Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Supporting Information
for

Multi-Platform Synthesis of Ondansetron Featuring Process Intensification in Flow

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1. General Information

Methods:

All reactions were performed with commercially available reagents and solvents that were used as received unless otherwise specified. The reagents and solvents were purchased from Sigma Aldrich, Alfa Aesar, TCI, Combi-Blocks, Thermo Scientific, Oakwood Chemical or STREM Chemicals. Batch reactions were performed in round bottom flasks under an argon or nitrogen atmosphere unless otherwise noted. Flow reactions were performed using the commercially available components supplied from IDEX Health & Science, Upchurch Scientific, Swagelok Company, Harvard Apparatus, Syrris, Vapourtec, Zaiput Flow Technologies and Luzchem Research. Reactions were monitored by thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC) or proton nuclear magnetic resonance (^{1}H NMR). Concentration and removal of solvents was performed using a Buchi Rotavapor R-210. Column chromatography was carried out using a prepackaged Teledyne ISCO RediSep High-Performance silica gel column on a Biotage Isolera chromatography system.

Instrumentation:

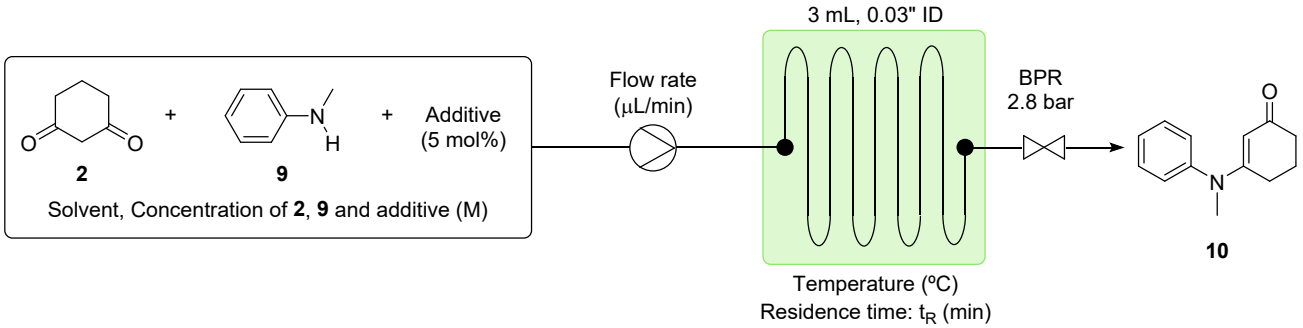
Proton nuclear magnetic resonance (^{1}H NMR) spectra and proton-decoupled carbon nuclear magnetic resonance (^{13}C{^{1}H} NMR) spectra were recorded on either a two-channel Bruker avance-III HD Nanobay spectrometer, a three-channel Bruker Avance Neo spectrometer, or a two-channel JEOL ECZ spectrometer at ambient temperature at operating frequencies of 500/400 MHz (^{1}H) or 125/100 MHz (^{13}C). Chemical shifts (δ) are reported in parts per million (ppm) relative to the solvent residual peak ($CDCl_3$; 7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, o = overlap), coupling constants (*J*) in Hertz (Hz), integration. 1,3,5-Trimethoxybenzene and dimethyl terephthalate were used as an internal standard for quantitative ^{1}H NMR spectroscopy. High-performance liquid chromatography (HPLC) analysis was performed using an Agilent 1200 series quaternary HPLC system with an Agilent Poroshell 120 EC-C18 2.7 μm, 4.6x50 mm column. The HPLC measurement conditions were as follows: flow rate: 1.000 mL/min, UV detection wavelength: 254 and 210 nm, mobile phase: [A] is 0.1% trifluoroacetic acid containing aqueous solution and [B] is 0.1% trifluoroacetic acid containing acetonitrile solution, gradient: linear gradient of 5% to 100% solvent [B] for 10 minutes was performed and 100% solvent [B] was maintained for 2 minutes and 5% solvent [B] was maintained for 2 minutes, column temperature: 35 °C, injection volume: 2.00 μL, sample preparation: an appropriate amount of samples was dissolved in 1 mL of 80% MeCN aq. High-resolution mass spectrometry data were acquired on a JEOL AccuTOF 4F LC-plus equipped with an ionSense DART (Direct Analysis in Real Time) source. IR spectra were recorded on a Bruker Alpha II FTIR spectrometer with a Diamond Crystal ATR (attenuated total reflectance) accessory and only significant absorptions were listed.

Abbreviations used:

aq = aqueous, eq = equivalent, DCE = 1,2-dichloroethane, MeCN = acetonitrile, DOX = 1,4-dioxane, EtOH = ethanol, EtOAc = ethyl acetate, AcOH = acetic acid, ID = inside diameter, BPR = back pressure regulator, t_R = residence time, *p*-TsOH·H_2O = *p*-toluenesulfonic acid monohydrate, $NaHCO_3$ = sodium hydrogencarbonate, $MgSO_4$ = magnesium sulfate, NMP = 1-methyl-2-pyrrolidinone, DMF = dimethylformaldehyde, DMA = dimethylacetaldehyde, DMSO = dimethylsulfoxide, THF = tetrahydrofurane, MeOH = methanol, IPA = 2-propanol, TFA = trifluoroacetic acid, Ac_2O = acetic anhydride, MsOH = methanesulfonic acid.

2. Experimental Procedures, Compound Characterization and Spectra

Reaction condition screening of step 1:



entry	reaction parameter						NMR yield (%)[a]	
	solvent	additive	conc. (M) [**2**, **9**, additive]	temp. (°C)	t_R (min)	flow rate (μL/min)	**9**	**10**
1	DCE	*p*-TsOH·H_2O	0.2, 0.2, 0.01	110	30	100	14	79
2[b]	DCE	*p*-TsOH·H_2O	0.2, 0.2, 0.01	130	30	100	15	79
3[b]	DCE	*p*-TsOH·H_2O	0.2, 0.2, 0.01	130	60	50	11	81
4	MeCN	*p*-TsOH·H_2O	0.2, 0.2, 0.01	110	30	100	30	61
5[b]	EtOH	*p*-TsOH·H_2O	0.2, 0.2, 0.01	110	30	100	64	25
6	DOX	*p*-TsOH·H_2O	0.2, 0.2, 0.01	110	30	100	21	70
7	AcOH	*p*-TsOH·H_2O	0.2, 0.2, 0.01	110	30	100	2.7	97
8	AcOH	-	0.2, 0.2, -----	110	30	100	6.7	90
9	AcOH	-	0.24, 0.2, -----	110	30	100	2.3	96
10	AcOH	-	1.2, 1.0, -----	110	30	100	2.3	94
11	AcOH	-	1.2, 1.0, -----	110	5	600	2.7	97
12	AcOH	-	2.4, 2.0, -----	110	5	600	3.3	96

13	AcOH	-	2.4, 2.0, -----	120	5	600		4.0	96
14	AcOH	-	2.4, 2.0, -----	130	5	600		4.0	94
15	AcOH	*p*-TsOH·H_2O	2.2, 2.0, -----	110	5	600		5.3	91

[a]The NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard. [b]6.9 bar of the back pressure was applied.

Procedure for entries 1-9:
N-Methylaniline **9** (0.54 mL, 5 mmol, 1 eq), 1,3-cyclohexanedione **2** (561 mg, 5 mmol, 1 eq or 673 mg, 6 mmol, 1.2 eq) and *p*-TsOH·H_2O (0 mg, 0 mmol, 0 eq or 48 mg, 0.25 mmol, 0.05 eq) were added to a 25 mL volumetric flask. The designated solvent was added to the 25 mL line of the volumetric flask.

The reactor was constructed from the fluorinated ethylene propylene (FEP) tubing (1/16'' outside diameter, 0.03'' inside diameter, 658 cm, 3 mL), the complementary polyether ether ketone (PEEK) fittings, and the Upchurch Scientific's back pressure regulator (40 psi, 2.8 bar or 100 psi, 6.9 bar).

The prepared reactant solutions were pumped into the reactor by the Syrris Asia pump at the designated flow rate (50 or 100 μL/min). The reaction tube was immersed in an oil bath and heated at the designated temperature (110 or 130 °C). The reaction was equilibrated for 90 or 180 minutes, which was three times longer than the residence time. After the equilibration, 6 mL of the solution was collected for 60 or 120 minutes, depending on the flow rate. To the collected solution, was added 1,3,5-trimethoxybenzene (67.3 mg, 0.4 mmol, 1/3 eq of the collected reaction scale) as a standard compound. 0.1 mL of this solution was washed with 5% $NaHCO_3$ aq (6 mL), extracted with EtOAc three times (6+6+6 mL), dried over $MgSO_4$, filtered, concentrated and analyzed by ^{1}H NMR. The methoxy peak (3.77 ppm, 9H) or the aromatic peak (6.08 ppm, 3H) of 1,3,5-trimethoxybenzene was used as a reference. The methyl peak (3.24 ppm, 3H) of the target compound **10**[1] and the methyl peak (2.84 ppm, 3H) of *N*-methylaniline **9** were used to determine the NMR yields.

Procedure for entries 10-11:
N-Methylaniline **9** (2.71 mL, 25 mmol, 1 eq), 1,3-cyclohexanedione **2** (3.36 g, 30 mmol, 1.2 eq) were added to a 25 mL volumetric flask. AcOH was added to the 25 mL line of the volumetric flask.

The reactor was constructed from the fluorinated ethylene propylene (FEP) tubing (1/16'' outside diameter, 0.03'' inside diameter, 658 cm, 3 mL), the complementary polyether ether ketone (PEEK) fittings, and the Upchurch Scientific's back pressure regulator (40 psi, 2.8 bar).

The prepared reactant solutions were pumped into the reactor by the Syrris Asia pump at the designated flow rate (100 or 600 μL/min). The reaction tube was immersed in an oil bath and heated at the designated temperature (110 °C). The reaction was equilibrated for 15 or 90 minutes, which was three times longer than the residence time. After the equilibration, 6 mL of the solution was collected for 10 or 60 minutes, depending on the flow rate. To the collected solution, was added 1,3,5-trimethoxybenzene (336 mg, 2.0 mmol, 1/3 eq of the collected reaction scale) as a standard compound. 0.1 mL of this solution was washed with 5% $NaHCO_3$ aq (6 mL), extracted with EtOAc three times (6+6+6 mL), dried over $MgSO_4$, filtered, concentrated and analyzed by ^1H NMR. The methoxy peak (3.77 ppm, 9H) or the aromatic peak (6.08 ppm, 3H) of 1,3,5-trimethoxybenzene was used as a reference. The methyl peak (3.24 ppm, 3H) of the target compound **10**[1] and the methyl peak (2.84 ppm, 3H) of *N*-methylaniline **9** were used to determine the NMR yields.

Procedure for entries 12-14:

N-Methylaniline **9** (5.42 mL, 50 mmol, 1 eq), 1,3-cyclohexanedione **2** (6.73 g, 60 mmol, 1.2 eq) were added to a 25 mL volumetric flask. AcOH was added to the 25 mL line of the volumetric flask.

The reactor was constructed from the fluorinated ethylene propylene (FEP) tubing (1/16'' outside diameter, 0.03'' inside diameter, 658 cm, 3 mL), the complementary polyether ether ketone (PEEK) fittings, and the Upchurch Scientific's back pressure regulator (40 psi, 2.8 bar).

The prepared reactant solutions were pumped into the reactor by the Syrris Asia pump at the designated flow rate (600 μL/min). The reaction tube was immersed in an oil bath and heated at the designated temperature (110, 120 or 130 °C). The reaction was equilibrated for 15 minutes, which was three times longer than the residence time. After the equilibration, 6 mL of the solution was collected for 10 minutes. To the collected solution, was added 1,3,5-trimethoxybenzene (673 mg, 4.0 mmol, 1/3 eq of the collected reaction scale) as a standard compound. 0.1 mL of this solution was washed with 5% $NaHCO_3$ aq (6 mL), extracted with EtOAc three times (6+6+6 mL), dried over $MgSO_4$, filtered, concentrated and analyzed by ^1H NMR. The methoxy peak (3.77 ppm, 9H) or the aromatic peak (6.08 ppm, 3H) of 1,3,5-trimethoxybenzene was used as a reference. The methyl peak (3.24 ppm, 3H) of the target compound **10**[1] and the methyl peak (2.84 ppm, 3H) of *N*-methylaniline **9** were used to determine the NMR yields.

