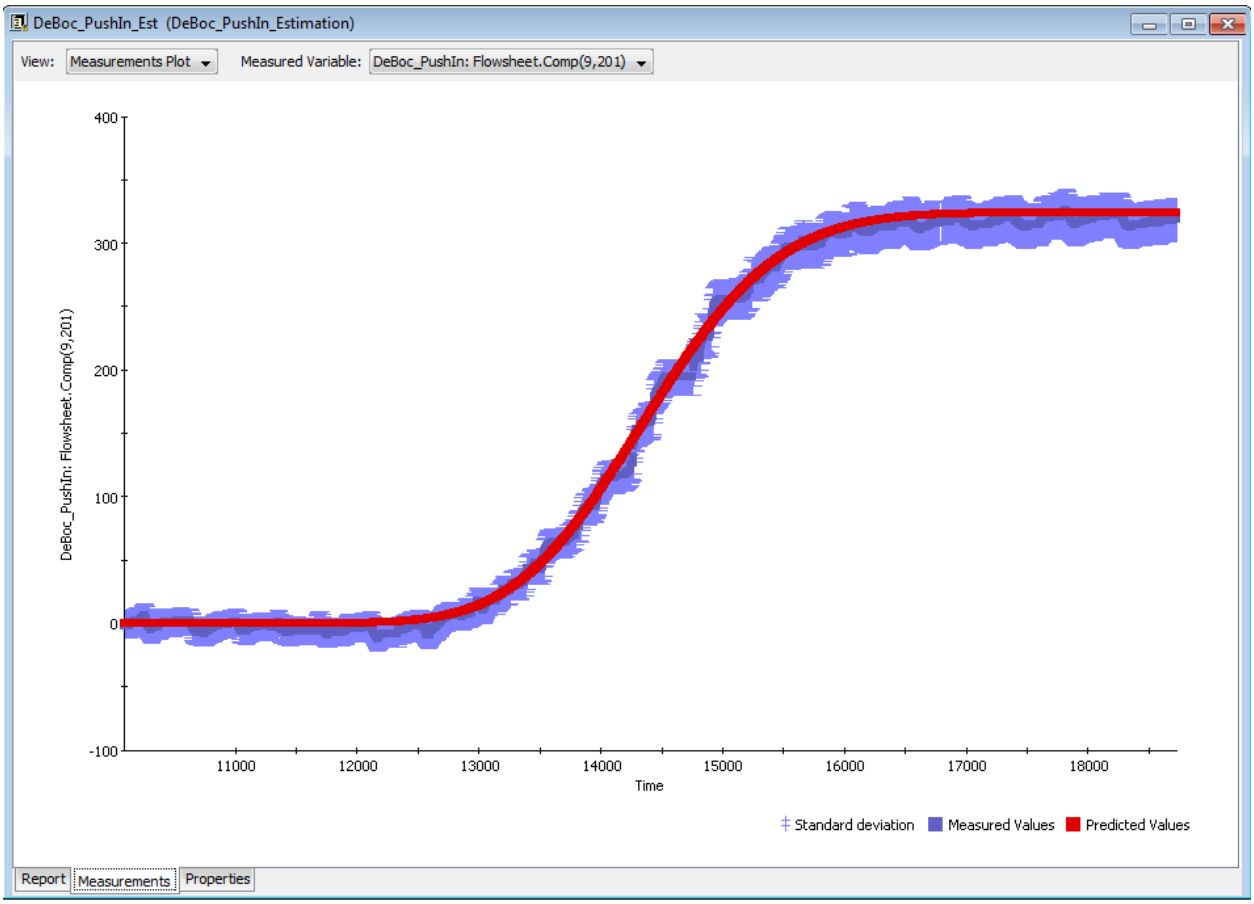


Figure S22. Transition curve showing model vs. experimental for Step 3 PFR.

Similar to the S_NAr reactor, the DeBoc reactor is discretized into 200 elements and the equations are solved by the 4th order CFDM.

Analysis of Breakthrough and Clearance

A simulation was run utilizing the entire process train to understand the timing of breakthrough of a suddenly introduced component (e.g. an impurity), as well as the clearance of that component from the system by sudden removal from the inlet.

As shown in the plot below, upon introduction of an impurity to the inlet of the S_NAr reactor, the outlet of the DeBoc reactor will exceed 1% of the impurity concentration at 8.16 hr, and it will exceed 5% at 9.06 hr. From the first sign of the impurity at the S_NAr outlet, these times are 6.08 hr and 6.98 hr, respectively.

