

Supporting Information for

Improved Continuous Flow Processing: Benzimidazole Ring Formation via Catalytic Hydrogenation of an Aromatic Nitro Compound

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1. HPLC Method for Analysis of hydrogenation of 4.

Column: Waters X-Terra MS C-18 3.5 μ m, 4.6 X 150 mm

Flow Rate: 1.0 ml/min

Solvent A: 10 mM aqueous ammonium bicarbonate, pH=9

Solvent B: Acetonitrile

Wavelength: 220 and 254 nm

Timetable:

<u>Time</u>	<u>%Solvent B</u>
0.00	0
15.00	90
17.00	90
17.01	0
19.00	0

Stop Time: 19 minutes

Post Time: 3 minutes

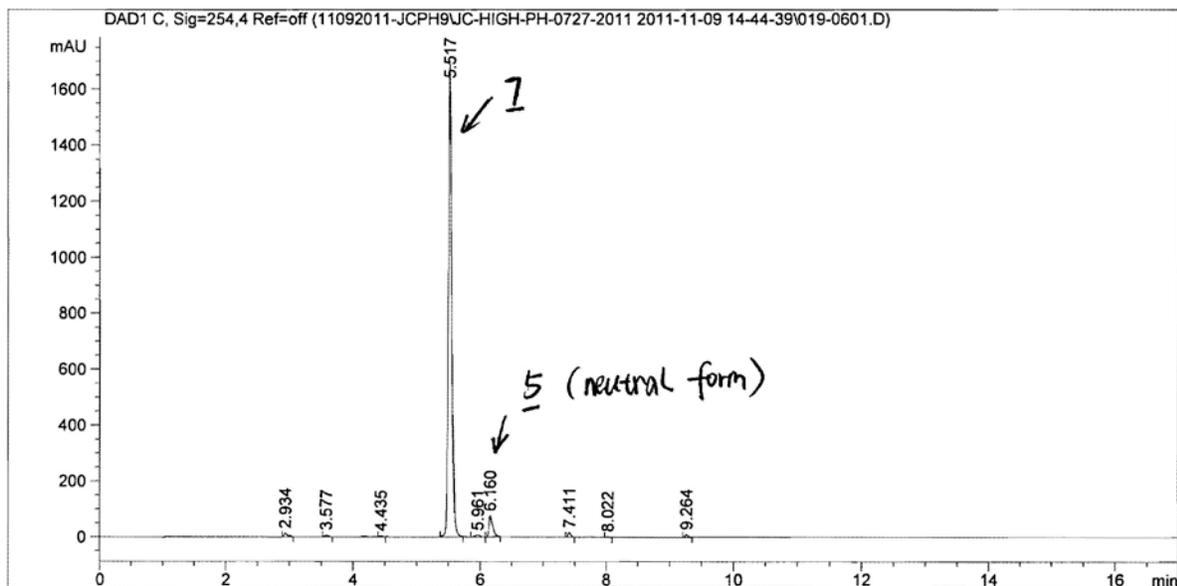
2. Representative HPLC spectrum for in-process analysis of flow hydrogenation of 4

Data File C:\CHEM32\1\DATA\11092011-JCPH9\JC-HIGH-PH-0727-2011 2011-11-09 14-44-39\019-0601.D
 Sample Name: 11-BMC-006x (Fract 16)

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=====
Acq. Operator   : jc                               Seq. Line :    6
Acq. Instrument : LC-0703-PD                       Location  : Vial 19
Injection Date  : 11/9/2011 4:43:53 PM           Inj       :    1
                                                    Inj Volume: 5 µl
Different Inj Volume from Sequence !   Actual Inj Volume : 2 µl
Acq. Method    : C:\Chem32\1\DATA\11092011-JCPH9\JC-HIGH-PH-0727-2011 2011-11-09 14-44-39\
                NEW-HIGHPH-JAN6-2011-MOD.M
Last changed   : 7/27/2011 10:34:33 AM by jc
Analysis Method : C:\Chem32\1\DATA\10312011-JCPH9\JC-HIGH-PH-0727-2011 2011-10-31 11-02-56\
                NEW-HIGHPH-JAN6-2011-MOD.M
Last changed   : 7/27/2011 10:34:33 AM by jc
Method Info    : new High pH metjod, new column installed on July27,2011
                cat No. 728975-902, s/n USHEP001445
                Agilent zorbax extended C18 600bar 4.6x1mm, 1.8um
    
