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Electronic Supplementary Information

Flow oriented synthetic design in the continuous preparation of the aryl piperazine drug flibanserin

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General

Solvents and chemicals were purchased from commercial vendors and were used without any further purification. Isopropyl acetate (98%) and 37% hydrochloric acid was obtained from Honeywell. THF (99.9%) was purchased from Merck. Di-*tert*-butyl dicarbonate (≥98%), 2,2-dimethoxyacetaldehyde solution (60 w/w% in H_2O), DBU (98%) and sand (50-70 mesh particle size) were obtained from Sigma-Aldrich. *o*-Phenylenediamine (≥98%) was obtained from Fluka. 1-(3-(Trifluoromethyl)phenyl)piperazine (98%) was purchased from Combi-Blocks. Purified (Milli-Q®) water was used for hydrogen generation in the H-Cube Pro™ and H-Cube® equipment.

^{1}H and **^{13}C NMR** spectra were measured on a Bruker Avance III HDX 400 MHz spectrometer equipped with CryoProbe Prodigy at 399.8 MHz for ^{1}H, and 100.5 MHz for ^{13}C.

Electron impact high-resolution MS measurements (**EI-HRMS**) were performed on a Thermo Q-Exative GC Orbitrap mass spectrometer (Thermo Fisher Scientific, Bremen, Germany). The ion source temperature was set at 250 °C, the applied ionization energy was 70 eV. Resolving power of 60,000 (FWHM) at *m/z* 400. Data acquisition and analysis were accomplished with Xcalibur software version 4.0 (Thermo Fisher Scientific Inc.).

Electrospray high-resolution MS measurements (vpoe**ESI-HRMS**) were performed on a Thermo Velos Pro Orbitrap Elite Hybrid mass spectrometer. The ionization method was ESI operated in positive ion mode. The capillary temperature was set at 275 °C. Samples were infused into the ESI source MeOH solutions at a flow rate of 3 μL min^{-1}. Resolving power of 60,000 (FWHM) at *m/z* 400. Data acquisition and analysis were accomplished with Xcalibur software version 3.0.

Electrospray high-resolution MS measurements (ltqft**ESI-HRMS**) were performed on a Thermo LTQ FT Ultra spectrometer. The ionization method was ESI operated in positive ion mode. The ion transfer capillary temperature was set at 280 °C. Samples were infused into the ESI source MeOH solutions at a flow rate of 10 μL min^{-1}. Resolving power of 50,000 (FWHM) at *m/z* 400. Data acquisition and analysis were accomplished with Xcalibur software version 2.1.

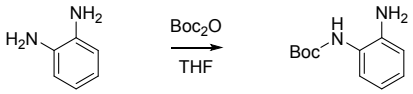
Considerations for solvent selection

The proposed synthesis applies diverse conditions. Consequently, resistance against hydrogenation, hydrolysis, both basic and acidic conditions, as well as thermal stability, and low vapor pressure were desirable. Solvents that are toxic or reactive under the applied transformations (e.g. ketones) were not considered. Also, an ideal solvent allows simple separations (i.e. water immiscible) and should be compatible with facile product isolation or further downstream processing operations, such as the final purification and API formulation. The solvents listed in Table S1 were promising in most reactions, except the one indicated problematic transformation.

Table S1. Alternative solvents considered for the synthetic route.

Solvent	Problematic step	Nature of the problem
THF	step 4: reductive amination using 1-(3-trifluoromethylphenyl)piperazine	significant amounts of the *N*-hydroxybutyl derivative of 1-(3-trifluoromethylphenyl)piperazine as by-product
MTBE	step 1: reductive alkylation using 2,2-dimethoxyacetaldehyde	poor reactivity and selectivity
CH_3CN	step 4: reductive amination using 1-(3-trifluoromethylphenyl)piperazine	significant amounts of the *N*-ethyl derivative of 1-(3-trifluoromethylphenyl)piperazine as by-product
EtOAc	step 3: acidic deprotection	ethylated derivatives of the product as by-products in significant amounts

Synthesis of the starting material *tert*-butyl (2-aminophenyl)carbamate (2)



The solution of di-*tert*-butyl dicarbonate (10.1 g, 46.3 mmol, 1.0 eq.) in THF (25 mL) was slowly added to a stirred solution of *o*-phenylenediamine (5.0 g, 46.2 mmol) in THF (25 mL) at 0°C under N_2 atmosphere. Evolution of gas was observed for 30 minutes, after which the solvent was evaporated under reduced pressure. The resulting solid residue was recrystallized using a mixture of hexane (45 mL) and ethyl acetate (15 mL) to yield white crystals (6.26 g, 65%). Spectral data were identical with the literature.[1]

Stepwise synthesis of flibanserin (1) in continuous-flow equipment

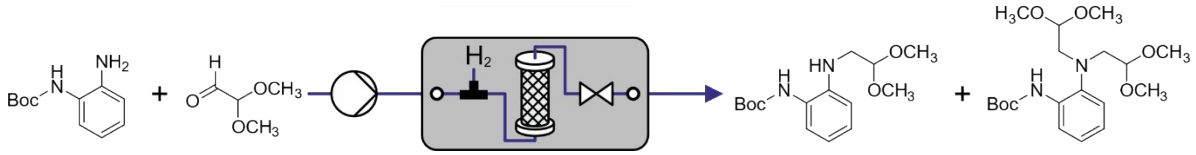
Each of the four steps were optimized in single-step continuous-flow experiments starting from purified intermediates (Tables S2 – S5). Then, the entire flow synthesis was carried out in a stepwise manner, using the crude solutions of the previous steps, without altering their composition and concentration. The settings and the flow equipment (for details see Table S6 and S8) used in the stepwise experiments were identical to the elements used in the four-step system, apart from a few necessary modifications.

Aliquots of the crude mixtures were taken for analysis (LC-MS for steps 1, 2 and 4; GC-MS for step 3) to determine conversion and impurity profile. Small amounts of the crude mixtures were purified and analyzed by NMR and HR-MS. Analytical data of intermediates **2**, **4-6** and the product **1** are listed below.

Step 1: initial reductive amination

Selected optimization data is presented in Table S2.

Table S2. Optimization of the solvent, temperature and pressure in the initial reductive amination step.[a]



Entry	Solvent	Temperature [°C]	Pressure [bar]	Conversion [%]	Selectivity (mono : bis)
1	MTBE	100 °C	100 bar	> 99%	1 : 0.240
2	CH_3CN	100 °C	100 bar	87%	1 : 0.037
3	EtOAc	100 °C	100 bar	76%	1 : 0.051
4	iPrOAc	80 °C	100 bar	93%	1 : 0.037
5	iPrOAc	100 °C	100 bar	95%	1 : 0.038
6	iPrOAc	100 °C	10 bar	94%	1 : 0.046
7	iPrOAc	100 °C	10 bar	> 99% [b]	1 : < 0.01
8	iPrOAc	120 °C	100 bar	92%	1 : 0.100
9	iPrOAc	140 °C	100 bar	93%	1 : 0.133
10	iPrOAc	150 °C	100 bar	— [c]	—

[a] Conditions: 0.1 mmol substrate dissolved in the solvent (0.05 M), pre-mixed with 1 equiv. of aldehyde, introduced by a single pump at 0.5 mL min^{-1} flow rate into the H-Cube® or H-Cube Pro™ hydrogenation reactor using 10% Pd/C CatCart® (30 mm; t_R = ca. 8 s). Conversion was determined by LC-MS-DAD (220 nm).