Procedure for entry 15:

N-Methylaniline **9** (5.42 mL, 50 mmol, 1 eq), 1,3-cyclohexanedione **2** (6.17 g, 55 mmol, 1.1 eq) and *p*-TsOH·H_2O (476 mg, 2.5 mmol, 0.05 eq) were added to a 25 mL volumetric flask. AcOH was added to the 25 mL line of the volumetric flask.

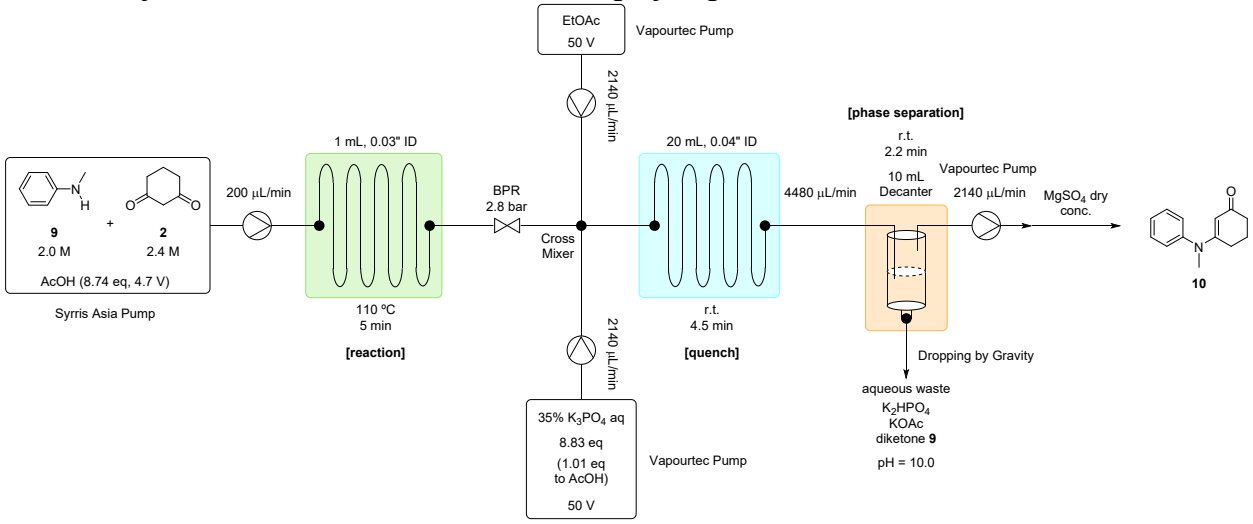
The reactor was constructed from the fluorinated ethylene propylene (FEP) tubing (1/16'' outside diameter, 0.03'' inside diameter, 658 cm, 3 mL), the complementary polyether ether ketone (PEEK) fittings, and the Upchurch Scientific's back pressure regulator (40 psi, 2.8 bar).

The prepared reactant solutions were pumped into the reactor by the Syrris Asia pump at the designated flow rate (600 μL/min). The reaction tube was immersed in an oil bath and heated at the designated temperature (110 °C). The reaction was equilibrated for 15 minutes, which was three times longer than the residence time. After the equilibration, 6 mL of the solution was collected for 10 minutes. To the collected solution, was added 1,3,5-trimethoxybenzene (673 mg, 4 mmol, 1/3 eq of the collected reaction scale) as a standard compound. 0.1 mL of this solution was washed with 5% $NaHCO_3$ aq (6 mL), extracted with EtOAc three times (6+6+6 mL), dried over $MgSO_4$, filtered, concentrated and analyzed by ^1H NMR. The methoxy peak (3.77 ppm, 9H) or the aromatic peak (6.08 ppm, 3H) of 1,3,5-trimethoxybenzene was used as a reference. The methyl peak (3.24 ppm, 3H) of the target compound **10**[1] and the methyl peak (2.84 ppm, 3H) of *N*-methylaniline **9** were used to determine the NMR yields.

Caution:

The target compound **10** tends to be lost into the aqueous phase during the extraction process and *N*-methylaniline **9** can be evaporated during the concentration process. These factors can affect the reproducibility of the experiments.

Procedure for continuous reaction and work-up of step 1:



time (hr)	NMR yield (%)[a]	
	9	**10**
0	3.3	94
1	3.0	96
2	2.7	97

3		3.0	95
4		3.7	96
5		3.7	96
6		3.3	95
7		3.0	97

[a]The NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard.

N-Methylaniline **9** (21.67 mL, 200 mmol, 1 eq), 1,3-cyclohexanedione **2** (26.91 g, 240 mmol, 1.2 eq) were added to a 100 mL volumetric flask. AcOH was added to the 100 mL line of the volumetric flask.

The reactor was constructed from the fluorinated ethylene propylene (FEP) tubing (1/16'' outside diameter, 0.03'' inside diameter, 219 cm, 1 mL), the complementary polyether ether ketone (PEEK) fittings, and the Upchurch Scientific's back pressure regulator (40 psi, 2.8 bar).

The quenching and extraction tube was constructed from the perfluoroalkoxy (PFA) tubing (1/16'' outside diameter, 0.04'' inside diameter, 2467 cm, 20 mL), and the complementary polyether ether ketone (PEEK) fittings.

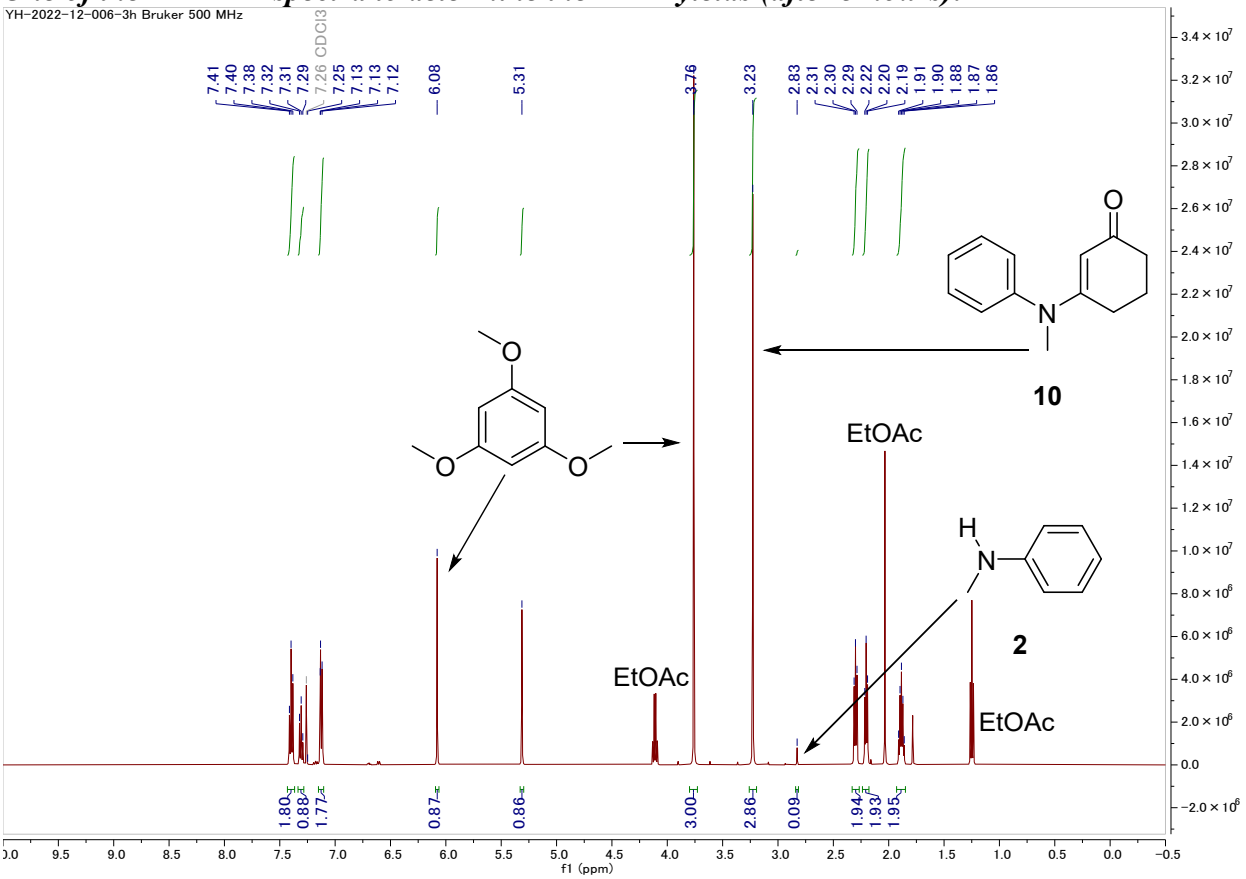
The decanter was constructed from the 10 mL glass syringe, the complementary polyether ether ketone (PEEK) fittings, and the rubber septa.

The prepared reactant solutions were pumped into the reactor by the Syrris Asia pump at the designated flow rate (200 μL/min). The reaction tube was immersed in an oil bath and heated at the designated temperature (110 °C). 35% K_3PO_4 aq and EtOAc were pumped into the quenching and extraction tube by the Vapourtec pumps at the designated flow rate (2.14 mL/min). The organic phase was pumped out of the decanter into the storage tank at the designated flow rate (2.14-2.19 mL/min). The system was equilibrated for 36 minutes, which was three times longer than the residence time. After the equilibration, 32.1 mL of the organic phase was collected for 15 minutes every hour. To each of the collected solution, was added 1,3,5-trimethoxybenzene (336.4 mg, 2 mmol, 1/3 eq of the collected reaction scale) as a standard compound. This solution was dried over $MgSO_4$, filtered, concentrated and analyzed by ^1H NMR. The methoxy peak (3.77 ppm, 9 H) or the aromatic peak (6.08 ppm, 3 H) of 1,3,5-trimethoxybenzene was used as a reference. The methyl peak (3.24 ppm, 3H) of the target compound **10**[1] and the methyl peak (2.84 ppm, 3H) of *N*-methylaniline **9** were used to determine the NMR yields.

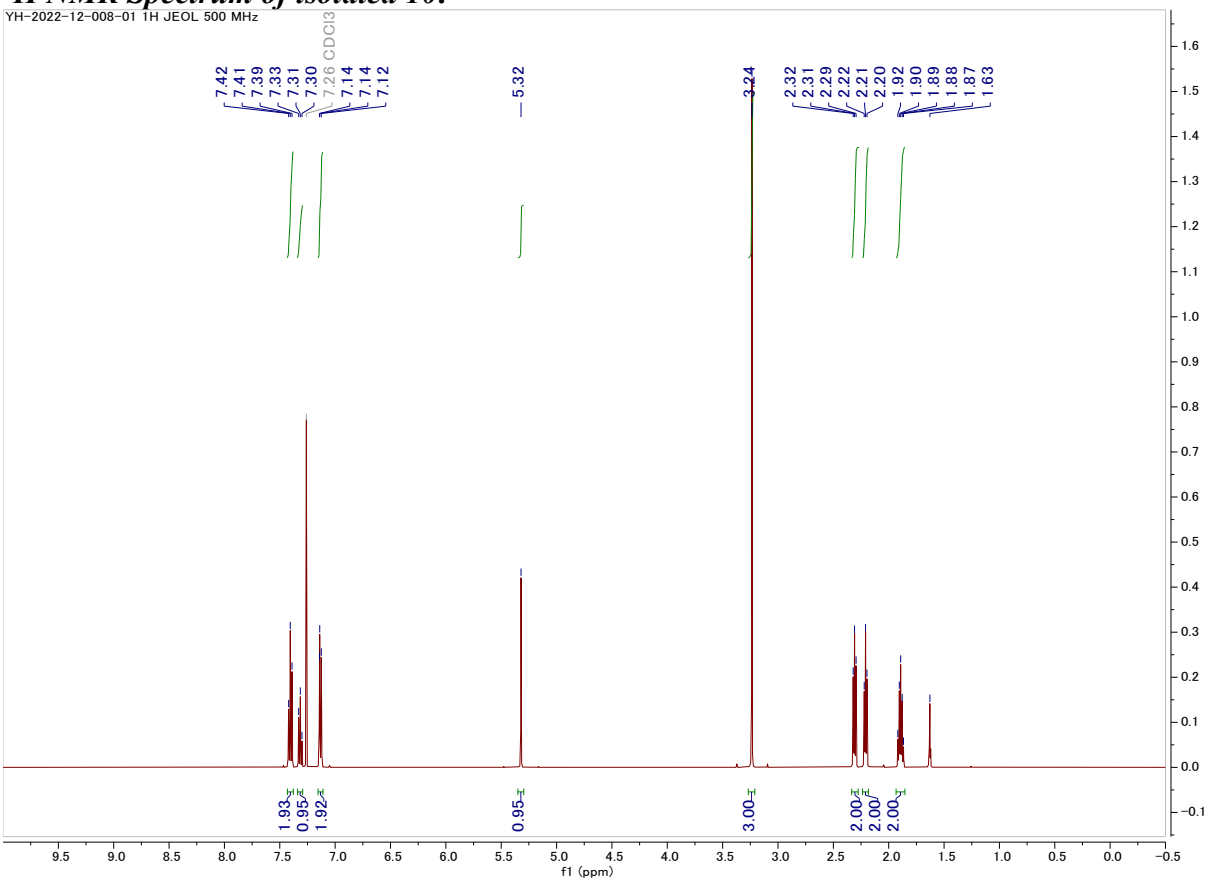
To the 674 mL of the organic phase which was collected for 315 minutes, was added $MgSO_4$ (6.7 g, 0.01 W). The mixture, which could contain 25.41 g of the target compound **10** theoretically, was filtered, washed with EtOAc and concentrated to 31.10 g. To the residue, was