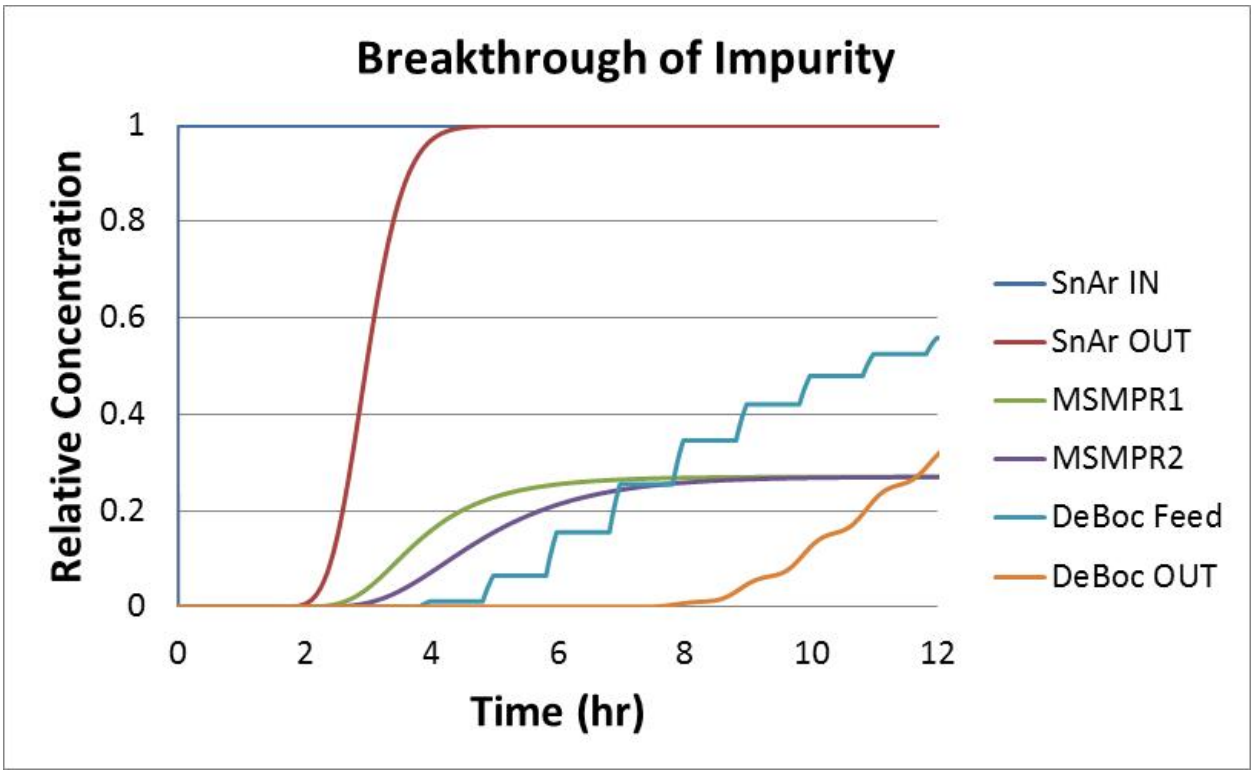


Figure S23. Plot illustrating the introduction of a disturbance in the Stage 2 system.

After allowing the impurity to reach steady state throughout the system, the impurity level was set to zero instantaneously to calculate the amount of time needed to clear the system. The figure below shows clearance curves for the system. The amount of time needed to clear the entire system is quite long (18.5 hr to get below 5% and 23.7 hr to get below 1%) due to the large surge volume in the DeBoc feed vessel. The amount of time needed to clear MSMPR2 is much shorter (6.19 hr for 5% and 8.22 hr for 1%).