[b] Conducted on 2 mmol scale, using freshly recrystallized starting material.

[c] Failed due to rupture of the catalyst bed sealing.

Continuous-flow procedure: A 10% Pd/C CatCart® (30 mm) was loaded into the H-Cube Pro™ continuous-flow hydrogenation reactor, and the system was washed with ethanol, followed by iPrOAc. Reaction parameters were set to 100 °C temperature, 10 bar pressure, 20% gas to liquid ratio and 0.5 mL min^{-1} flow rate. Washing with iPrOAc was continued until steady state was reached.

The solution of 1.04 g (5.00 mmol) of *tert*-butyl (2-aminophenyl)carbamate in 100 mL of iPrOAc (0.05 M) was transferred by an AZURA® P4.1S HPLC pump at 0.5 mL min^{-1} flow rate, and the mixture of 754 µl (5.00 mmol; 1 eq.) of the 60 w/w% aqueous solution of 2,2-dimethoxyacetaldehyde and 246 µl of water (5.0 M) was transferred by an Asia Syringe Pump at 5 µL min^{-1} flow rate.

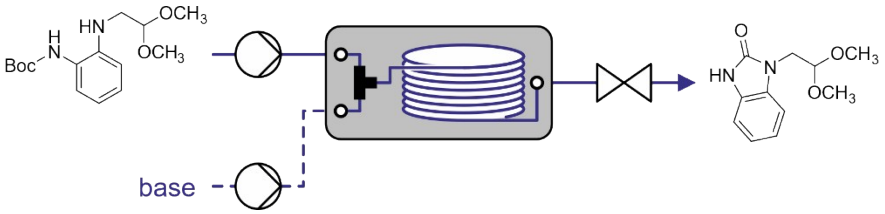
The streams were mixed in a T-piece and directed into the reactor. The dead volume was discarded to the waste, until the reaction mixture appeared at the output. Then, the product mixture was collected, until the starting solution is consumed.

The system was shut-down and washed with ethanol.

Step 2: base-mediated ring closure

Selected optimization data is presented in Table S3.

Table S3. Optimization of the base and temperature in the ring closure step.[a]



Entry	Base [equivalent amount]		Temperature [°C]	Conversion [%]
1	DBU	(0.5 eq.)	160 °C	16%
2	DBU	(0.5 eq.)	180 °C	37%
3	DBU	(0.5 eq.)	200 °C	60%
4	DBU	(1 eq.)	180 °C	58%
5	DBU	(1 eq.)	200 °C	88%
6	DBU	(1.5 eq.)	200 °C	94%
7	DBU	(1.5 eq.)	200 °C	96% [b]
8	DBU	(1.5 eq.)	200 °C	96% [c]
9	DBU	(2 eq.)	200 °C	93%
10	TBD	(< 0.5 eq. [d])	200 °C	93%

[a] Conditions: 0.1 mmol substrate dissolved in iPrOAc (0.05 M), pre-mixed with the base, introduced by a single pump at 0.5 mL min^{-1} flow rate into a 4 mL SS coil reactor (t_R = 8 min) followed by 17 bar BPR. Conversion was determined by LC-MS-DAD (220 nm).

[b] Conducted on 2 mmol scale, using the crude product mixture of the first step.

[c] Conducted on 4 mmol scale, using the crude product mixture of the first step. Two separate pumps were used for the substrate (0.5 mL min^{-1}) and the base (1 M solution in iPrOAc, 37.5 µL min^{-1}).

[d] Due to its poor solubility, TBD was partially dissolved, the saturated solution was used for the experiment after filtration.

Continuous-flow procedure: A system is constructed, consisting of an AZURA® P4.1S HPLC pump, and an Asia Syringe Pump connected to the inlets of a 4 mL SS coil reactor housed in an Asia Heater, followed by a Zaiput BPR set to 17 bar pressure.

The system was washed with ethanol, followed by iPrOAc. Heating was set to 200 °C and washing with iPrOAc was continued until steady temperature was reached.

80 mL of the crude product solution (0.05 M in iPrOAc) obtained in step 1 was transferred by the HPLC pump at 0.5 mL min^{-1} flow rate, and the solution of 900 µL (6.02 mmol; 1.5 eq.) of DBU in 6.0 mL of iPrOAc (1 M) was transferred by the continuous syringe pump at 37.5 µL min^{-1} flow rate.

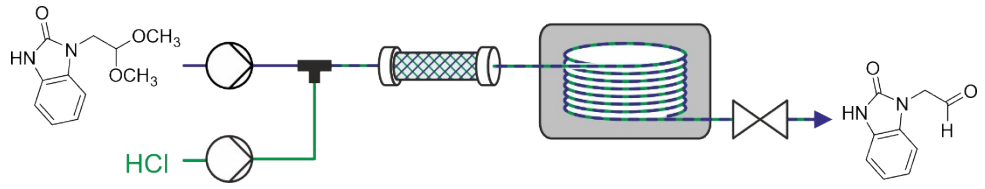
After starting both pumps, the dead volume was discarded to the waste, until the reaction mixture appeared at the output. Then, the product mixture was collected until the starting solution was consumed.

The system was shut-down and washed with ethanol.

Step 3: biphasic acidic deprotection

Selected optimization data is presented in Table S4.

Table S4. Optimization of the acid promoted deprotection step.[a]



Entry	HCl conc. [M]	Volume ratio [b]	Mixing unit [c] (vol., temp.)	Residence time unit [d] (vol., temp.)	Total res. time [min]	Organic phase composition [%] [e] (s.m. : p. : impurities)	Conv.[f] [%]	Org. recov.[g] [%]	Calc. yield [h] [%]
1	1 M	1 : 1	—	10 mL, 80 °C	10 min	66 : 30 : 4	31%	n.d.	n.d.
2	1 M	1 : 1	—	10 mL, 100 °C	10 min	6 : 71 : 23	92%	57%	40%
3	2 M	1 : 10	—	10 mL, 100 °C	18 min	16 : 77 : 7	83%	81%	63%
4	2 M	1 : 10	0.4 mL, r.t.	4 mL, 100 °C	8 min	38 : 41 : 21	52%	86%	35%
5	4 M	1 : 10	0.4 mL, r.t.	4 mL, 100 °C	8 min	16 : 81 : 3	84%	88%	72%
6	4 M	1 : 10	0.4 mL, 100 °C	4 mL, 100 °C	8 min	2 : 78 : 20	98%	81%	63%
7	4 M	1 : 5	0.4 mL, r.t.	4 mL, 100 °C	7 min	5 : 77 : 18	94%	47%	36%

[a] Conditions: 10 mL of the 0.05 M crude solution of the substrate dissolved in iPrOAc (0.5 mmol) is pumped at 0.5 mL min^{-1} flow rate into a T-mixer together with the HCl solution from a separate pump. The reactor is followed by a 17 bar BPR.

[b] Flow rate ratio of the substrate (organic) and the reagent (aqueous) streams.

[c] An appropriately sized glass column, filled with sand (50-70 mesh), kept at room temperature (r.t.) or heated in a Syrris Asia Heater with Solid Phase Reactor Adaptor.

[d] Custom made PTFE coil reactor (0.8 mm i.d.), heated in a HPLC column oven.

[e] Organic phase composition after work-up, determined by GC-MS measurements. (s.m.: starting material; p.: desired product)

[f] Conversion is calculated from the ratio of the starting material and product.