```

Sample Info : Fraction # 16
 Ra-Ni (1st used Nov 7, 2011) 70 C, atmospheric, 5 mL/min,
 Cephalon Midi



Data File C:\CHEM32\1\DATA\11092011-JCPH9\JC-HIGH-PH-0727-2011 2011-11-09 14-44-39\019-0601.D
 Sample Name: 11-BMC-006x (Fract 16)

=====
 Area Percent Report
 =====

Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000
 Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 C, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.934	BB	0.0579	57.38243	13.70268	0.8601
2	3.577	BB	0.0527	25.33611	6.75968	0.3798
3	4.435	BB	0.0445	13.23274	4.60412	0.1983
4	5.517	BB	0.0541	6134.24854	1700.34949	91.9445 ← 1
5	5.961	BV	0.0796	38.28207	7.49327	0.5738
6	6.160	VB	0.0577	309.82016	75.75986	4.6438 ← 5 (neutral form)
7	7.411	BB	0.0471	52.28430	16.88376	0.7837
8	8.022	BB	0.0427	6.91345	2.46449	0.1036
9	9.264	BB	0.0492	34.18744	10.45136	0.5124

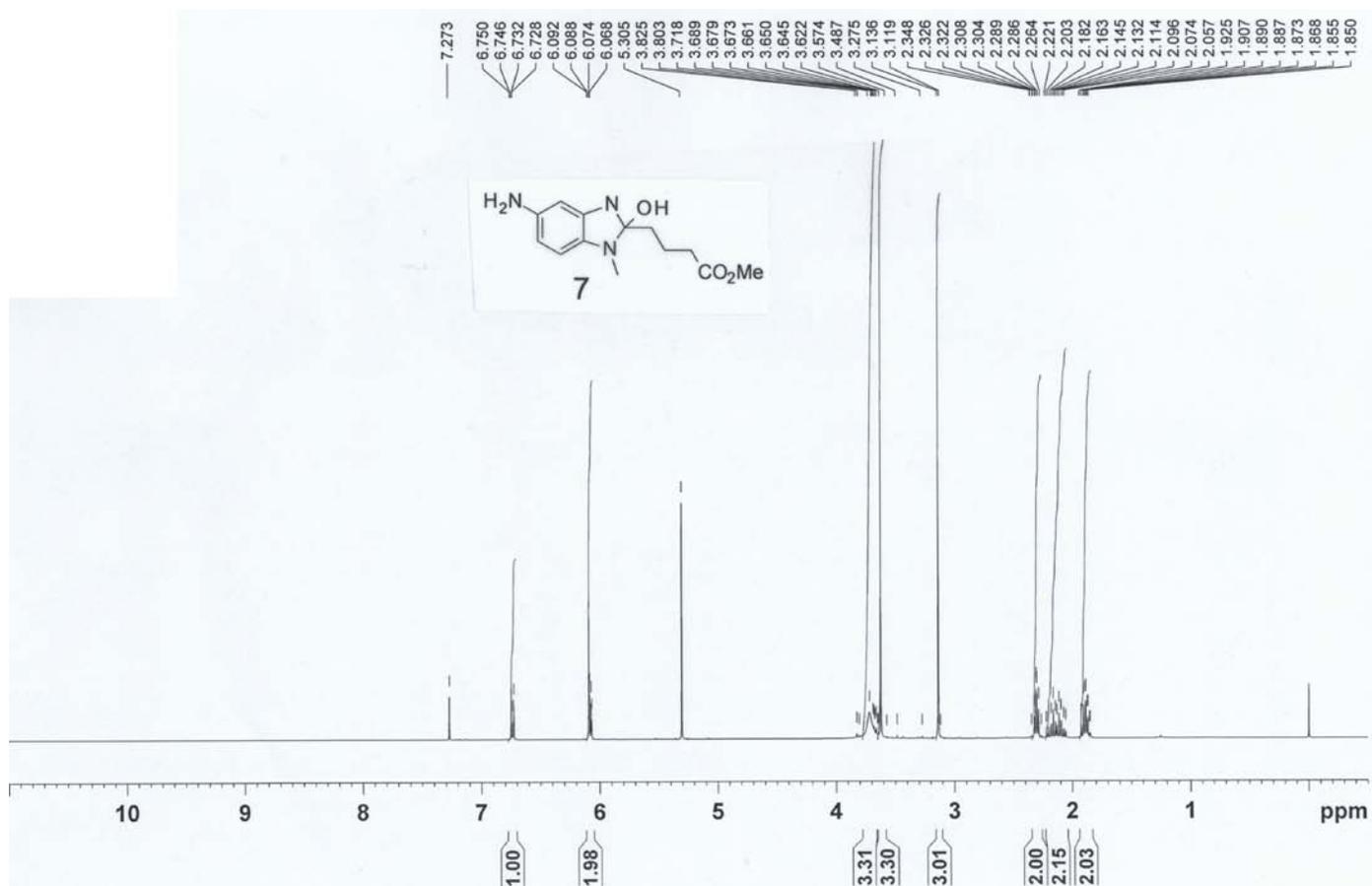
Totals : 6671.68725 1838.46871

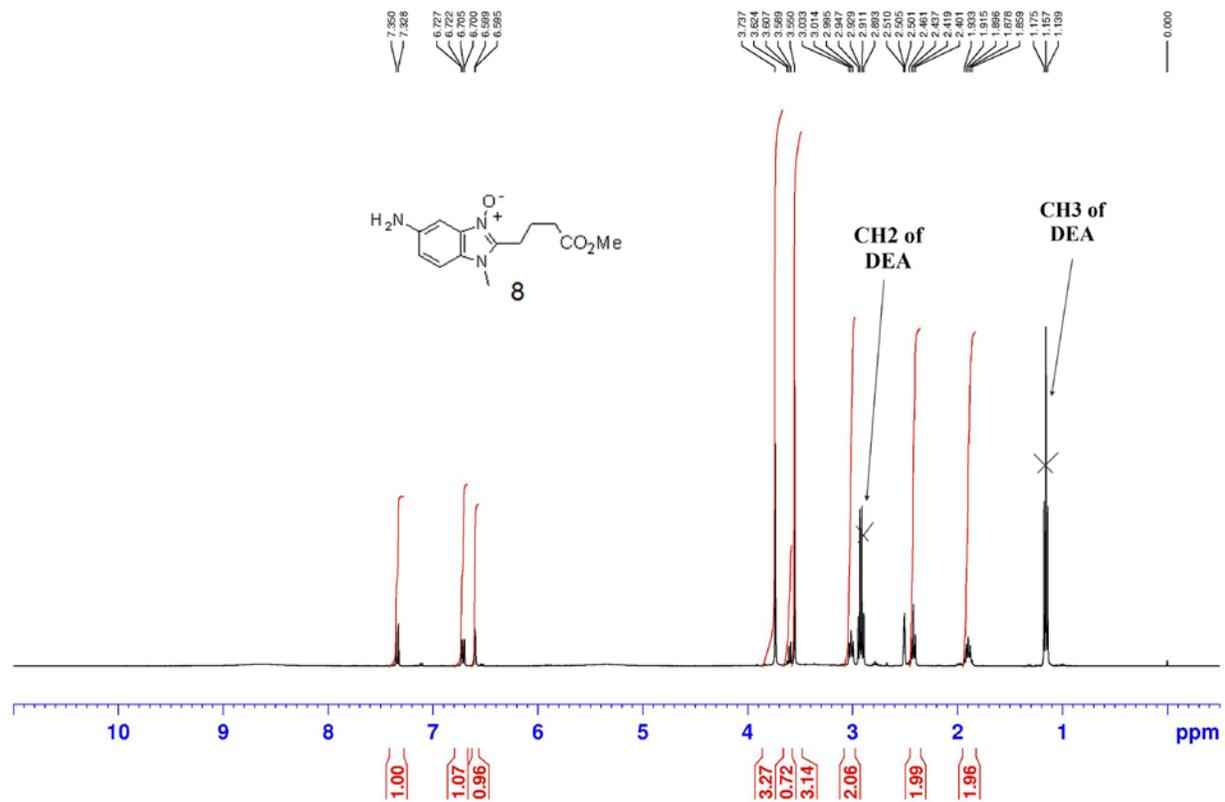
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 *** End of Report ***

Representative experiment for DoE study. Under nitrogen atmosphere, compound **4** (2.5 g, 7.69 mmol) was completely dissolved in methanol at varied concentrations at room temperature. The relevant reaction parameters, including temperature, pressure, liquid flow rate, and hydrogenation gas pressure, were selected on H-cube Midi[®], and the system was conditioned by pumping only pure solvent (methanol) through