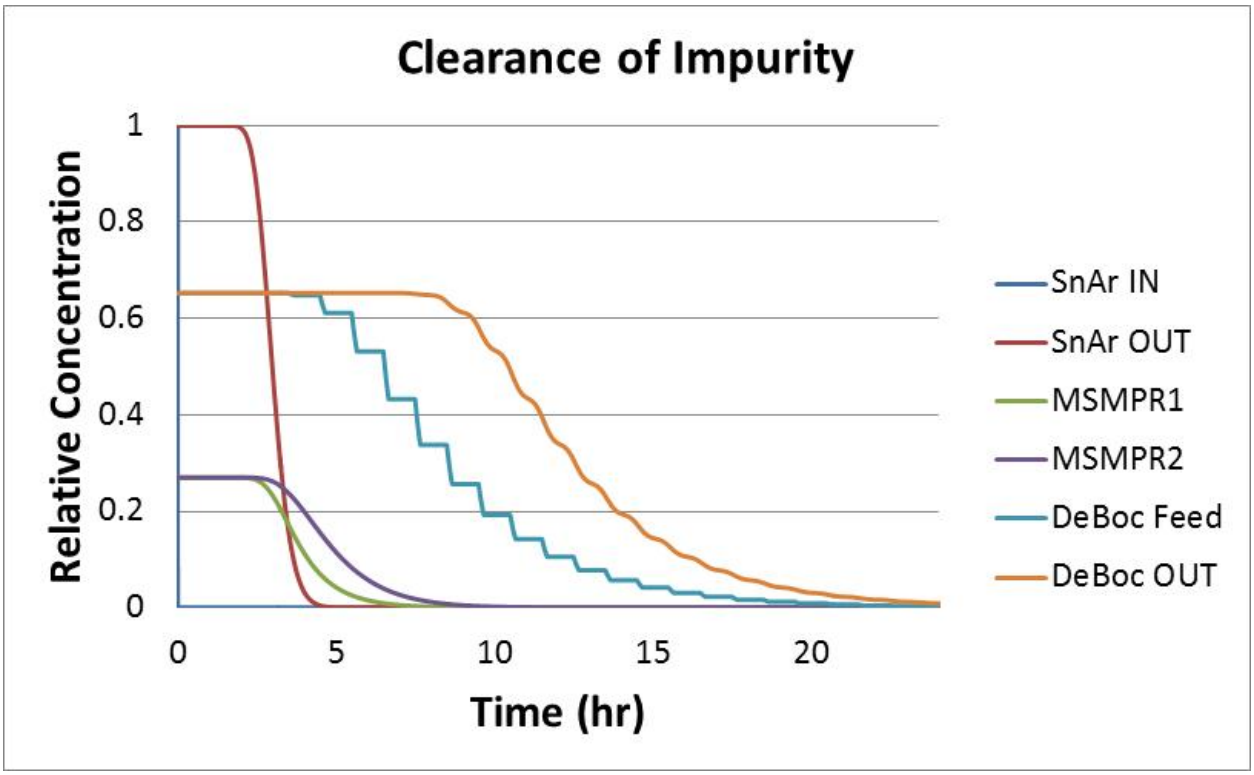


Figure S24. Plot illustrating the clearance of a disturbance in the Stage 2 system.

Figure S25. Photograph of 1.4 L stainless steel PFR.

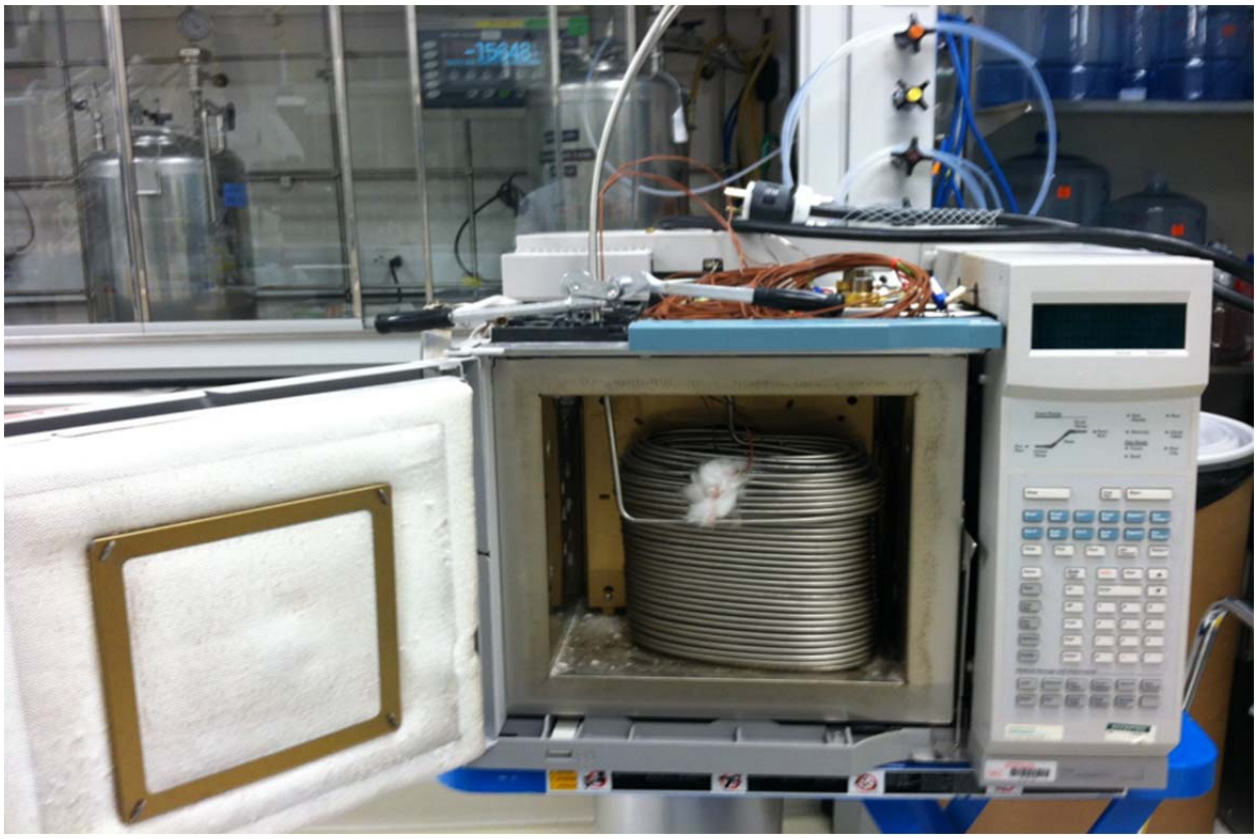


Figure S26. Photograph of gas chromatography oven with PFR inside it.