[g] Percentage of the weight of the organic phase after work-up, compared to the theoretical weight of the desired product. (n.d.: not determined)

[h] Calculated from the organic recovery and product percentage.

Continuous-flow procedure: A system is constructed, consisting of an AZURA® P4.1S HPLC pump, and an Asia Syringe Pump connected to a T-adaptor, followed by an Omnifit® BenchMark™ microbore column (3 mm i.d. x 100 mm) filled with sand (50-70 mesh particle size), and a 4 mL coil reactor (PTFE tubing, 1/16 in. o.d., 0.8 mm i.d.) housed in a LaChrom column thermostat. A Zaiput BPR set to 17 bar pressure is connected to the output of the reactor.

The system was washed with ethanol, followed by iPrOAc and distilled water. Heating of the coil reactor was set to 100 °C and washing with iPrOAc and water was continued until steady temperature was reached. Other parts were kept at ambient temperature.

60 mL of the crude product solution (0.05 M in iPrOAc) obtained in step 2 was transferred by the HPLC pump at 0.5 mL min^{-1} flow rate, and 6.0 mL (24.0 mmol; 8 eq.) of 4 M aqueous hydrochloric acid solution was transferred by the continuous syringe pump at 50 µL min^{-1} flow rate.

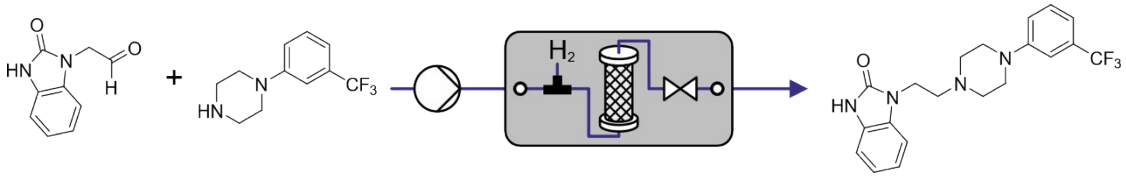
After starting both pumps, the dead volume was discarded to the waste, until the reaction mixture appeared at the output. Then, the biphasic product mixture was collected until the starting solution was consumed. The phases of the crude mixture were left to settle and then carefully separated in a separatory funnel. The acidic aqueous phase was discarded.

The system was shut-down and washed with ethanol.

Step 4: final reductive amination

Selected optimization data is presented in Table S5.

Table S5. Optimization of the temperature and hydrogen to liquid ratio in the final reductive amination step.[a]



Entry	Temperature [°C]	Pressure [bar]	Hydrogen to liquid ratio [%]	Conversion [a] [%]
1	80 °C	10 bar	7% [b]	94.0%
2	90 °C	10 bar	7% [b]	94.2%
3	100 °C	10 bar	7% [b]	94.4%
4	100 °C	10 bar	50% [c]	86.0%

[a] Conditions: 0.1 mmol of the aldehyde dissolved in iPrOAc (0.05 M, with 5% MeOH cosolvent), pre-mixed with 1 equiv. of piperazine, introduced by a single pump at 0.5 mL min^{-1} flow rate into the H-Cube® or H-Cube Pro™ hydrogenation reactor using 10% Pd/C CatCart® (30 mm). Conversion of the piperazine to the product was determined by LC-MS-DAD (220 nm).

[b] The H-Cube™ hydrogenation reactor was used in "Controlled mode" setting.

[c] The H-Cube Pro™ hydrogenation reactor was used with 50% H_2 setting.

Continuous-flow procedure: A 10% Pd/C CatCart® (30 mm) was loaded into the H-Cube® continuous-flow hydrogenation reactor, and the system was washed with ethanol, followed by iPrOAc. Reaction parameters were set to 100 °C temperature, 10 bar pressure, and 0.5 mL min^{-1} flow rate. Washing with iPrOAc was continued until steady state was reached.

40 mL of the crude solution (0.05 M in iPrOAc) obtained in step 3 was transferred by an AZURA® P4.1S HPLC pump at 0.5 mL min^{-1} flow rate, and the solution of 553 mg (2.40 mmol; 1.2 eq.) of 1-(3-trifluoromethylphenyl)piperazine in 2.4 mL of iPrOAc (1 M) was transferred by an Asia Syringe Pump at 30 µL min^{-1} flow rate.

The streams were mixed in a T-piece and directed into the reactor. The dead volume was discarded to the waste, until the reaction mixture appeared at the output. Then, the product mixture was collected until the starting solution was consumed.

The system was shut-down and washed with ethanol.

Construction of the four-step continuous-flow system

Photographic and simplified schematic representation of the entire flow system for the four-step synthesis of flibanserin are shown on Figure S1 – S2. The description of the labeled fluidic equipment is listed in Table S6, the connecting tubing in Table S7, and the detailed information of parts and consumables used for the construction are summarized in Table S8.