added hexane (127 mL, 5 V). The solution was concentrated to 28.63 g. To the residue, was added hexane (127 mL, 5 V). The solution was concentrated to 30.51 g. To the residue, the seed crystal was added if necessary. To the solid, was added hexane (127 mL, 5 V). The slurry was stirred at 5 °C for 1 h. The slurry was filtered, washed with cold hexane (127 mL, 5 V), and air-dried overnight to afford the title compound **10**[1] (24.115 g, 94.9% yield, 97.62 pa%, yellow solid, MWL loss: 1.4%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41 (t, J = 7.7 Hz, 2H), 7.31 (t, J = 7.4 Hz, 1H), 7.15-7.11 (m, 2H), 5.32 (s, 1H), 3.24 (s, 3H), 2.31 (t, J = 6.5 Hz, 2H), 2.21 (t, J = 6.2 Hz, 2H), 1.89 (p, J = 6.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.7, 165.1, 145.5, 129.8 (2C), 127.6, 127.3 (2C), 100.7, 40.9, 36.3, 28.7, 22.7. IR (neat) ν: 3042, 2938, 2891, 1610, 1556 cm^{-1}. HRMS (DART) m/z: calcd for $C_{13}H_{16}NO^+$ [(M+H)$^+$] 202.1226, found 202.1220.

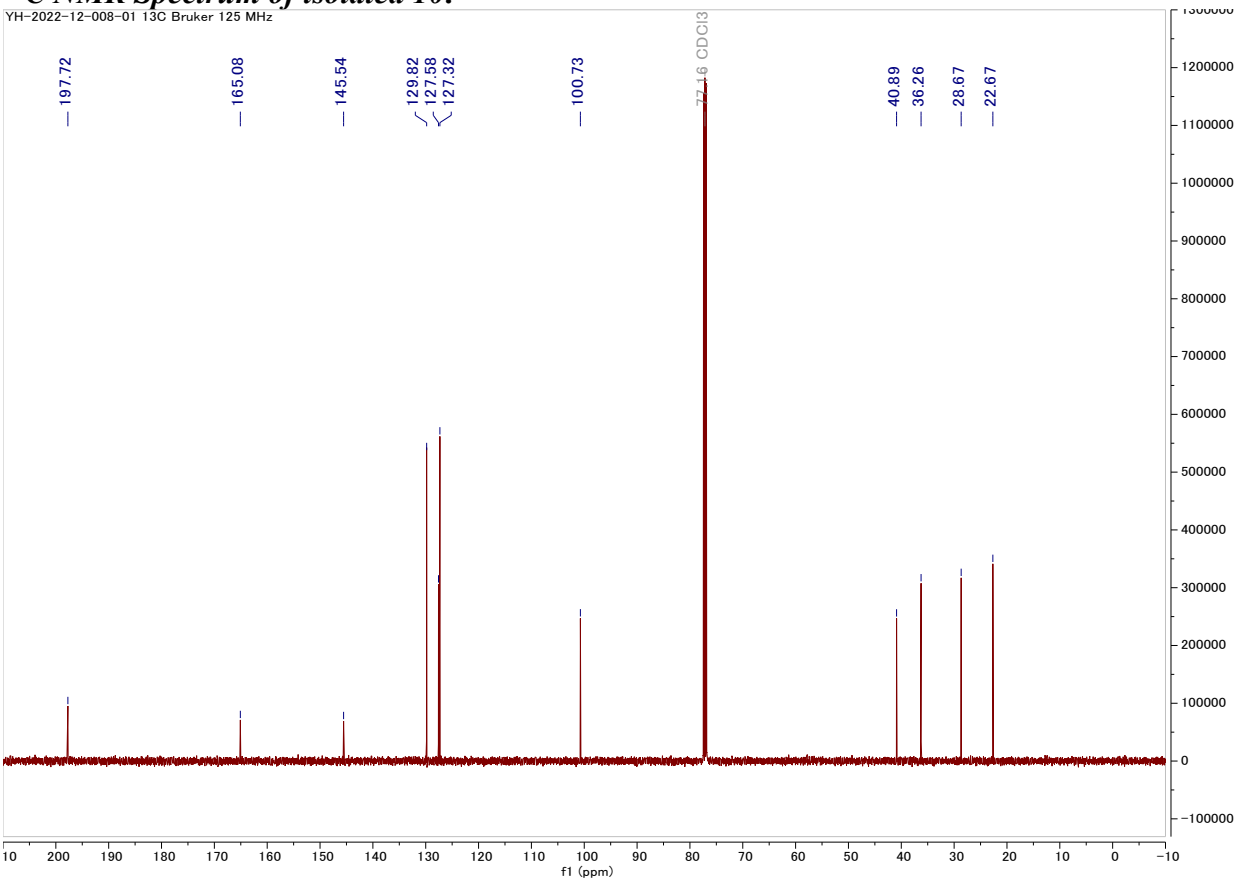
One of the ^{1}H NMR spectra to determine the NMR yields (after 3 hours):



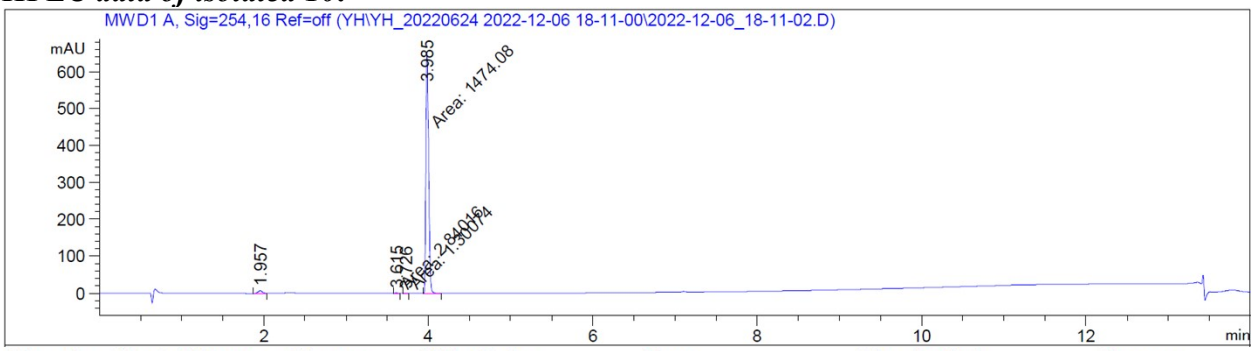
^{1}H NMR Spectrum of isolated 10:



^{13}C NMR Spectrum of isolated 10:

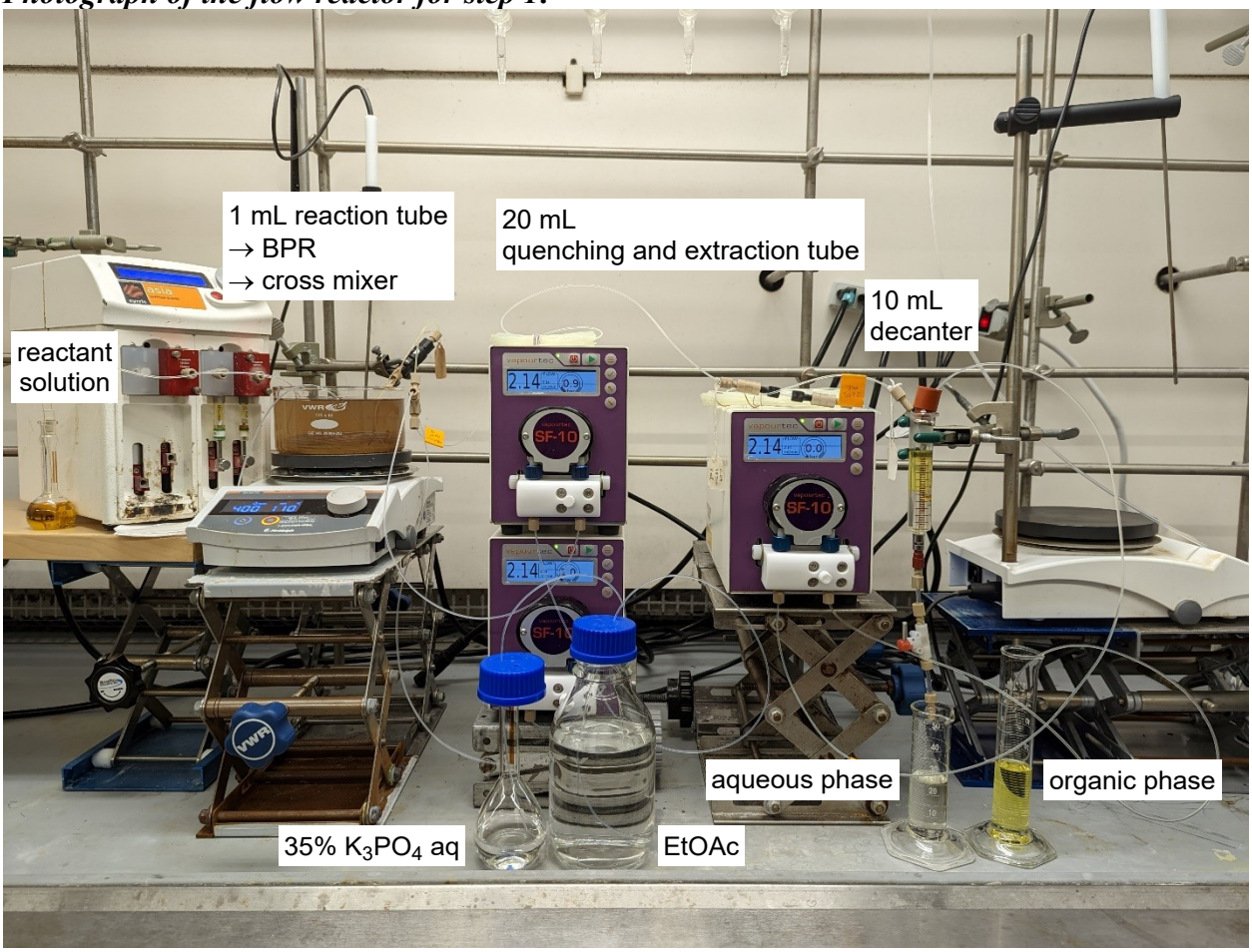


HPLC data of isolated 10:

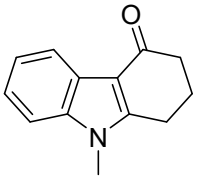
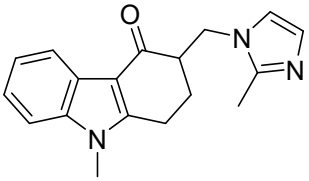


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.957	BV	0.0661	31.78567	7.54864	2.1050
2	3.615	MM	0.0323	2.84016	1.46593	0.1881
3	3.726	MM	0.0325	1.30074	6.67698e-1	0.0861
4	3.985	MM	0.0374	1474.07886	657.73804	97.6208

Photograph of the flow reactor for step 1:

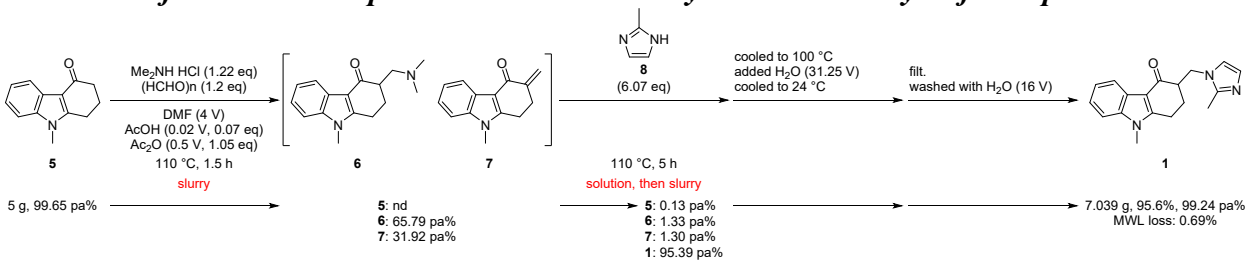


Solubility of the substrate 5 and ondansetron 1:

Solvents	**Solubility (Substrate 5)**  **5**	**Solubility (ondansetron 1)**  **1**
NMP	3.49 g/100 g NMP	2.29 g/100 g NMP
DMF	2.46 g/100 g DMF	1.27 g/100 g DMF
DMA	2.53 g/100 g DMA	1.22 g/100 g DMA

DMSO	1.59 g/100 g DMSO	0.82 g/100 g DMSO
THF	0.97 g/100 g THF	0.25 g/100 g THF
MeCN	1.07 g/100 g MeCN	0.35 g/100 g MeCN
MeOH	0.59 g/100 g MeOH	0.67 g/100 g MeOH
IPA	0.23 g/100 g IPA	0.25 g/100 g IPA
TFA	>15.7 g/100 g TFA	>18.7 g/100 g TFA
AcOH	3.73 g/100 g AcOH	>27.3 g/100 g AcOH
Ac_2O	0.57 g/100 g Ac_2O	Swelled, could not be filtered
Toluene	0.37 g/100 g Toluene	0.023 g/100 g Toluene
DCE	2.65 g/100 g DCE	0.53 g/100 g DCE

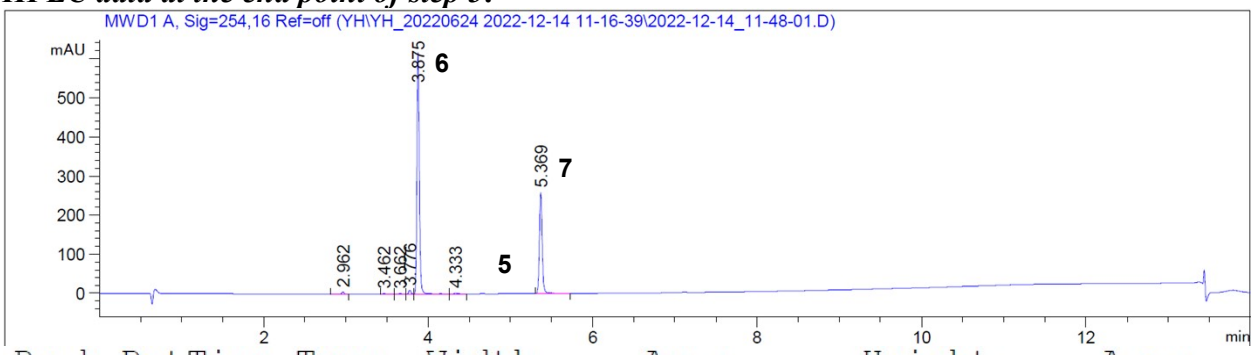
Procedure of the batch one-pot condition invented by Hesoun and Hykl[2] for step 3 and 4:



To a 300 mL round bottomed flask, were added the substrate **5** (5.00 g, 25.09 mmol, 1 eq), dimethylamine hydrochloride (2.50 g, 30.61 mmol, 1.22 eq), paraformaldehyde (904 mg, 30.11 mmol, 1.20 eq), DMF (20 mL, 4 V), AcOH (0.1 mL, 1.76 mmol, 0.07 eq), and Ac_2O (2.49 mL, 26.35 mmol, 1.05 eq, 0.5 V) in this order. The reaction mixture was warmed to 110 °C and stirred at 110 °C for 1.5 hours. To the reaction mixture, was added 2-methylimidazole **8** (12.51 g, 152.32 mmol, 6.07 eq). The reaction mixture was stirred at 110 °C for 5 hours. The reaction mixture was cooled to 100 °C. To the mixture, was added H_2O (156.25 mL, 31.25 V) over 10 minutes. The reaction mixture was cooled to r.t., filtered and washed with H_2O (80 mL, 16 V).

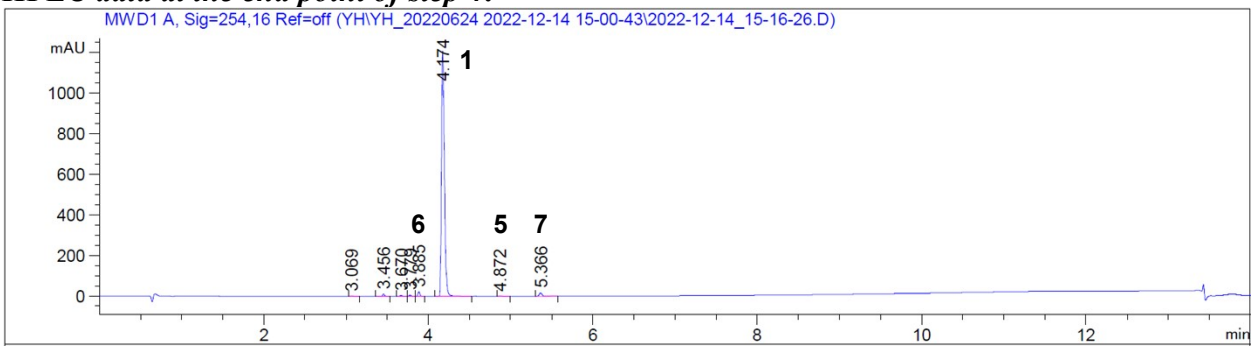
The solid was air-dried overnight to give ondansetron **1**[3] (7.039 g, 95.6% yield, 99.24 pa%, off-white solid, MWL loss: 0.69%).

HPLC data at the end point of step 3:



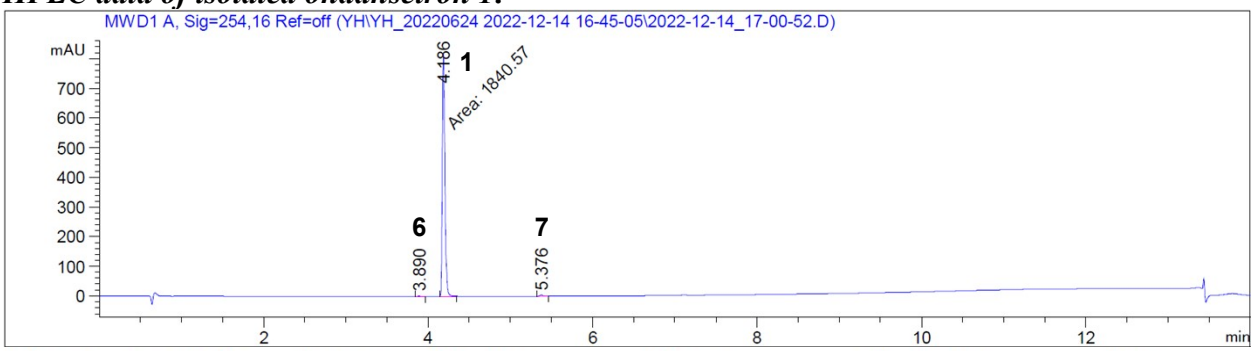
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.962	VB R	0.0288	11.49214	6.14242	0.5784
2	3.462	BV R	0.0298	3.72970	1.91132	0.1877
3	3.662	BB	0.0286	4.10604	2.21425	0.2066
4	3.776	BB	0.0282	18.57401	10.23405	0.9348
5	3.875	BV R	0.0327	1307.26282	616.86481	65.7910
6	4.333	BB	0.0372	7.50775	2.90043	0.3778
7	5.369	BV R	0.0376	634.32092	258.69705	31.9237

HPLC data at the end point of step 4:



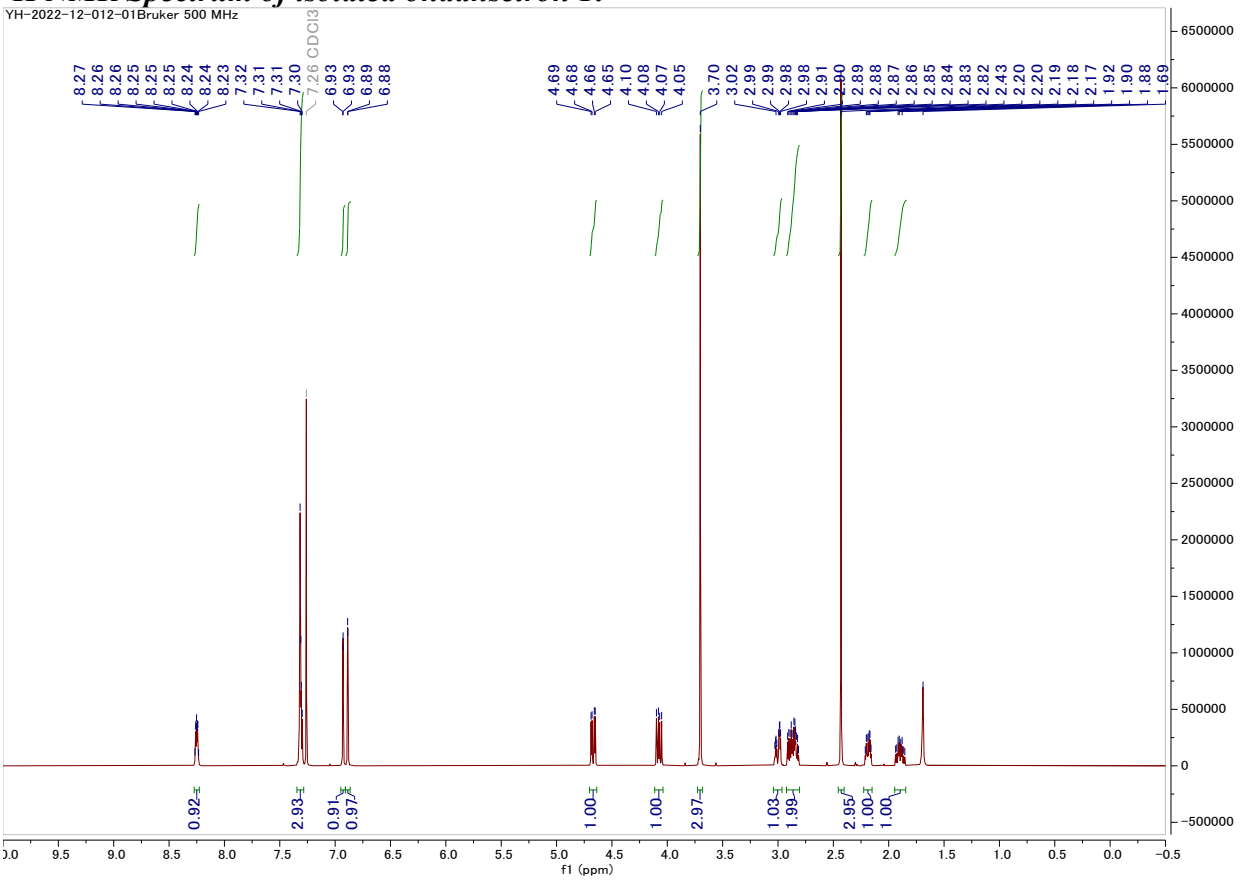
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.069	BV R	0.0289	7.96623	4.24664	0.2510
2	3.456	VB R	0.0286	23.74027	12.79580	0.7481
3	3.670	BV R	0.0347	13.94607	6.32046	0.4395
4	3.779	VB	0.0302	13.11312	6.89114	0.4132
5	3.885	BB	0.0300	42.05742	22.30237	1.3253
6	4.174	BV R	0.0392	3027.14038	1208.54138	95.3900
7	4.872	VB	0.0351	4.15706	1.78651	0.1310
8	5.366	BV R	0.0390	41.31509	16.61780	1.3019

HPLC data of isolated ondansetron 1:

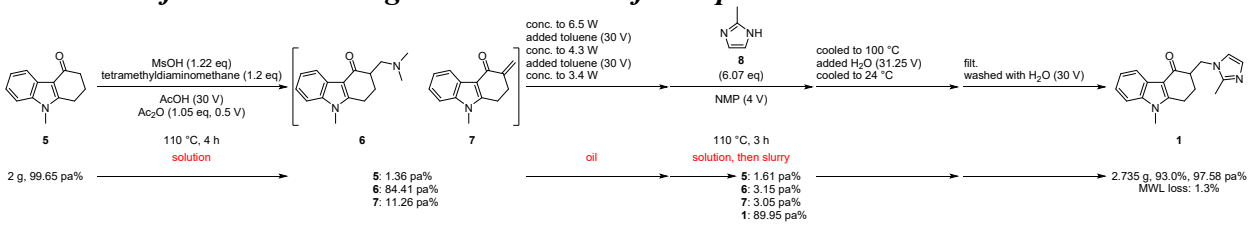


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.890	VB	0.0293	3.83831	2.00381	0.2070
2	4.186	MM	0.0373	1840.56738	822.49377	99.2390
3	5.376	BB	0.0374	10.27658	4.21708	0.5541