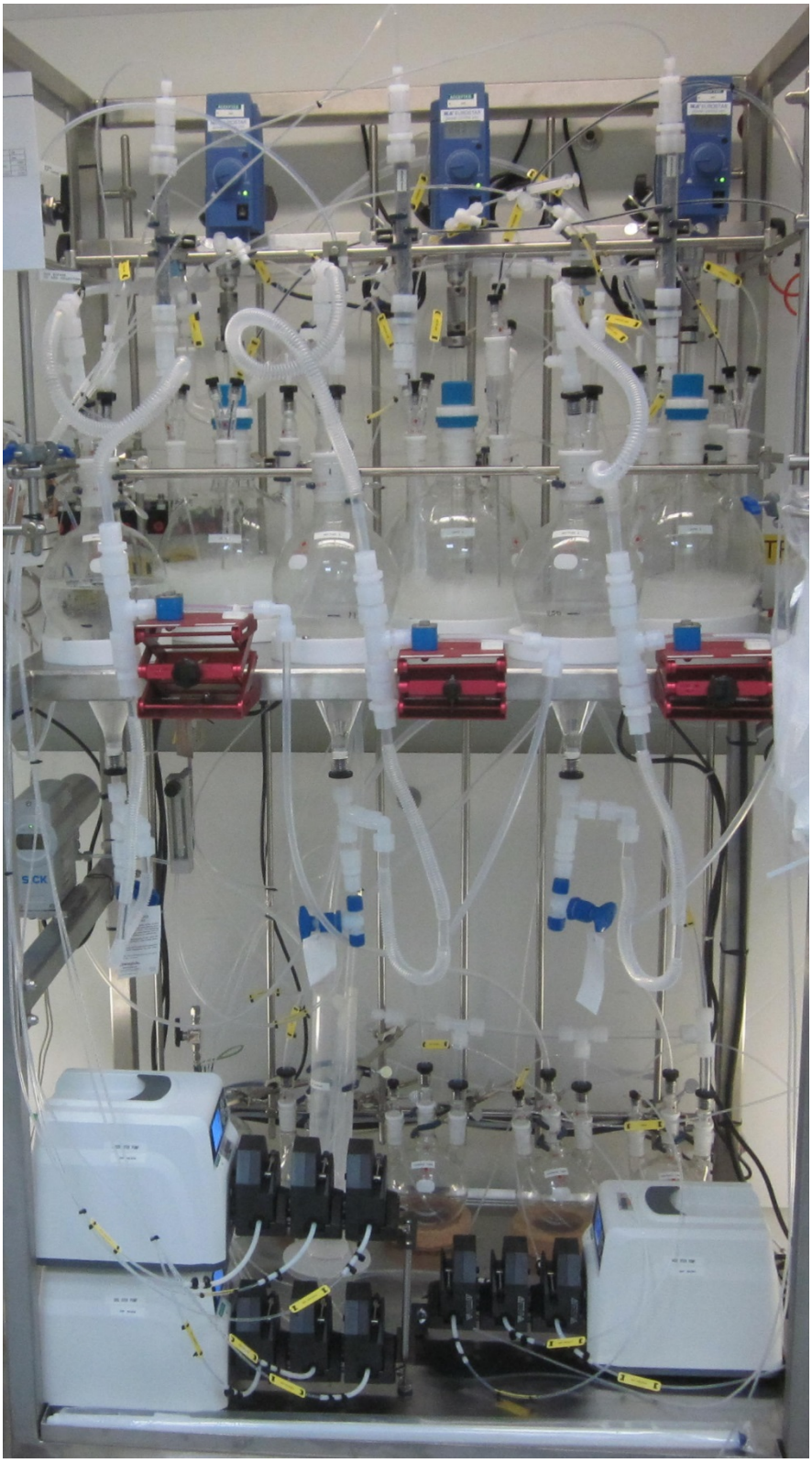


Figure S27. Photograph of continuous countercurrent extraction system.

Figure S28. Photograph of extraction system running.