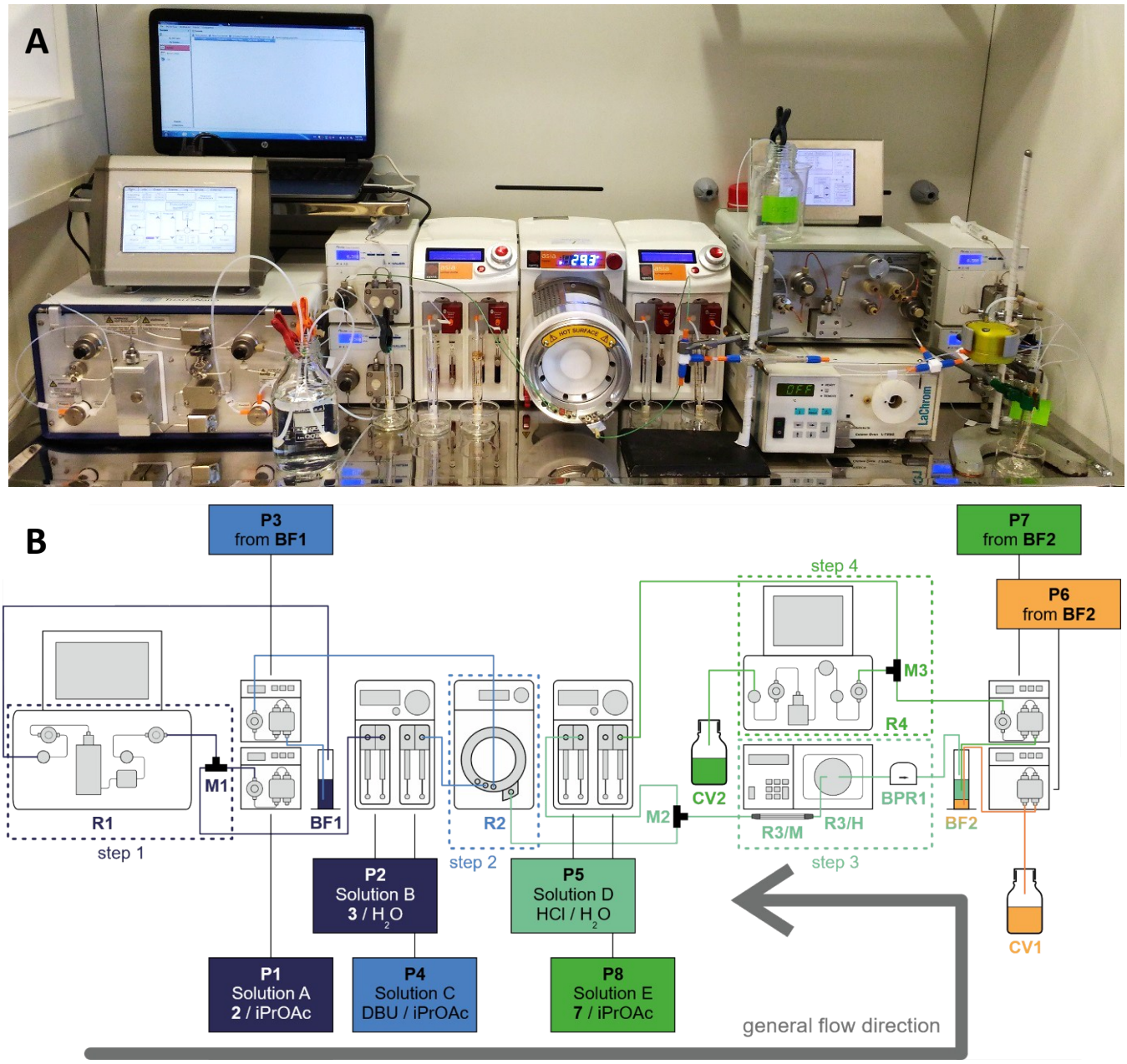


Figure S1. (A) Photograph of the entire flow system for the four-step synthesis of flibanserin constructed in a single fume hood. Completely assembled idle state is shown prior to a reaction run. (B) Schematic representation of the flow equipment (labeled according to the identifiers used in the flow diagram), showing the spatial arrangement of each equipment and the simplified path (general flow direction is counterclockwise, from the left side) of fluidic tubing. Tubing for input streams from stock solutions and the inlet valve before **P1** are not displayed. Horizontal gaps between modules are exaggerated for clarity, total physical width of the system is less than 150 cm.

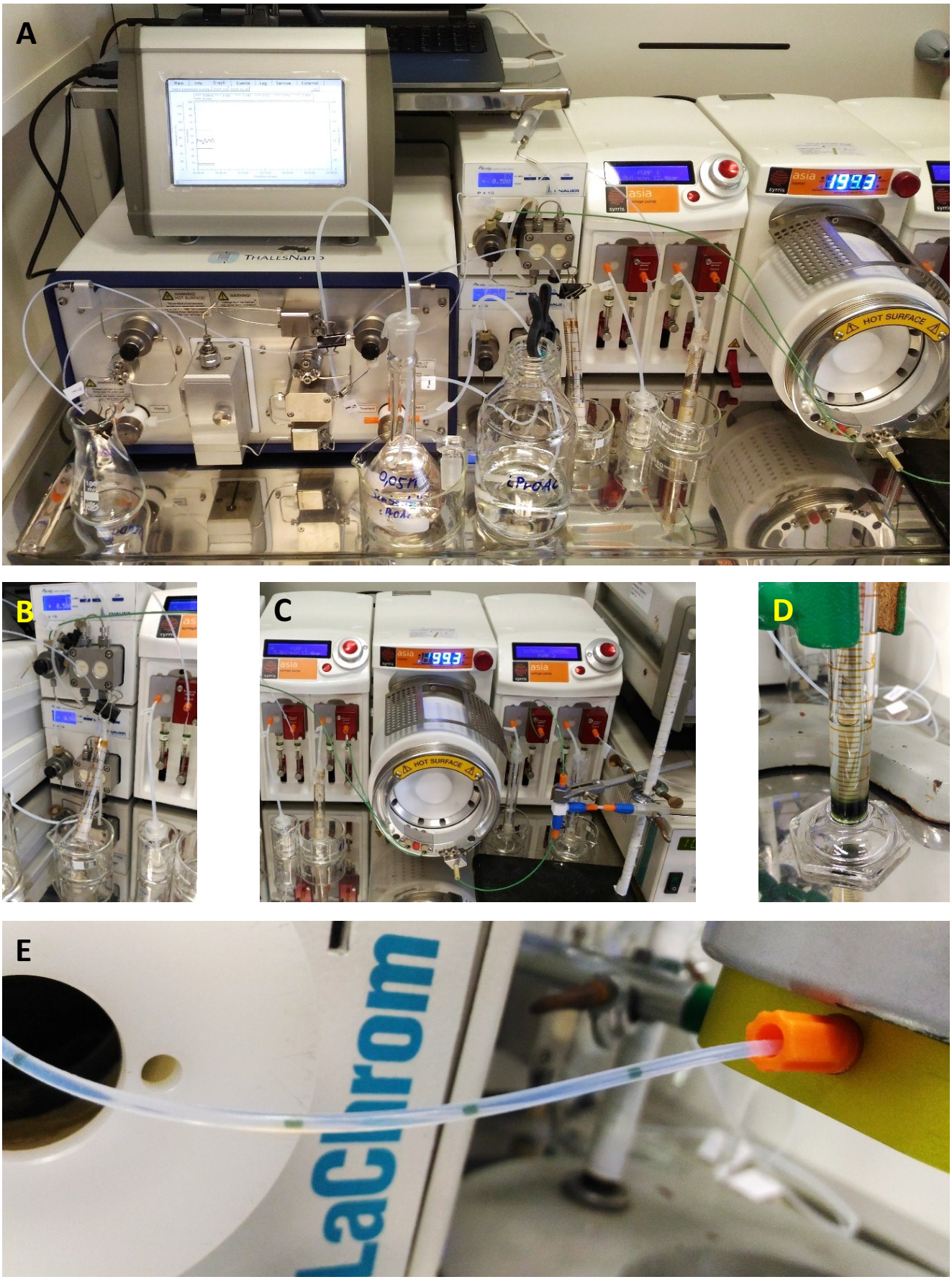


Figure S2. Key details of the system during operation: (A) The substrate solution and flow devices of steps 1 and 2. (B) The buffer flask **BF1** and pump **P3**. (C) Syringe pumps with the reagent solutions and reactor **R2**. (D) Close-up of the biphasic mixture inside buffer flask **BF2**. (E) Close-up of the biphasic stream exiting reactor **R3/H**.

Table S6. List of fluidic elements in the four-step flow system, in the order of the chemical reactions. The underlined pumps are the HLPC pumps responsible for transferring the reaction mixture, other pumps are continuous syringe pumps for the transferring of reagents. (f.r.: flow rate; PEEK: polyether ether ketone; i.d.: inner diameter; r.v.: reactor volume; d.v.: dead volume; SS: stainless steel; PTFE: polytetrafluoroethylene)