the flow reactor for at least 25 min. The production of hydrogen gas was measured using a gas buret to ensure that the desired reaction parameters were achieved, gaining a stable processing state. At this point, the substrate solution was introduced. The reaction was complete after a single passage through the apparatus, and the product stream was collected and analyzed by HPLC analysis.

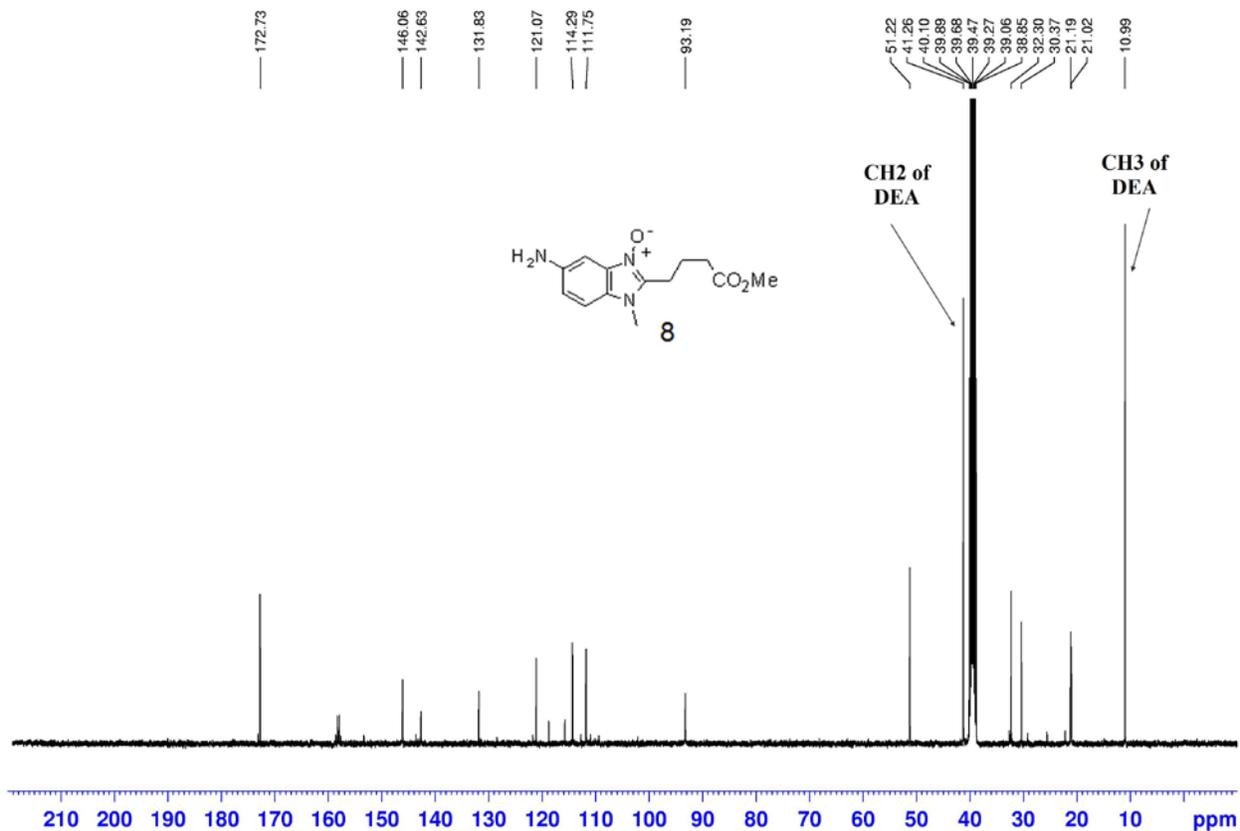
Raw data for DoE

Select	Std	Run	Factor 1 A:T C-deg	Factor 2 B:P bar	Factor 3 C:flow rate mL/min	Factor 4 D:Concentrat... M	Response 1 yielded A%
8		1	100.00	50.00	3.00	0.08	25.5
	1	2	20.00	1.00	0.30	0.01	98.7
	6	3	100.00	1.00	3.00	0.01	98.1
	2	4	100.00	1.00	0.30	0.08	89.3
	4	5	100.00	50.00	0.30	0.01	99