^{1}H NMR Spectrum of isolated ondansetron 1:



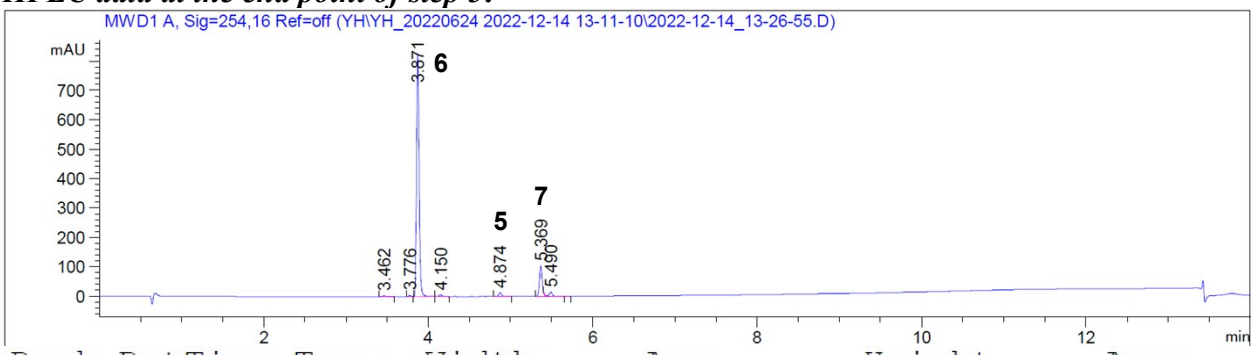
Procedure of the batch homogeneous condition for step 3 and 4:



To a 250 mL round bottomed flask, were added the substrate **5** (2.00 g, 10.04 mmol, 1 eq), and AcOH (60 mL, 30 V). The mixture was stirred at 24 °C for 10 minutes to make a homogeneous solution. To the solution, were added *N*,*N*,*N*,*N*-tetramethyldiaminomethane (1.64 mL, 12.04 mmol, 1.20 eq), MsOH (0.80 mL, 12.25 mmol, 1.22 eq), Ac_2O (1.00 mL, 10.54 mmol, 1.05 eq, 0.5 V) in this order. The reaction mixture was warmed to 110 °C and stirred at 110 °C for 4 hours. The reaction mixture was concentrated to 13.06 g, 6.53 W. To the residue, was added toluene (60 mL, 30 V). The reaction mixture was concentrated to 8.51 g, 4.26 W. To the residue, was added toluene (60 mL, 30 V). The reaction mixture was concentrated to 6.82 g, 3.41 W. To the residue, were added NMP (8 mL, 4 V) and 2-methylimidazole **8** (5.00 g, 60.93 mmol, 6.07 eq). The reaction mixture was warmed to 110 °C and stirred at 110 °C for 3 hours. The reaction mixture was cooled to 100 °C. To the mixture, was added H_2O (62.5 mL, 31.25 V) over 10 minutes. The reaction mixture was cooled to r.t., filtered and washed with H_2O (60 mL, 30 V).

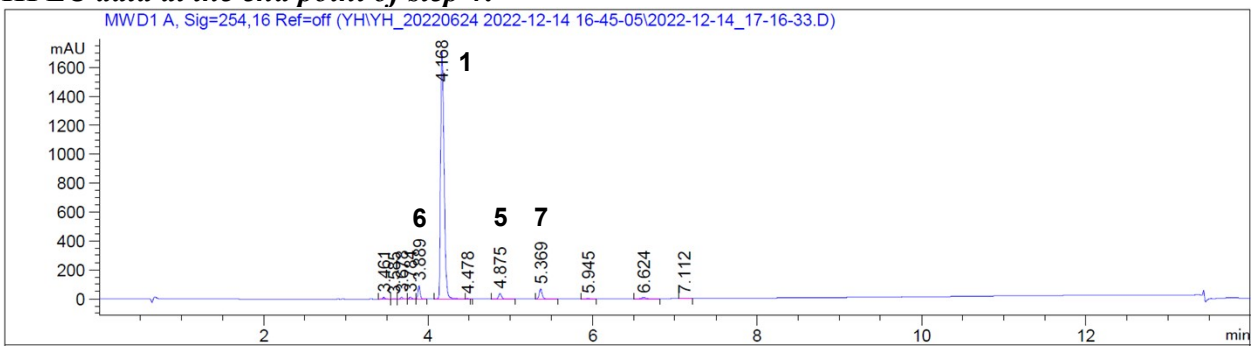
The solid was air-dried overnight to give ondansetron **1**[3] (2.735 g, 93.0% yield, 97.58 pa%, off-white solid, MWL loss: 1.3%).

HPLC data at the end point of step 3:



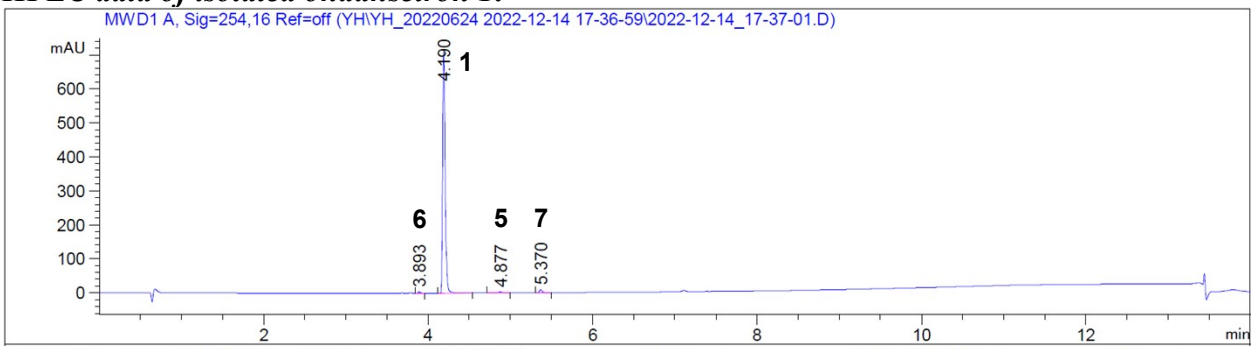
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.462	BB	0.0306	6.52084	3.36321	0.2987
2	3.776	BB	0.0270	7.09429	4.14243	0.3250
3	3.871	BV R	0.0349	1842.68030	829.82214	84.4108
4	4.150	BV R	0.0334	14.16360	6.51818	0.6488
5	4.874	BB	0.0360	29.62728	12.82197	1.3572
6	5.369	BV R	0.0371	245.73027	102.13350	11.2566
7	5.490	VV E	0.0395	37.17379	14.19628	1.7029

HPLC data at the end point of step 4:



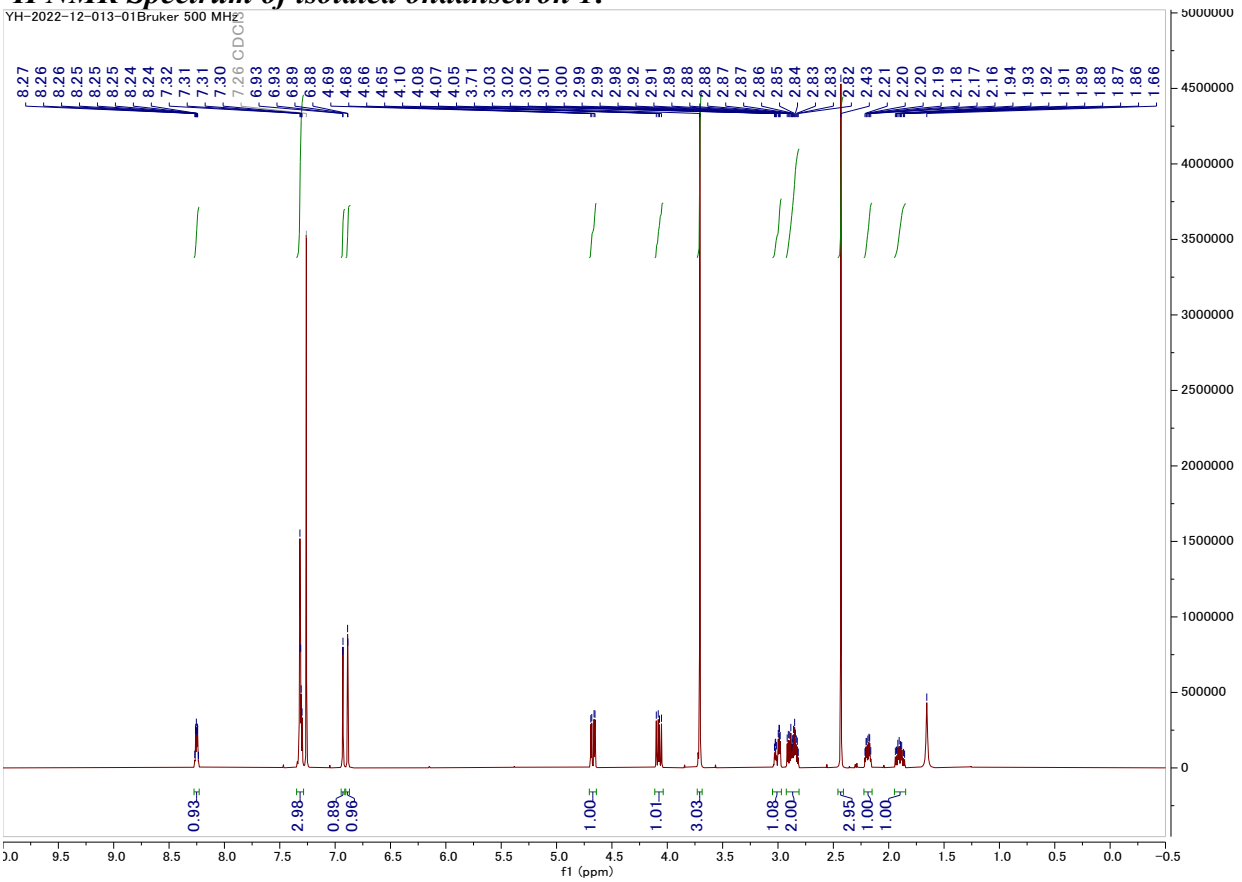
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.461	VB R	0.0292	22.53184	11.83943	0.4085
2	3.585	BB	0.0276	5.59639	3.16837	0.1015
3	3.678	BV R	0.0312	26.40295	13.25941	0.4786
4	3.784	BV R	0.0308	26.03684	12.73682	0.4720
5	3.889	VB	0.0291	173.73604	91.58176	3.1495
6	4.168	BV R	0.0457	4961.88086	1717.10291	89.9485
7	4.478	VB E	0.0292	4.46658	2.34788	0.0810
8	4.875	VV R	0.0361	88.95988	38.29840	1.6127
9	5.369	BV R	0.0377	168.11240	68.34435	3.0475
10	5.945	BB	0.0364	6.83746	2.80639	0.1239
11	6.624	BV R	0.0542	24.07673	6.82257	0.4365
12	7.112	BB	0.0500	7.72209	2.37225	0.1400

HPLC data of isolated ondansetron 1:

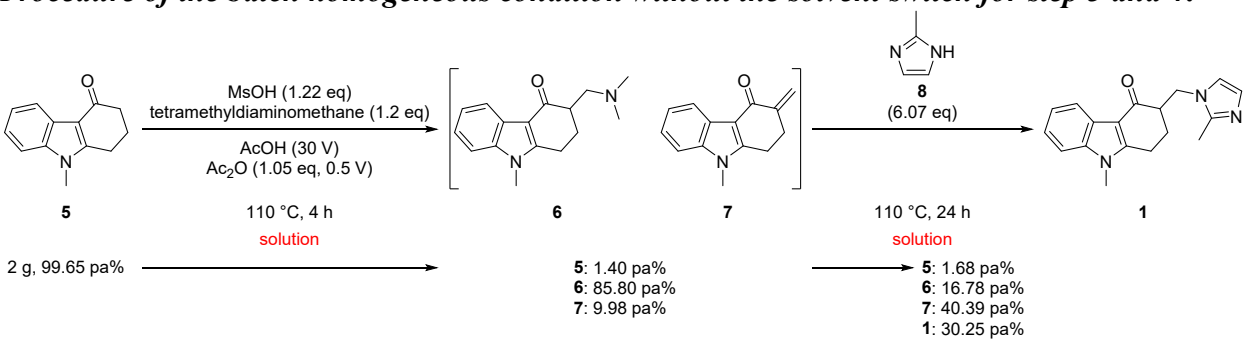


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.893	BB	0.0291	7.58967	4.00155	0.4739
2	4.190	BV R	0.0336	1562.67224	713.10742	97.5747
3	4.877	VB R	0.0399	9.09338	3.43326	0.5678
4	5.370	BB	0.0379	22.15879	8.95494	1.3836