Reaction step	Identifier	Fluidic element		Key settings
Step 1	**P1**	Knauer AZURA® P 4.1S pump		Solution A; 0.500 mL min^{-1} f.r.
	P2	Syrris Asia Syringe pump (green syringes)		Solution B; 5.0 µL min^{-1} f.r.
	M1	IDEX PEEK T-adaptor, 0.5 mm i.d.		ambient temperature
	R1	Thales Nano H-Cube Pro™ [a]		10% Pd/C, (30 mm CatCart®), 100 °C, 10 bar, 50% gas-liquid ratio t_R ca. 8 s (ca. 0.13 mL r.v.[b])
	BF1	buffer flask (10 mL graduated cylinder)		ca. 2 mL d.v.
Step 2	**P3**	Knauer AZURA® P 4.1S pump		from **BF1**; 0.500 mL min^{-1} f.r.
	P4	Syrris Asia Syringe pump (green syringes)		Solution C; 37.5 µL min^{-1} f.r.
	R2/M	Syrris Asia Heater with 4 mL SS coil reactor	internal mixer	200 °C
	R2/H		heating zone	200 °C t_R = 7.4 min (4.0 mL r.v.)
Step 3	**P5**	Syrris Asia Syringe pump (green syringes)		Solution D; 50.0 µL min^{-1}
	M2	Diba Omnifit® PTFE T-adaptor, 1.5 mm i.d.		ambient temperature
	R3/M	Diba Omnifit® column filled with sand, 3mm i.d. x 100mm		ambient temperature t_R ca. 41 s (ca. 0.4 mL r.v.[c])
	R3/H	4 mL PTFE coil reactor heated in Merck LaChrom column thermostat		100 °C t_R = 6.8 min (4.0 mL r.v.)
	BPR1	Zaiput BPR		17 bar
	BF2	buffer flask (10 mL graduated cylinder)		ca. 2 mL d.v.
	P6	Knauer AZURA® P 2.1S		from **BF2**, lower phase; 0.050 mL min^{-1} f.r.
	CV1	collection vessel for the aqueous waste		
Step 4	**P7**	Knauer AZURA® P 4.1S		from **BF2**, upper phase; 0.538 mL min^{-1} f.r.
	P8	Syrris Asia Syringe pump (green syringes)		Solution E; 30.0 µL min^{-1} f.r.
	M3	Diba Omnifit® PTFE T-adaptor, 1.5 mm i.d.		ambient temperature
	R4	Thales Nano H-Cube® [a]		10% Pd/C, (30 mm CatCart®), 100 °C, 10 bar t_R ca. 12 s (ca. 0.13 mL r.v.[b])
	CV2	collection vessel for the product		

[a] The H-Cube Pro™ and H-Cube® equipment are used as standalone units, without the factory provided HPLC pumps.
[b] Free internal volume for a 10% Pd/C filled CatCart®, provided by the manufacturer.
[c] Free internal volume is determined from weight difference upon filling the packed bed column with water.

Table S7. Tubing plan for the connection of the flow equipment in the four-step flow system, with the internal volumes indicated. PTFE tubing was used, except where noted.

Reaction step	Connected parts (beginning - end)	Length [cm]	Tubing i.d. [mm]	Internal volume [mL]	Fitting at beginning [a]	Fitting at end [a]
Step 1	before inlet valve (“solvent”)	45	1.5	0.80	inlet filter	C
	before inlet valve (“reactant”)	60	1.5	1.06	inlet filter	C
	inlet valve → **P1**	30	1.5	0.53	C	A
	P1 → **M1**	15	0.8	0.08	B	B
	before **P2**	20	1.5	0.35	inlet filter	C
	P2 → **M1**	30	0.8	0.15	D	B
	M1 → **R1**	30	0.8	0.15	B	B
	R1 internal tubing [b]	—	—	0.40	—	—
	R1 → **BF1**	80	0.8	0.40	D	—
Step 2	**BF1** → **P3**	15	1.5	0.27	inlet filter	A
	P3 → **R2** [c]	50	0.8	0.25	B	B
	before **P4**	20	1.5	0.35	inlet filter	C
	P4 → **R2** [c]	30	0.8	0.15	D	B
	internal tubing before **R2** [b]	—	—	0.10	—	—
	internal tubing before **R2** [b]	—	—	0.10	—	—
	cooling zone after **R2** [b]	—	—	2.20	—	—
Step 3	**R2** → **M2** [c]	20	0.8	0.10	E	D
	before **P5**	20	1.5	0.35	inlet filter	C
	P5 → **M2** [c]	30	0.8	0.15	D	D
	M2 → **R3/M**	5	1.5	0.09	C	C
	R3/M → **R3/H**	0	—	0	D	—
	R3/H → **BPR1**	0	—	0	—	D
	BPR1 internal volume [b]	—	—	0.08	—	—
	BPR1 → **BF2**	30	0.8	0.15	D	—
	BF2 → **P6**	70	0.8	0.35	—	A
	P6 → **CV1**	50	0.8	0.25	B	—
Step 4	**BF2** → **P7**	40	0.8	0.20	—	A
	P7 → **M3**	25	0.8	0.13	B	D
	before **P8**	20	1.5	0.35	inlet filter	C
	P8 → **M3**	35	0.8	0.18	D	D
	M3 → **R4**	8	0.8	0.04	D	B
	R4 internal tubing [b]	—	—	0.28	—	—
	R4 → **CV2**	50	0.8	0.25	B	—

[a] Fitting types used (material, thread): A: Bushing and sealing rings for 1/8 in. o.d. tubing pump inlet; B: PEEK two-piece fitting for 1/16 in. o.d. tubing, 10-32 thread; C: Orange end fitting with flangeless ferrules for 3.2 mm o.d. tubing, 1/4″-28 UNF thread; D: Orange end fitting with flangeless ferrules for 1.6 mm o.d. tubing, 1/4″-28 UNF thread; E: Large compact fitting with PTFE pipe gripper for 1.6 mm o.d. tubing, 1/4″-28 UNF thread.

[b] Approximate dead volume data for the H-Cube Pro™ (without the CatCart), Syrris Asia 4 mL SS coil reactor, Zaiput BPR, and H-Cube® (without the CatCart) equipment are provided by the manufacturers.

[c] PEEK tubing was used due to high temperature and high pressure environment.

Table S8. Detailed information of parts and consumables used for the construction of the four-step flow system. Source of the images: refs. 2 – 16. (PEEK: polyether ether ketone; i.d.: inner diameter; SS: stainless steel; PTFE: polytetrafluoroethylene)

Information		Image (not for scale)
Identifiers:	**P1, P3, P7**	
Manufacturer:	KNAUER Wissenschaftliche Geräte GmbH. (Berlin, Germany)	
Description:	**AZURA® P 4.1S**	
Product No.	APG20EB	
More information:	see ref. 2	
Identifiers:	**P6**	
Manufacturer:	KNAUER Wissenschaftliche Geräte GmbH. (Berlin, Germany)	
Description:	**AZURA® P 2.1S**	
Product No.	APG90EB	
More information:	see ref. 3	
Identifiers:	**P2, P4, P5, P8**	
Manufacturer:	Syrris Ltd. (Royston, UK)	
Description:	**Asia Syringe Pump**	
Product No.	2200292	
More information:	see ref. 4	
Identifiers:	**M1**	
Source:	IDEX Health & Science LLC. (Rohnert Park, CA, USA)	
Description:	**PEEK T-adaptor,** 0.5 mm i.d.	
Part No.	P-727	
More information:	see ref. 5	
Identifiers:	**R1**	
Manufacturer:	ThalesNano Nanotechnology Inc. (Budapest, Hungary)	
Description:	**H-Cube Pro™**	
Product No.	THS 09025	
More information:	see ref. 6	

Table S8 continued

Information		Image (not for scale)
Identifiers:	**R2**	
Manufacturer:	Syrris Ltd. (Royston, UK)	
Description:	**Asia Heater** with 4 mL SS coil reactor	
Product No.	2200527 and 2200543	
More information:	see ref. 7	
Identifiers:	**M2, M3**	
Manufacturer:	Diba Industries Ltd. (Cambridge, UK)	
Description:	**Omnifit® PTFE T-adaptor,** 1.5 mm i.d.	
Part No.	001010	
More information:	see ref. 8	
Identifiers:	**R3/M**	
Manufacturer:	Diba Industries Ltd. (Cambridge, UK)	
Description:	**Omnifit® BenchMark™ microbore column assembly,** 3 mm i.d. x 100 mm, PTFE frit	
Part No.	006BCC-03-10-FF	
More information:	see ref. 9	
Identifiers:	**R3/H**	
Manufacturer:	Merck – Hitachi (Darmstadt, Germany)	
Description:	**LaChrom column thermostat**	
Product No.	L-7350	
Identifiers:	**BPR1**	
Manufacturer:	Zaiput Flow Technologies (Cambridge, Massachusetts, USA)	
Description:	**Back Pressure Regulator**	
Part No.	BPR-10	
More information:	see ref. 10	