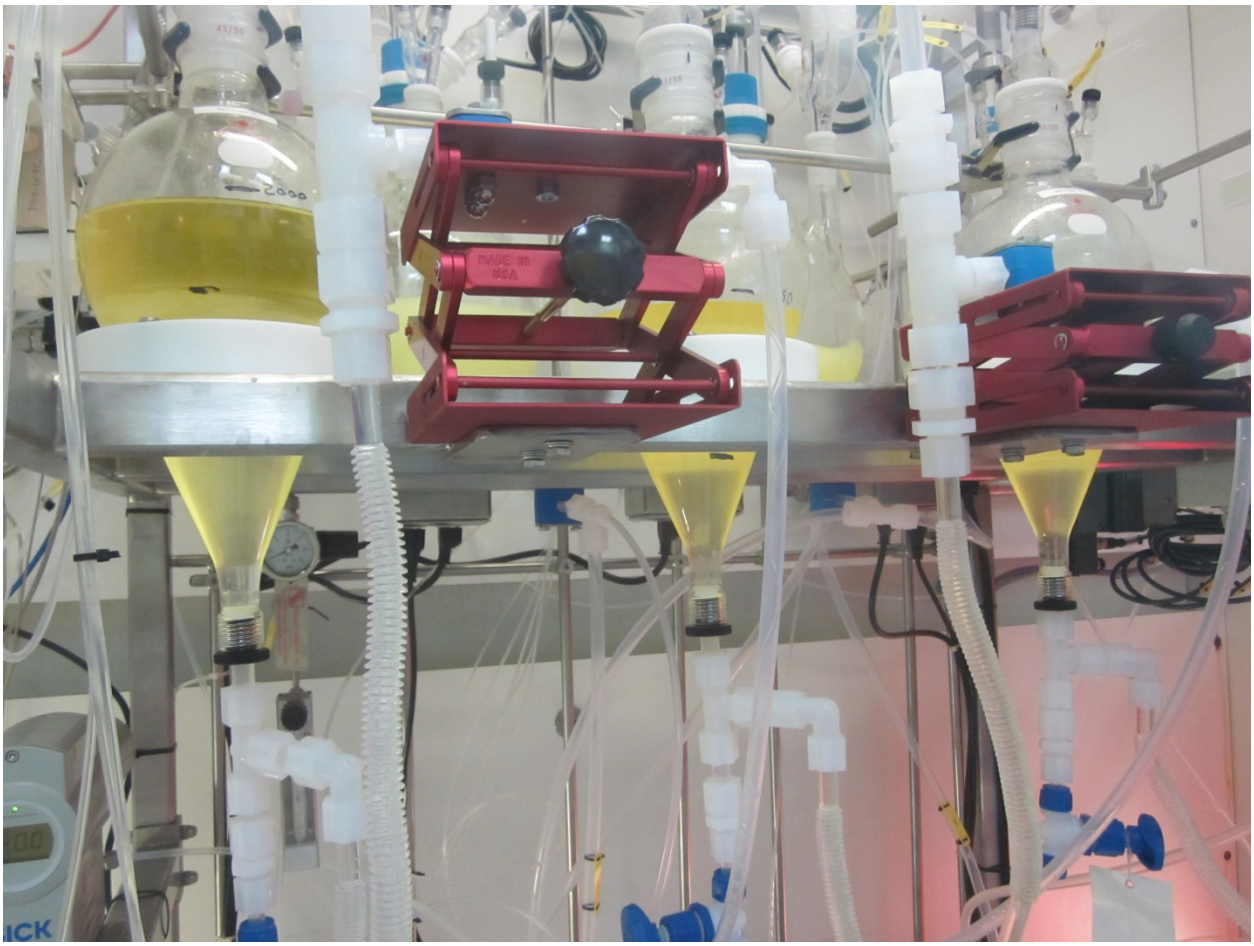


Figure S29. Photograph of extraction system running.

Figure S30. Photograph of automated rotary evaporator and charging module.

Figure S31. Photograph of the solution during an automated distillation.

Figure S32. Photograph of empty reactor for S_NAr.

Figure S33. Fume hood containing water bath and S_NAr reactor with automated HPLC dilution cart.

Figure S34. Photograph of fume hood containing continuous crystallizers and automated filters.

Figure S35. Photograph of continuous crystallizers during processing.

Figure S36. Photograph of empty gas/liquid PFR for deprotection step.