	9	6	60.00	25.50	1.65	0.04	97.2
	7	7	20.00	50.00	3.00	0.01	97.4
	3	8	20.00	50.00	0.30	0.08	72.5
	5	9	20.00	1.00	3.00	0.08	12.4

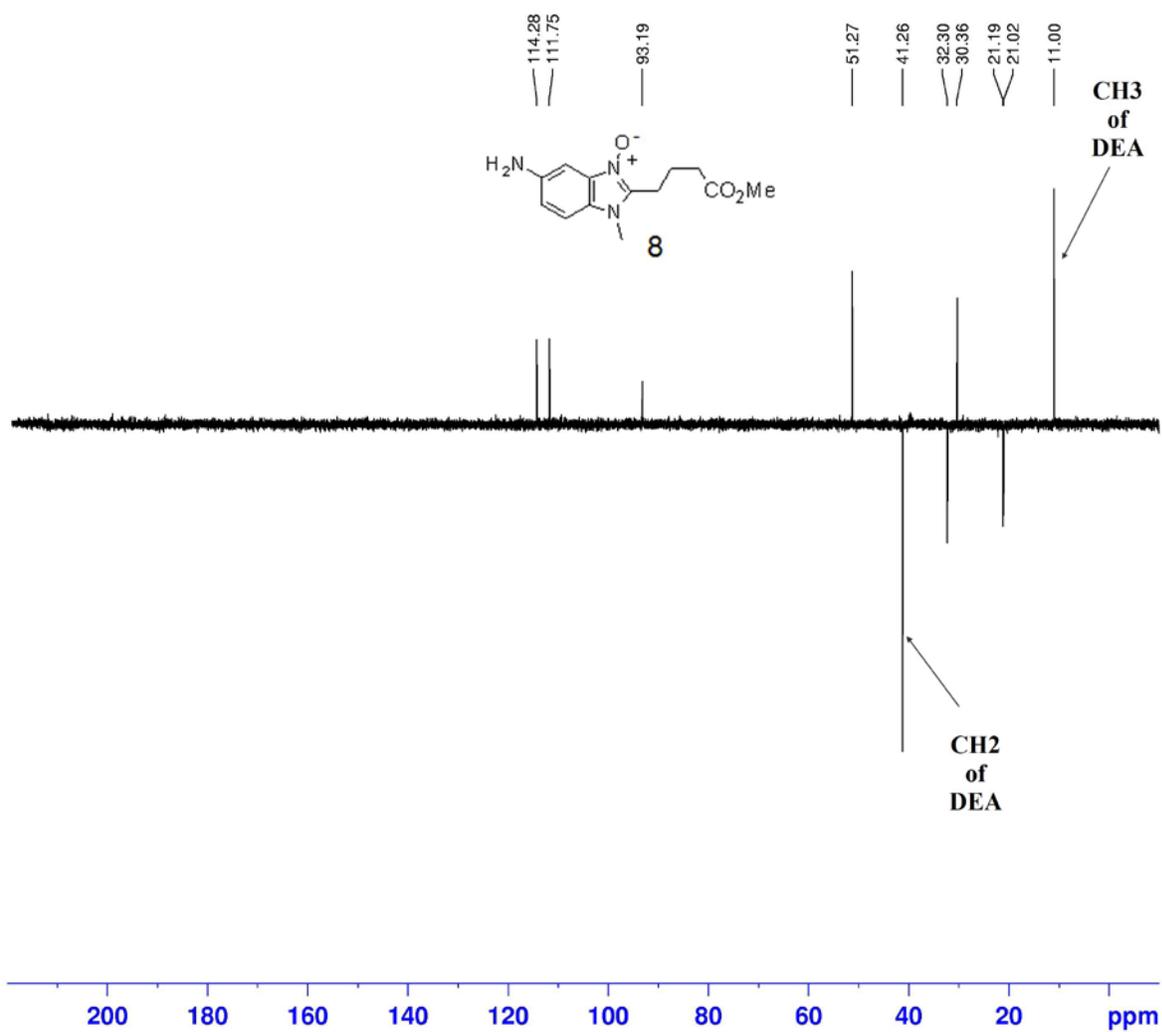




*DEA is the additive in the preparative supercritical fluid chromatography (SFC), which was used to isolate compound **8**.



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LC/MS was performed using an Agilent Ion Trap XCT LC-MSD equipped with an Agilent 1100 1100 binary pump and a photodiode array detector.

HPLC conditions: the same as that for hydrogenation of **4**.

MS conditions:

Ion polarity: Positive; Ion Source Type: ESI; Dry Temp: 300 °C; Nebulizer: 60 psi;

Dry gas 12 mL/min. Source: capillary 4000V, scan range 50–1200 Da.