Identifiers:	**R4**
Manufacturer:	ThalesNano Nanotechnology Inc. (Budapest, Hungary)
Description:	**H-Cube®**
Product No.	HC 2-1111121111
More information:	see ref. 11

Table S8 continued

Information		Image (not for scale)
Source: Description: Product No. More information:	Supelco Inc. **PTFE tubing**, 1/16 in. o.d. x 0.8 mm i.d. 58696-U see ref. 12	
Source: Description: Product No. More information:	Supelco Inc. **PTFE tubing**, 1/8 in. o.d. x 1.5 mm i.d. 58699 see ref. 13	
Source: Description: Product No. More information:	Supelco Inc. **PEEK tubing**, 1/16 in. o.d. x 0.03 in. i.d. Z226955 see ref. 14	
Manufacturer: Description: Product No. More information:	KNAUER Wissenschaftliche Geräte GmbH. **Bushing and sealing rings**, for 1/8 in. o.d. tubing pump inlet A1087 see ref. 15	
Source: Description: Product No. More information:	Supelco Inc. **PEEK two-piece fitting**, for 1/16 in. o.d. tubing, 10-32 thread 57654 see ref. 16	
Manufacturer: Description: Product No.	Syrris Ltd. **Orange end fitting** with flangeless ferrules, for 1.6 mm o.d. tubing, 1/4″-28 UNF thread 2200618	
Manufacturer: Description: Product No.	Syrris Ltd. **Orange end fitting** with flangeless ferrules, for 3.2 mm o.d. tubing, 1/4″-28 UNF thread 2200619	
Manufacturer: Description:	Syrris Ltd. **Large compact fitting** with PTFE pipe gripper, for 1.6 mm o.d. tubing, 1/4″-28 UNF thread	

Product No.	2200105, 2200102

Adjustment of the flow rates after the buffer flasks

The optimal flow rate settings of **P3**, **P6** and **P7** (feeding from buffer flask **BF1** and **BF2**) were determined by experimentation, to match the exact incoming flow rate and keep the level of the buffer flasks (and both phases in case of **BF2**) constant over longer periods of time.

The flow rate of **P3** was set to 500 µL/min (instead of the sum of incoming volumetric flow rates of **P1** and **P2** giving 505 µL/min). The possible reasons for this difference may include the evaporation of a minor amount of solvent during the outgassing of hydrogen after step 1, and the slight increase in density of the isopropyl acetate solvent after mixing with water (volume contraction).

In case of pumps **P6** and **P7**, no adjustment to the incoming organic and aqueous flow rates was necessary.

Method for operating the four-step continuous-flow system

A) Preparations

1. Pumps, reactors and other fluidic equipment (Table S6) are placed into a fume hood according to Figure S1, and connected by PTFE or PEEK (for high temperature sections under pressure) tubing as described in Table S7.
2. Syrris Asia modules were connected to a PC, and pressure readings on pumps and the temperature of the heater were constantly monitored using the Syrris Asia Manager software. KNAUER AZURA® P4.1S pumps were connected to a PC through RS-232 cables, and pressure readings were constantly monitored using a simple Python script for serial communication and data display.
3. Stock solutions are prepared in appropriately sized volumetric flasks according to Table S9, and the required amounts are transferred into graduated cylinders. (The volume of the solutions should allow priming of the pumps.)
4. All pumps, reactors and other fluidic equipment are primed with ethanol, followed by iPrOAc or distilled water (in case of **P2**, **P5**, **P6**).
5. The “solvent” branch of the inlet valve before **P1** is primed with iPrOAc, and the “reactant” branch is primed with the substrate solution (Solution A). The inlet valve is set to the “solvent” position.
6. The continuous syringe pumps (**P2**, **P4**, **P5**, **P8**) are primed with the reagent solutions (Solutions B – E, two cycles of filling and emptying the syringe pairs using the appropriate functions of the pumps).
7. The reactors are washed with iPrOAc for 2 hours using 0.5 mL min^{-1} flow rate set on the main stream HPLC pumps (**P1**, **P3**, **P7**). The BPRs (**R1/BPR**, **BPR1**, **R4/BPR**) are not active at this stage.

B) Start-up procedure

8. The main stream HPLC pumps (**P1**, **P3**, **P7**) transferring iPrOAc from solvent reservoirs are set to the prescribed flow rates and started. The HPLC pump for the aqueous waste (**P6**) is stopped.
9. The continuous syringe pumps (**P2**, **P4**, **P5**, **P8**) transferring the respective reagent solution (Solutions B – E) are set to the prescribed flow rates and started.
10. The prescribed pressures are set at the BPRs (**R1/BPR**, **BPR1**, **R4/BPR**).
11. Reactors (**R1**, **R2**, **R3/H**, **R4**) are heated to the prescribed temperatures.
12. Hydrogen generation and addition is initiated in the hydrogenation reactors (**R1**, **R4**).
13. Washing the system with iPrOAc and the reagent solutions is continued until steady pressures and reactor temperatures, as well as stable hydrogen – liquid ratios are reached at each of the reactors.

C) Initiation of the reaction sequence

14. The inlet valve before **P1** is switched to the “reactant” position in order to pump the substrate solution.
15. The dead volume of **R1** is discarded to the waste, until the reaction mixture appears at the output of **R1**. Then the output is placed into buffer flask **BF1** and 2 mL of the reaction stream is collected, at which point the inlet tubing of **P3** is placed into the buffer flask, thus its contents are transferred to the subsequent reactors (**R2**, **R3**). (This kind of operation of the buffer flask helps avoiding the processing of varying composition streams and long transient phases.)
16. The dead volume of **R2** and **R3** is discarded to the waste, until the reaction mixture appears at the output of **BPR1**. Then the output is placed into buffer flask **BF2** and 2.5 mL of the biphasic reaction stream is collected, at which point the inlet tubing of **P6** and **P7** are placed into the buffer flask, and **P6** is started. The lower phase is transferred to the collection vessel of the aqueous waste (**CV1**) using **P6**, and the upper phase is pumped to the subsequent reactor (**R4**) using **P7**.

17. The dead volume of **R4** is discarded to the waste, until the product mixture appears at the output of **R4**. Then the product stream is collected into **CV2**. The system is operated without human intervention, until the run time elapsed.

D) Shutdown procedure

18. The inlet valve before **P1** is switched to the "solvent" position and solvent is pumped. The other pumps and reactors are still operating unchanged, until the product is no longer emerging from the output of **R4**.
19. After product collection is finished, continuous syringe pumps (**P2**, **P4**, **P5**, **P8**) and the HPLC pump for the aqueous waste (**P6**) are stopped, while **P1**, **P3**, **P7** are pumping solvent. Heating of the reactors (**R1**, **R2**, **R3/H**, **R4**) are shut down. After all reactor temperatures sink below 80 °C, hydrogen generation (**R1**, **R4**) is ceased and BPRs (**R1/BPR**, **BPR1**, **R4/BPR**) are deactivated.
20. All pumps, reactors and other fluidic equipment are washed with ethanol for at least 1 hour using 1 mL min^{-1} flow rate.
21. Buffer flasks (**BF1**, **BF2**) and collection vessels (**CV1**, **CV2**) are emptied and cleaned properly.