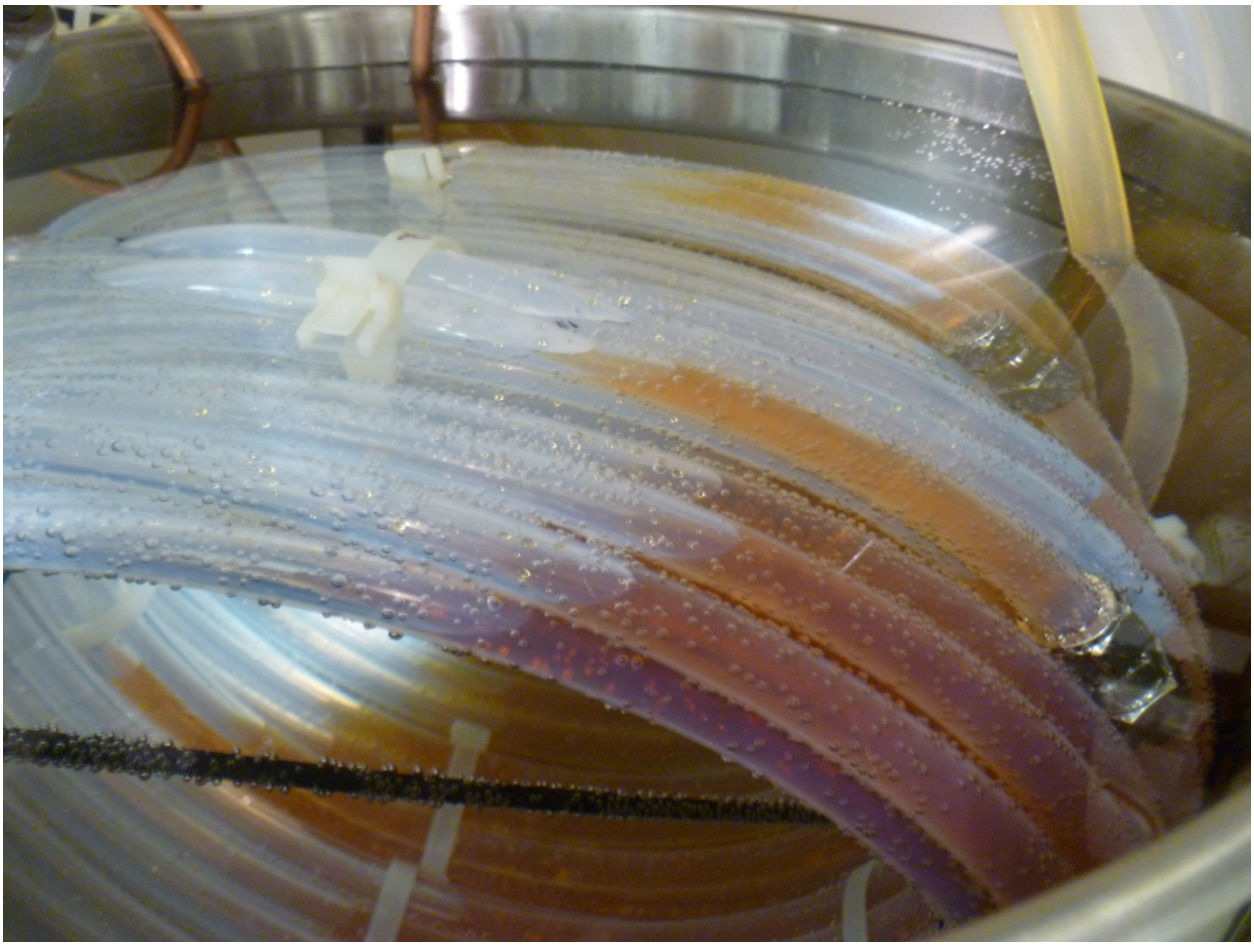


Figure S37. Photograph of deprotection gas/liquid reactor during processing.