^{1}H NMR Spectrum of isolated ondansetron 1:

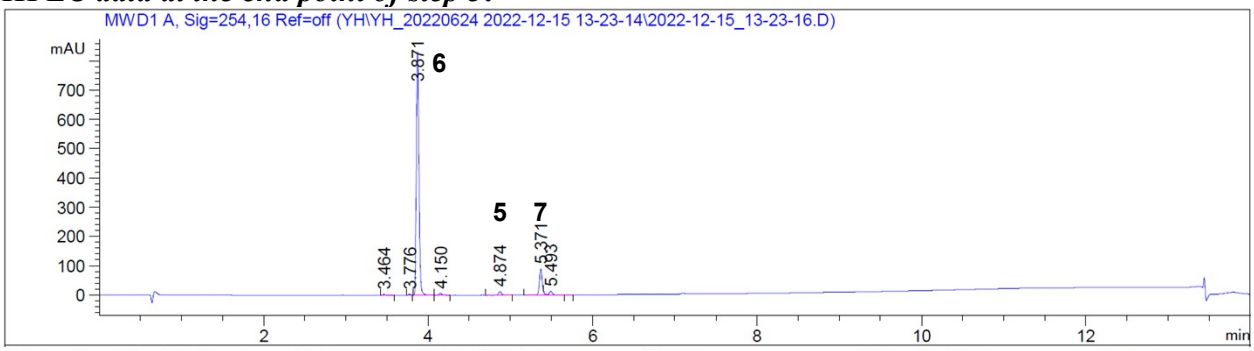


Procedure of the batch homogeneous condition without the solvent switch for step 3 and 4:



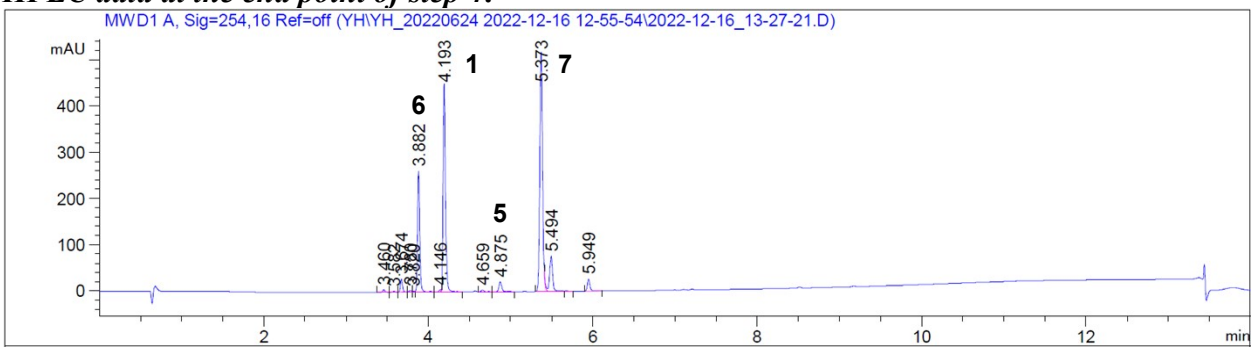
To a 250 mL round bottomed flask, were added the substrate **5** (2.00 g, 10.04 mmol, 1 eq), and AcOH (60 mL, 30 V). The mixture was stirred at 24 °C for 10 minutes to make a homogeneous solution. To the solution, were added *N*,*N*,*N*,*N*-tetramethyldiaminomethane (1.64 mL, 12.04 mmol, 1.20 eq), MsOH (0.80 mL, 12.25 mmol, 1.22 eq), Ac_2O (1.00 mL, 10.54 mmol, 1.05 eq, 0.5 V) in this order. The reaction mixture was warmed to 110 °C and stirred at 110 °C for 4 hours. To the reaction mixture, was added 2-methylimidazole **8** (5.00 g, 60.93 mmol, 6.07 eq). The reaction mixture was stirred at 110 °C for 24 hours.

HPLC data at the end point of step 3:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.464	BB	0.0294	6.42071	3.34815	0.2971
2	3.776	BB	0.0269	6.34129	3.71639	0.2934
3	3.871	BV R	0.0339	1854.40637	834.02509	85.7972
4	4.150	VB	0.0341	15.55631	6.70434	0.7197
5	4.874	VV R	0.0371	30.29416	12.55980	1.4016
6	5.371	BV R	0.0381	215.79150	89.52969	9.9840
7	5.493	VV E	0.0400	32.57296	12.27128	1.5070

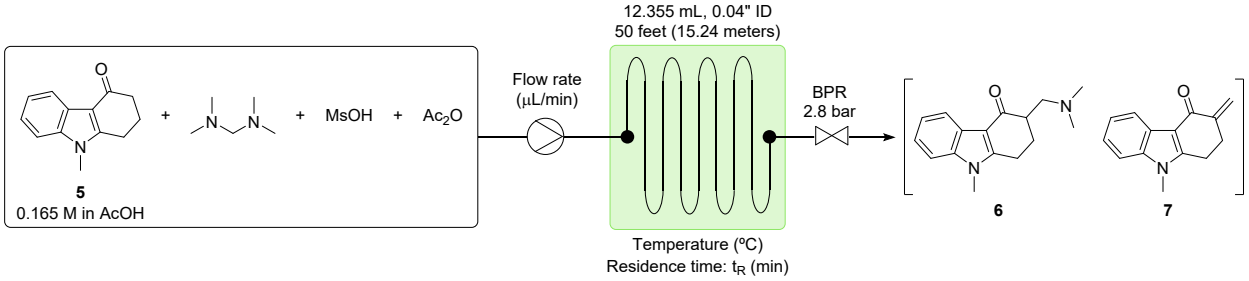
HPLC data at the end point of step 4:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.460	VB R	0.0282	9.51389	5.23200	0.3099
2	3.582	BB	0.0277	3.31533	1.86562	0.1080
3	3.674	BB	0.0276	49.48617	28.01710	1.6119
4	3.780	BV E	0.0315	6.40532	3.17712	0.2086
5	3.820	VV E	0.0258	3.18498	1.87234	0.1037
6	3.882	VV R	0.0310	515.16412	261.74942	16.7805
7	4.146	BV E	0.0231	6.26398	4.26238	0.2040
8	4.193	VV R	0.0320	928.65729	450.82239	30.2493

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
9	4.659	VV R	0.0374	8.16894	3.23970	0.2661
10	4.875	VV R	0.0357	51.64676	21.76896	1.6823
11	5.373	BV R	0.0369	1238.37024	518.41809	40.3377
12	5.494	VV E	0.0388	192.76735	75.56142	6.2791
13	5.949	BB	0.0336	57.06334	25.96767	1.8587

Reaction condition screening of step 3:



entry	reaction parameter				HPLC (pa%)			
	equivalent [diamine, MsOH, Ac_2O]	temp. (°C)	t_R (min)	flow rate (µL/min)	**5**	**6**	**7**	**5**+**6**+**7**
1	1.20, 1.22, 1.05	110	60	206	8.10	84.31	6.09	98.50
2	1.20, 1.22, 1.05	120	60	206	2.08	73.93	19.45	95.46

3	1.20, 1.22, 1.05	120	45	275		4.01	80.67	12.55	97.23
4	1.20, 1.22, 1.05	130	45	275		1.23	56.50	34.35	92.08
5	1.20, 1.22, 1.05	130	30	412		3.23	69.99	21.84	95.06
6	1.20, 1.22, 1.05	130	25	494		4.17	73.61	18.68	96.46
7	1.20, 1.22, 1.05	130	20	618		7.78	74.85	14.13	96.76
8	1.20, 1.22, 0	120	45	275		3.82	74.44	17.76	96.02
9	1.20, 1.22, 2.10	120	45	275		3.83	84.46	8.90	97.19
10	1.20, 1.22, 3.15	120	45	275		4.77	83.43	8.50	96.70
11	1.20, 1.22, 0	130	25	494		5.10	67.90	22.96	95.96
12	1.20, 1.22, 2.10	130	25	494		4.19	79.56	13.18	96.93
13	1.20, 1.22, 3.15	130	25	494		5.85	77.53	12.88	96.26
14	1.20, 1.22, 0	130	30	412		2.85	62.02	29.40	94.27
15	1.20, 1.22, 2.10	130	30	412		2.18	77.88	15.16	95.22
16	1.20, 1.22, 3.15	130	30	412		5.46	74.47	15.07	95.00

Procedure for entries 1-16:

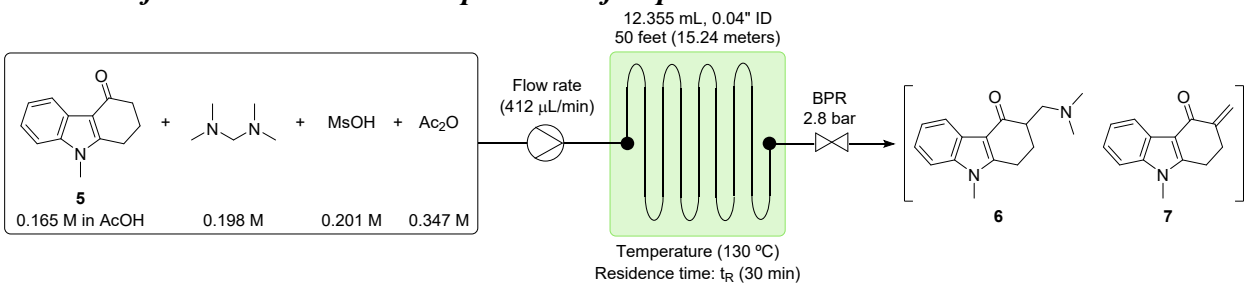
The substrate **5** (1.64 g, 8.25 mmol, 1 eq), *N*,*N*,*N*,*N*-tetramethyldiaminomethane (1.35 mL, 9.90 mmol, 1.2 eq), MsOH (0.65 mL, 10.07 mmol, 1.22 eq) and Ac_2O (0 mL, 0 mmol, 0 eq, or 0.82 mL, 8.66 mmol, 1.05 eq, or 1.64 mL, 17.32 mmol, 2.10 eq, or 2.46 mL, 25.99 mmol, 3.15 eq) were added to a 50 mL volumetric flask. AcOH was added to the 50 mL line of the volumetric flask.

The reactor was constructed from the perfluoroalkoxy (PFA) tubing (1/16'' outside diameter, 0.04'' inside diameter, 15.24 m (= 50 feet), 12.355 mL), the complementary polyether ether ketone (PEEK) fittings, and the Upchurch Scientific's back pressure regulator (40 psi, 2.8 bar).

The prepared reactant solutions were pumped into the reactor by the Syrris Asia pump at the designated flow rate (206, 275, 412, 494 or 618 μL/min). The reaction tube was immersed in an oil bath and heated at the designated temperature (110, 120 or 130 °C). The reaction was equilibrated for 60, 75, 90, 135 or 180 minutes, which was three times longer than the residence time. After the equilibration, 6.18 mL of the solution was collected for 10, 12.5, 15, 22.5 or 30

minutes, depending on the flow rate. The collected solution was analyzed by HPLC to determine the conversion.