Table S9. Composition of the stock solutions used in the four-step flow system. The indicated amounts are calculated for a 4 hour run using the described flow settings, with the necessary pre- and postrun volumes. (iPrOAc: isopropyl acetate; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene)

Solution	Composition	Pump (flow rate)	Preparation
Solution A	**2** (0.05 M) in iPrOAc	**P1** (0.500 mL min^{-1})	In a 250.0 mL volumetric flask, 2.605 g (12.5 mmol) of *tert*-butyl (2-aminophenyl)carbamate (**2**) is dissolved and diluted to 250.0 ml using iPrOAc, the solution is degassed by sonication. 120.0 mL of the solution, containing 1.250 g (6.0 mmol) substrate is consumed in a 4 hour run.
Solution B	**3** (5 M) in water	**P2** (5.0 µL min^{-1})	In a 5.0 mL volumetric flask, 3.77 mL (d = 1.15, 25 mmol) of the 60 w/w% aqueous solution of 2,2-dimethoxyacetaldehyde (**3**) is diluted to 5.0 mL using distilled water, the solution is degassed by sonication. 1.2 mL of the solution, containing 0.9 mL (6.0 mmol) of the 60 w/w% solution of the reagent is consumed in a 4 hour run.
Solution C	DBU (1 M) in iPrOAc	**P4** (37.5 µL min^{-1})	In a 25.0 mL volumetric flask, 3.75 mL (d = 1.018, 25.14 mmol) of DBU is dissolved and diluted to 25.0 mL using iPrOAc, the solution is degassed by sonication. 9.0 mL of the solution, containing 1.35 mL (9.0 mmol) of DBU is consumed in a 4 hour run.
Solution D	HCl (4 M) in water	**P5** (50.0 µL min^{-1})	In a 50.0 mL volumetric flask, 16.6 mL (d = 1.19, 200.2 mmol) of 37% hydrochloric acid is diluted to 50.0 mL using distilled water, the solution is degassed by sonication. 12.0 mL of the solution, containing 3.99 mL (48.0 mmol) of 37% HCl is consumed in a 4 hour run.
Solution E	**7** (1 M) in iPrOAc	**P8** (30.0 µL min^{-1})	In a 25.0 mL volumetric flask, 5.76 g (25.0 mmol) of 1-(3-(trifluoromethyl)phenyl)piperazine (**7**) is dissolved and diluted to 25.0 mL using iPrOAc, the solution is degassed by sonication. 7.2 mL of the solution, containing 1.34 mL (7.2 mmol) of reagent is consumed in a 4 hour run.

Composition of the crude product mixture after the four-step continuous-flow system

During the operation of the four-step continuous-flow system, samples were taken every 20 minutes from the crude product solution (ca. 11 mL) collected in **CV2**, starting from the beginning of the product stream collection after **R4**. The samples were evaporated and analyzed by HPLC. The composition of the crude product mixture (Figure S3) shows the result of an initial, temporary disturbance (inadequate conversion in step 1, the unreacted starting material formed benzimidazolone in step 2, which can be found in significant amounts in the crude product between the 80 min and 160 min samples), after which the system recovered, and a steady-state was reached at 180 min and maintained for more than 2 hours.

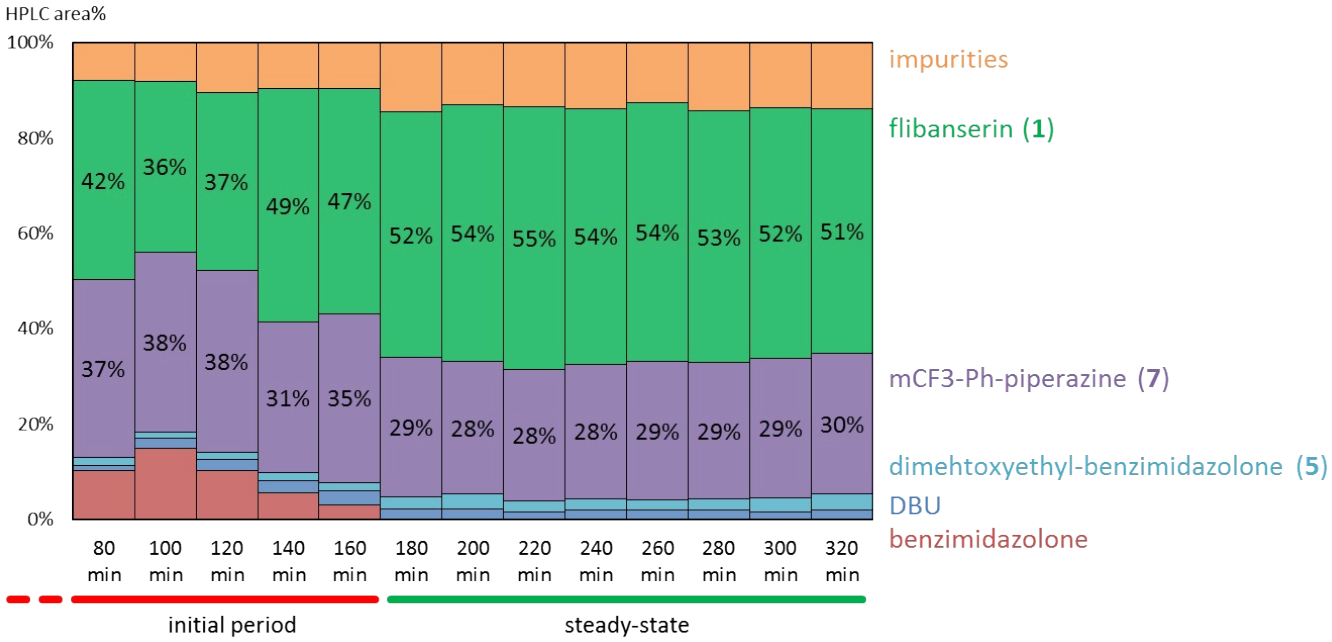


Figure S3. Composition of the crude product mixture determined by HPLC measurements of samples taken every 20 minutes. The main identified components are shown to the right, the duration of the steady state period is marked below.

Isolation of the product after the four-step continuous-flow system

During steady-state operation of the four-step continuous-flow system, the crude product solution (ca. 11 mL) collected in **CV2** over an exactly measured period of 20 min (theoretical amount of product based on the molar rate of the substrate (**2**) at **P1**, during the same time period is 0.5 mmol) is evaporated in vacuum. 199 mg of crude evaporation residue is obtained this way.

To the evaporation residue, 0.2 mL of concentrated hydrochloric acid and 2.0 mL of 2-propanol is added. The resulting crystals are collected by filtration, recrystallized from 2-propanol (2.0 mL), washed with 2-propanol and diethyl ether, and dried in vacuum. 67 mg (0.157 mmol; **31% isolated yield**) of the hydrochloride salt of flibanserin (**1**) is obtained as a white crystalline solid, in 98.9% purity (HPLC).