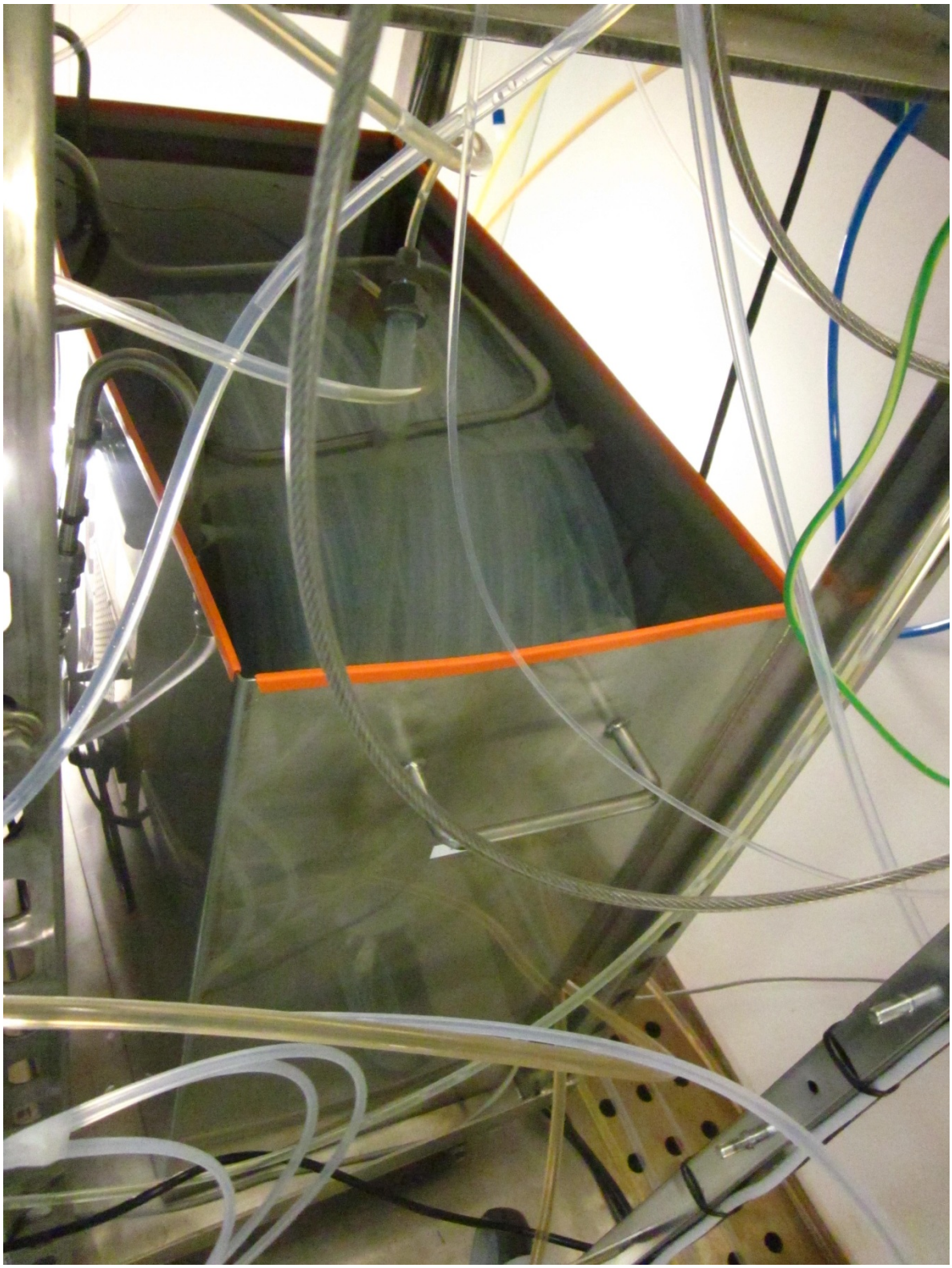


Figure S38. Photograph of deprotection gas/liquid PFR in thermostatic bath.

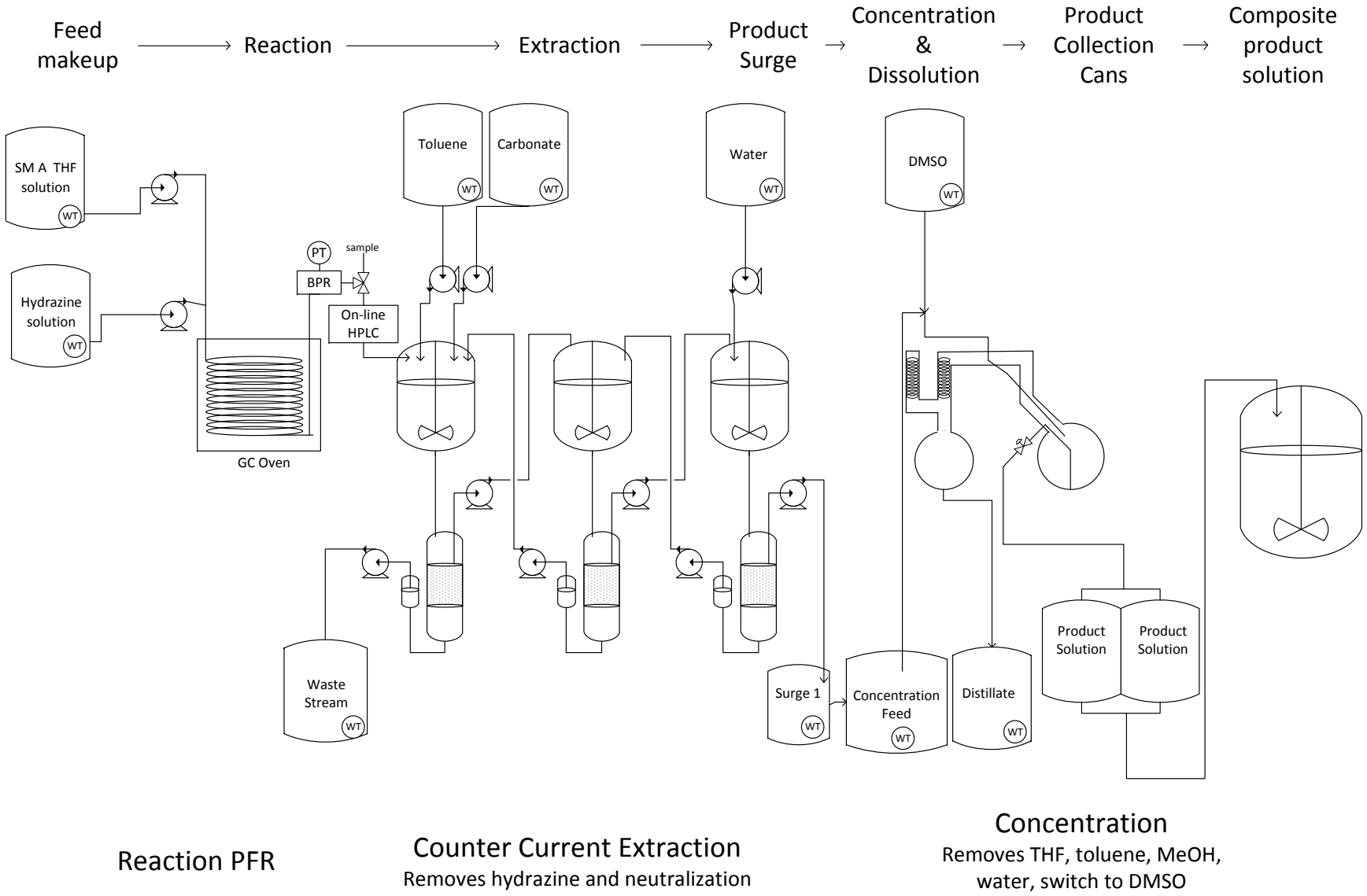


Figure S39. Equipment drawing for Stage 1.