Procedure for the extended-time experiment of step 3:



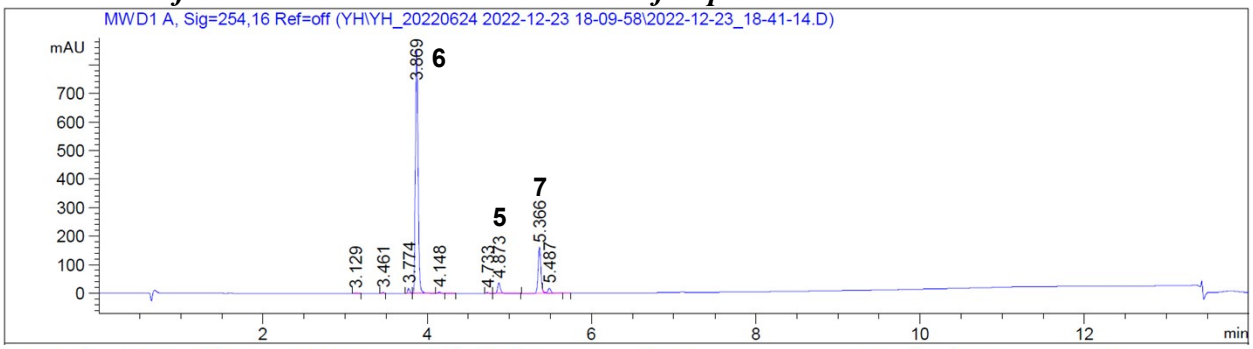
time (hr)	HPLC (pa%) reactant solution	HPLC (pa%) reacted solution			
	5	**5**	**6**	**7**	**5+6+7**
-1.5	99.59	-	-	-	-
0	99.45	3.61	76.87	15.47	95.95
1	99.18	3.47	77.18	15.29	95.94
2	99.11	3.50	76.80	15.55	95.85
3	99.12	3.46	76.84	15.56	95.86
4	99.09	3.37	77.17	15.31	95.85
5	98.99	3.38	76.93	15.52	95.83
6	99.00	3.37	77.16	15.50	96.03
7	99.02	3.38	77.22	15.20	95.80
all collected solution	-	3.45	76.95	15.46	95.86

The substrate **5** (8.22 g, 41.25 mmol, 1 eq), *N*,*N*,*N*,*N*-tetramethyldiaminomethane (6.75 mL, 49.50 mmol, 1.2 eq), MsOH (3.27 mL, 50.33 mmol, 1.22 eq) and Ac_2O (8.19 mL, 86.62 mmol, 2.10 eq) were added to a 250 mL volumetric flask. AcOH was added to the 250 mL line of the volumetric flask.

The reactor was constructed from the perfluoroalkoxy (PFA) tubing (1/16'' outside diameter, 0.04'' inside diameter, 15.24 m (= 50 feet), 12.355 mL), the complementary polyether ether ketone (PEEK) fittings, and the Upchurch Scientific's back pressure regulator (40 psi, 2.8 bar).

The prepared reactant solutions were pumped into the reactor by the Syrris Asia pump at the designated flow rate (412 μL/min). The reaction tube was immersed in an oil bath and heated at the designated temperature (130 °C). The reaction was equilibrated for 90 minutes, which was three times longer than the residence time. After the equilibration, 173.04 mL of the solution was collected for 420 minutes. The collected solution was analyzed by HPLC to determine the conversion, stored at 0 °C and used in the next step.

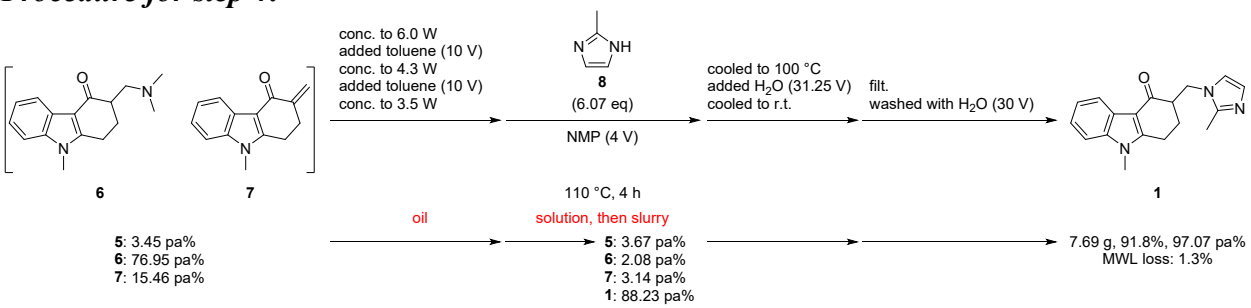
HPLC data of the all collected reaction solution of step 3:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.129	BB	0.0278	3.10031	1.73593	0.1240
2	3.461	BV	0.0296	7.20165	3.88174	0.2880
3	3.774	BB	0.0281	32.67974	18.05499	1.3067
4	3.869	BV R	0.0343	1924.39746	854.07697	76.9460
5	4.148	VV E	0.0296	9.23029	4.76701	0.3691
6	4.733	VB	0.0310	5.78605	2.93345	0.2314
7	4.873	BV R	0.0361	86.35268	37.18100	3.4528
8	5.366	BV R	0.0370	386.70047	161.17082	15.4620

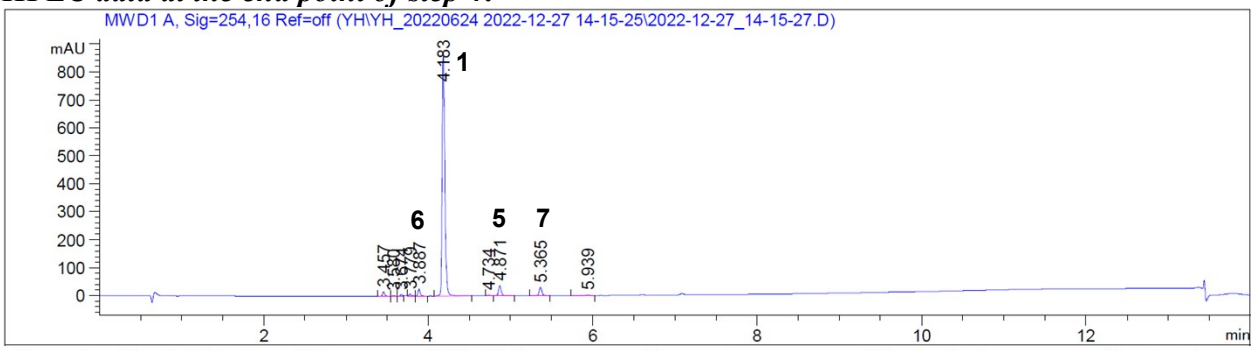
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
9	5.487	VV E	0.0408	45.52272	16.70822	1.8202

Procedure for step 4:



The collected solution was concentrated to 34.05 g, 5.98 W. To the residue, was added toluene (57 mL, 10 V). The reaction mixture was concentrated to 24.64 g, 4.33 W. To the residue, was added toluene (57 mL, 10 V). The reaction mixture was concentrated to 19.69 g, 3.46 W. To the residue, were added NMP (22.8 mL, 4 V) and 2-methylimidazole **8** (14.23 g, 173.30 mmol, 6.07 eq). The reaction mixture was warmed to 110 °C and stirred at 110 °C for 4 hours. The reaction mixture was cooled to 100 °C. To the mixture, was added H_2O (177.8 mL, 31.25 V) over 10 minutes. The reaction mixture was cooled to r.t., filtered and washed with H_2O (170.7 mL, 30 V). The solid was air-dried overnight to give ondansetron **1**[3] (7.69 g, 91.8% yield, 97.07 pa%, off-white solid, MWL loss: 1.3%).

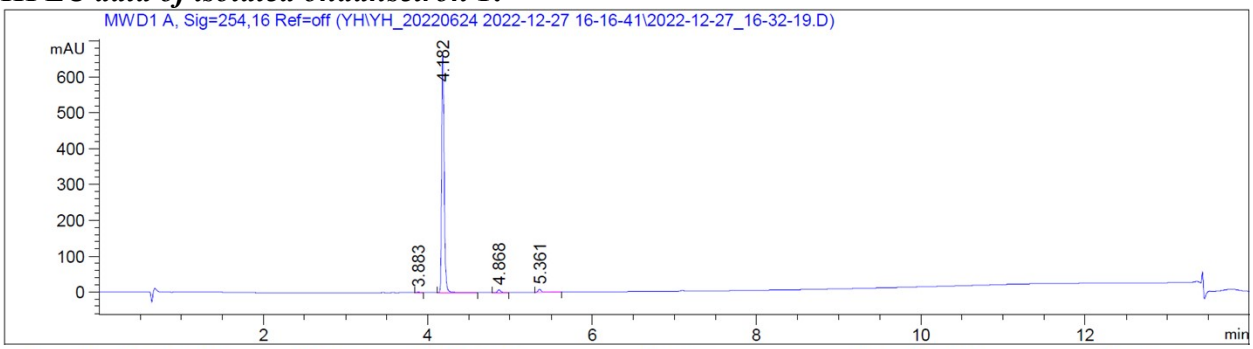
HPLC data at the end point of step 4:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.457	VB R	0.0287	29.20734	15.68218	1.2742
2	3.580	BB	0.0292	4.47421	2.46785	0.1952
3	3.674	BV	0.0289	9.70148	5.16617	0.4232
4	3.779	VB	0.0314	12.57678	6.27656	0.5487
5	3.887	BV R	0.0305	47.66397	24.70266	2.0794
6	4.183	BV R	0.0349	2022.37585	878.58850	88.2271
7	4.734	BV E	0.0299	5.36549	2.85551	0.2341
8	4.871	VV R	0.0364	84.02622	35.79015	3.6657

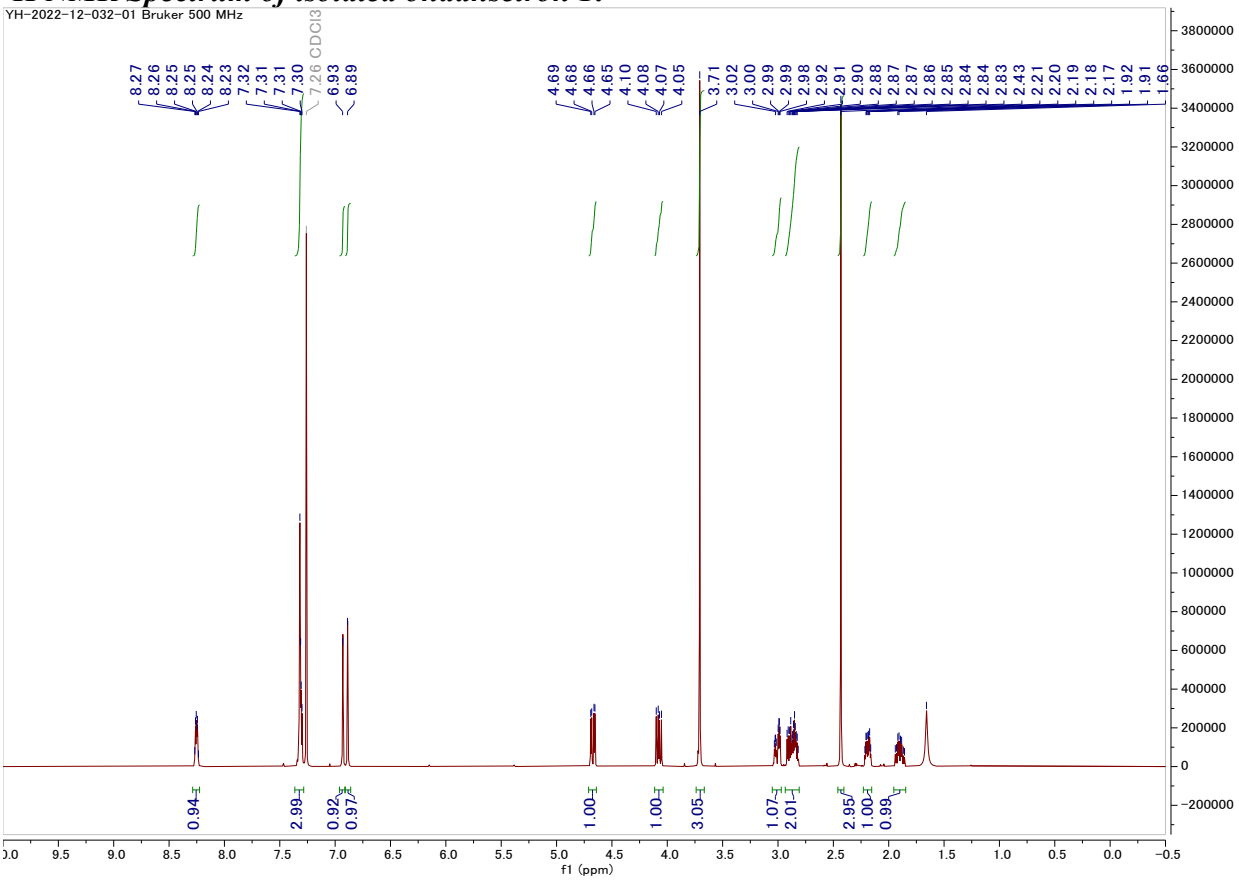
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
9	5.365	VB R	0.0375	72.03531	29.47495	3.1426
10	5.939	VB R	0.0380	4.81184	1.87369	0.2099

HPLC data of isolated ondansetron 1:

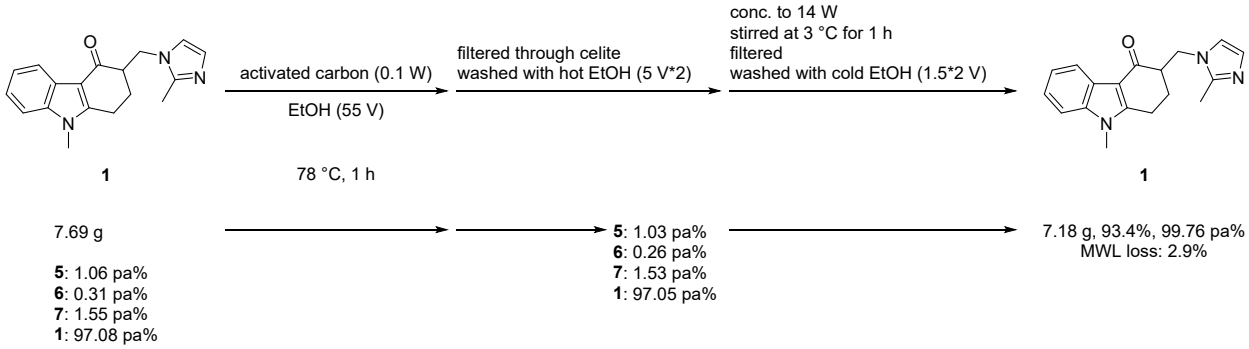


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.883	BB	0.0305	4.17423	2.16185	0.2754
2	4.182	BV R	0.0334	1471.43689	675.91406	97.0651
3	4.868	BB	0.0371	17.56759	7.29451	1.1589
4	5.361	BV R	0.0388	22.74981	8.90006	1.5007

^{1}H NMR Spectrum of isolated ondansetron 1:



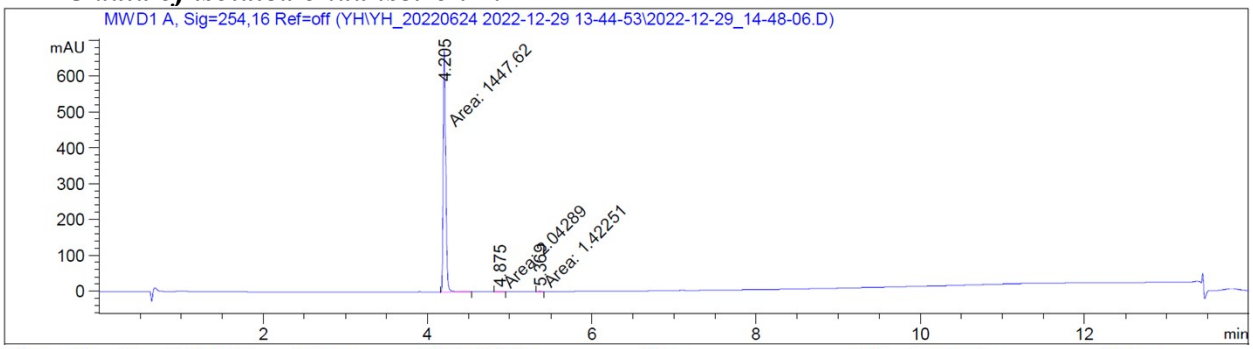
Procedure for the recrystallization of ondansetron 1:



To a 1 L flask, were added ondansetron **1** (7.69 g, 26.21 mmol) prepared in the preceding step, activated charcoal (769 mg, 0.1 W) and EtOH (423 mL, 55 V). The slurry was stirred at 78 °C for 1 h. The hot slurry was filtered through celite and washed with hot EtOH (38+38 mL, 5+5 V). The solution was concentrated to 107.66 g, 14 W. The resulted slurry was cooled to 5 °C and stirred at 5 °C for 1 h. The slurry was filtered and washed with cold EtOH (11.5+11.5 mL, 1.5+1.5 V) to afford ondansetron **1**[3] (7.18 g, 93.4% yield, 99.76 pa%, off-white solid, residual EtOH 4200 ppm, MWL loss: 2.9%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.29-8.22 (m, 1H), 7.36-7.28 (m, 3H), 6.93 (d, J = 1.3 Hz, 1H), 6.89 (d, J = 1.5 Hz, 1H), 4.67 (dd, J = 14.6, 4.3 Hz, 1H),

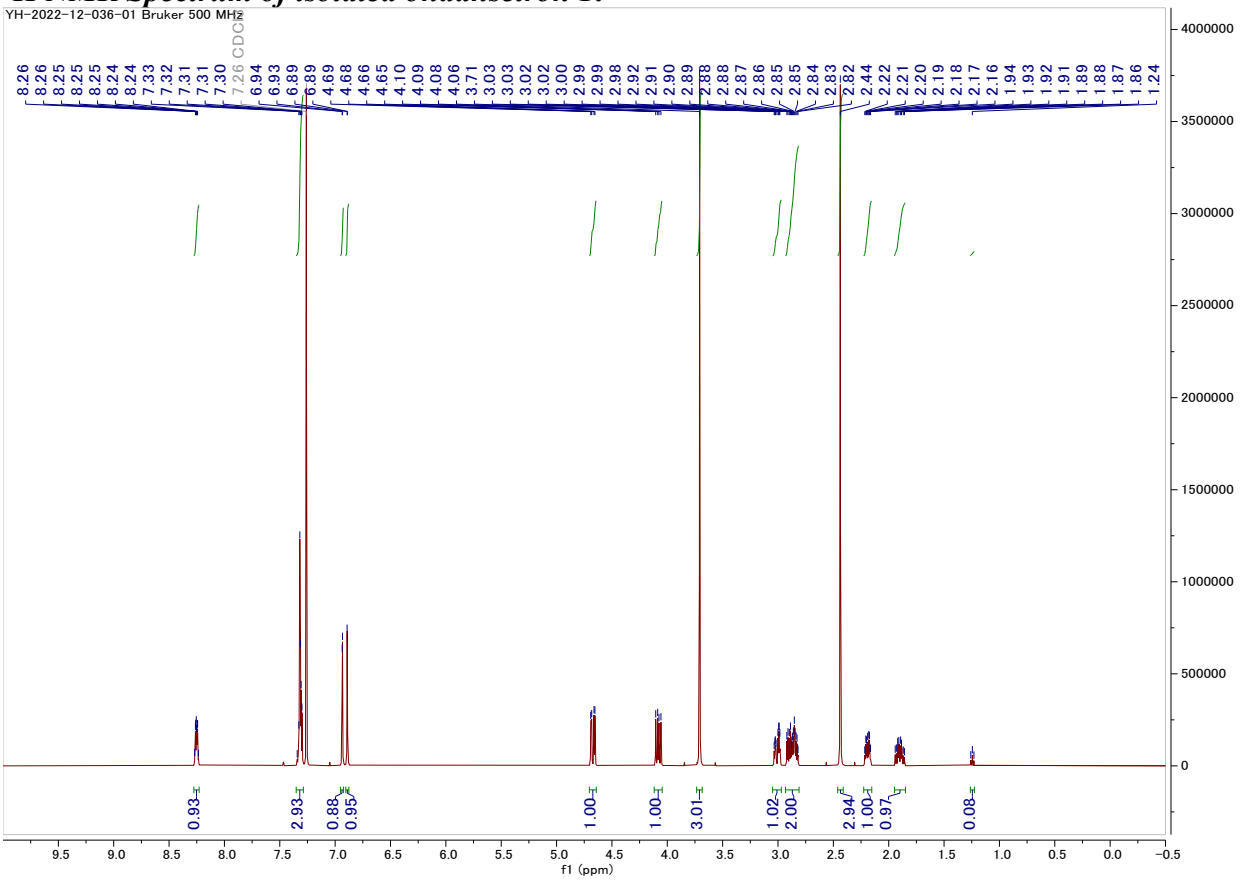
4.08 (dd, J = 14.6, 8.9 Hz, 1H), 3.71 (s, 3H), 3.01 (ddd, J = 17.2, 5.2, 3.4 Hz, 1H), 2.94-2.80 (m, 2H), 2.44 (s, 3H), 2.23-2.15 (m, 1H), 1.96-1.84 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 191.7, 151.4, 145.1, 137.8, 127.6, 124.8, 123.5, 123.1, 121.7, 119.9, 112.4, 109.5, 47.4, 45.8, 30.0, 26.7, 21.6, 13.5. IR (neat) v: 3125, 3100, 2934, 2872, 1621, 1578, 1529, 1479, 1458 cm^{-1}. HRMS (DART) m/z: calcd for $C_{18}H_{20}N_3O^+$ [$(M+H)^+$] 294.1601, found 294.1607.

HPLC data of isolated ondansetron 1:

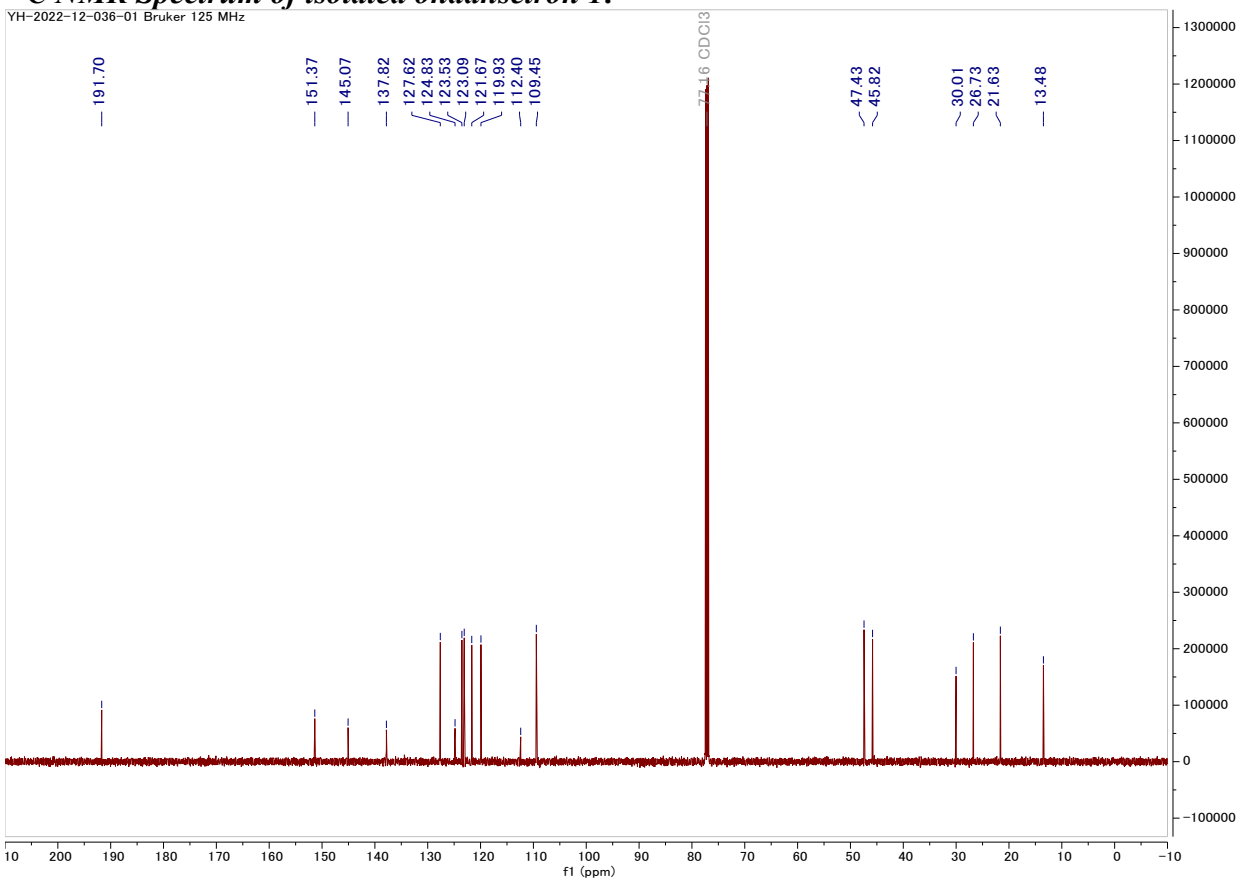


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.205	MM	0.0357	1447.61560	675.30463	99.7612
2	4.875	MM	0.0521	2.04289	6.54063e-1	0.1408
3	5.369	MM	0.0390	1.42251	6.07507e-1	0.0980

[1]H NMR Spectrum of isolated ondansetron 1:



^{13}C NMR Spectrum of isolated ondansetron 1:



3. References

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