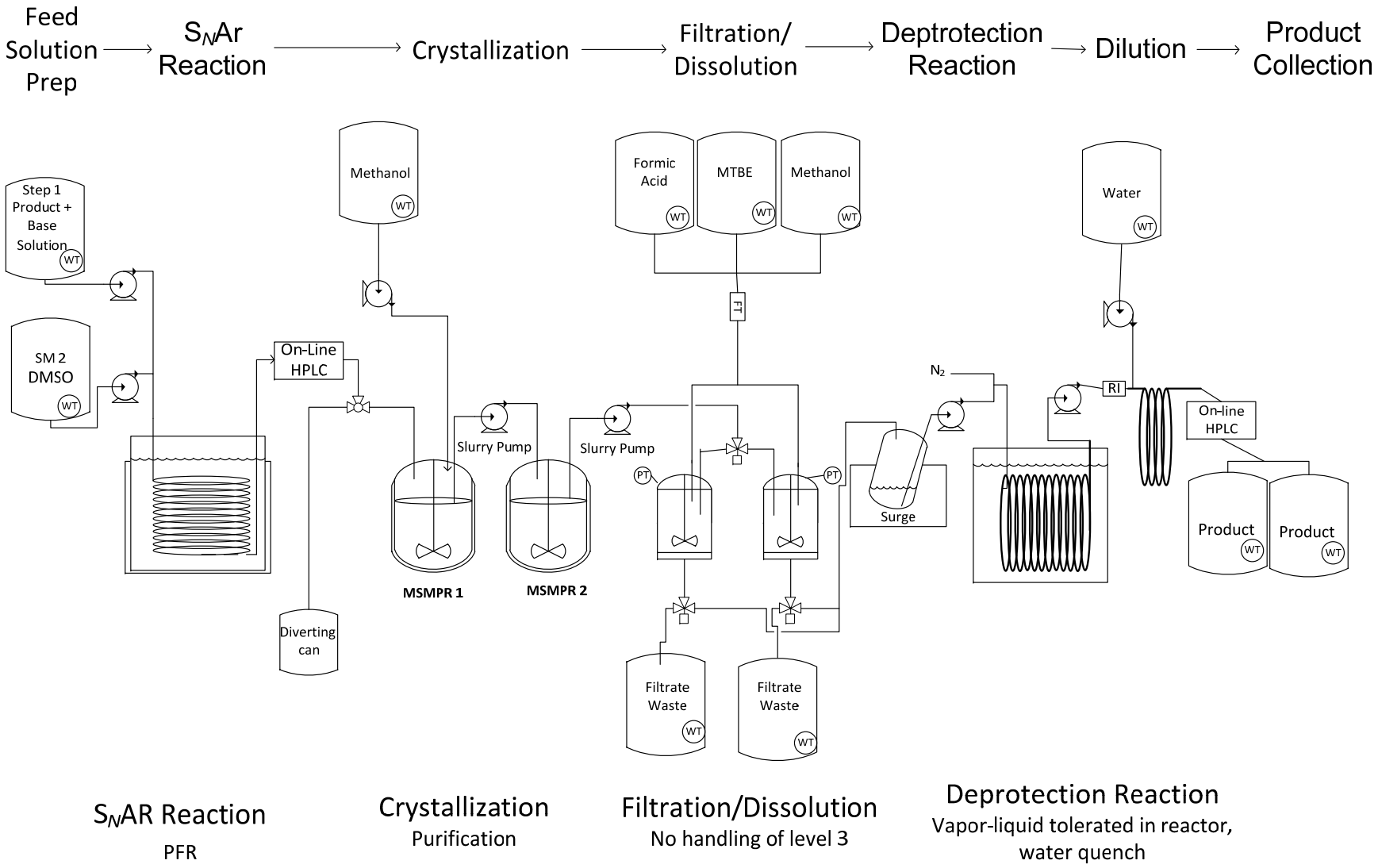


Figure S40. Equipment drawing for Stage 2 system.

Table S7. Possible Reasons for use of Surge Vessels in Continuous Processing.

Number	Driver
1	Decoupling the unit operations.
2	Simplifying operational logistics.
3	Simplifying startup and shutdown transitions.
4	Simplifying automation and control.
5	Allowing brief stoppages of individual unit operations for troubleshooting or scheduled cleanouts of crystallizers or slurry reactors.
6	Reducing the need for in-line redundancy of things like online process analytical technology (PAT)
7	Providing distinct points where the quality of the material can be assessed and forward processed or diverted (need 3 vessels in parallel).
8	Dampening out process disturbances.
9	Eliminating startup and shutdown transition waste in some circumstances
10	Simplifying investigation of the impact of procedural deviations

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