Productivity in terms of flibanserin base:

$$productivity\ (base) = \frac{n(isolated)\ \cdot\ M(base)}{time\ period} = \frac{0.157\ mmol\ \cdot\ 390.41\ g/mol}{0.333\ h} = 184\ mg/h$$

Characterization data of intermediates 2, 4-6, and product 1 · HCl

tert-butyl (2-aminophenyl)carbamate (2)

^{1}H NMR (400 MHz, DMSO-*d*6): *δ* = 8.26 (br s, 1H), 7.17 (d, *J*=7.7 Hz, 1H), 6.83 (td, *J*=8.0, 1.4 Hz, 1H), 6.67 (dd, *J*=7.9, 1.3 Hz, 1H), 6.52 (td, *J*=7.8, 1.4 Hz, 1H), 4.80 (br s, 2H), 1.45 (s, 9H).

tert-butyl (2-((2,2-dimethoxyethyl)amino)phenyl)carbamate (4)

^{1}H NMR (400 MHz, DMSO-*d*6) δ = 8.45 (br s, 1H), 7.08 (d, *J*=7.6, 1H), 7.03 – 6.96 (m, 1H), 6.68 – 6.63 (m, 1H), 6.59 (td, *J*=7.6, 1.2, 1H), 4.72 (t, *J*=5.7, 1H), 4.54 (t, *J*=5.4, 1H), 3.31 (s, 6H), 3.13 (t, *J*=5.6, 2H), 1.45 (s, 9H).

^{13}C NMR (101 MHz, DMSO-*d*6) δ = 153.79, 142.20, 125.89, 125.61, 123.94, 116.17, 111.11, 102.21, 78.62, 53.17, 44.83, 28.01.

ltqft**ESI-HRMS**: calcd for $C_{15}H_{25}O_4N_2$ [M+H]$^+$: 297.18088; found: 297.18081; delta= -0.25 ppm.

1-(2,2-dimethoxyethyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (5)

^{1}H NMR (400 MHz, DMSO-*d*6) δ = 10.87 (br s, 1H), 7.17 – 7.11 (m, 1H), 7.02 – 6.96 (m, 3H), 4.66 (t, *J*=5.4, 1H), 3.86 (d, *J*=5.5, 2H), 3.28 (s, 6H).

^{13}C NMR (101 MHz, DMSO-*d*6) δ = 154.13, 130.35, 128.05, 120.74, 120.38, 108.54, 108.26, 101.00, 53.53, 41.82.

ltqft**ESI-HRMS**: calcd for $C_{11}H_{15}O_3N_2$ [M+H]$^+$: 223.10772; found: 223.10775; delta= 0.14 ppm.

2-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)acetaldehyde (6)

^{1}H NMR (400 MHz, DMSO-*d*6) δ = 10.95 (br s, 1H), 9.63 (s, 1H), 7.03 – 6.96 (m, 4H), 4.80 (s, 2H).

^{13}C NMR (101 MHz, DMSO-*d*6) δ = 197.51, 154.16, 130.28, 128.19, 120.99, 120.42, 108.70, 107.94, 49.75.

EI-HRMS: calcd for $C_9H_8O_2N_2$ [M]$^+$: 176.05801; found: 176.05803; delta= -0.11 ppm.

1-(2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one hydrochloride (flibanserin hydrochloride, 1 · HCl)

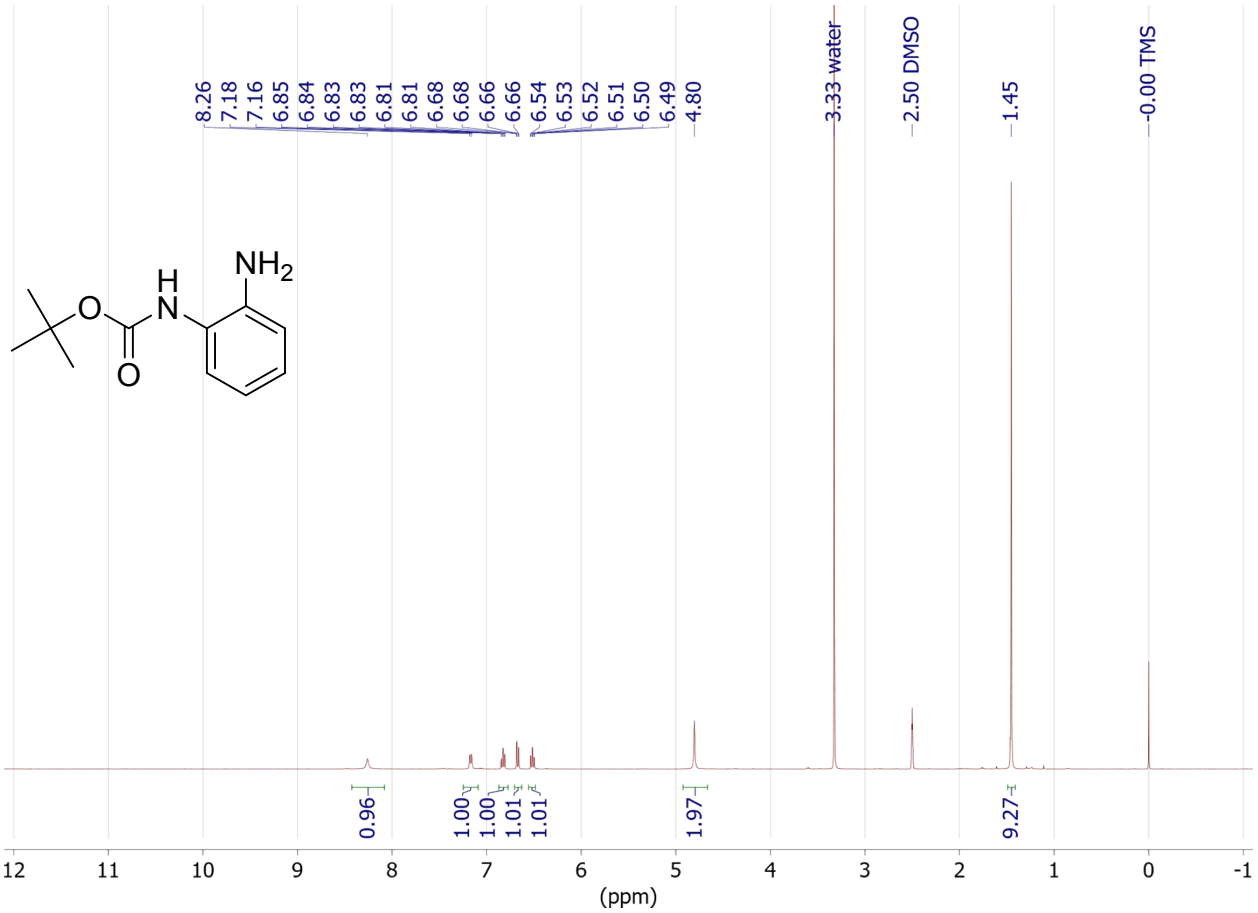
^{1}H NMR (400 MHz, DMSO-*d*6) δ = 11.06 (s, 1H), 10.89 (br s, 1H), 7.47 (t, *J*=7.9, 1H), 7.36 – 7.27 (m, 3H), 7.16 (d, *J*=7.6, 1H), 7.10 – 7.02 (m, 3H), 4.30 (t, *J*=6.2, 2H), 4.01 (d, *J*=11.8, 2H), 3.83 – 3.73 (m, 2H), 3.54 – 3.45 (m, 2H), 3.29 – 3.11 (m, 4H).

^{13}C NMR (101 MHz, DMSO-*d*6) δ = 154.16, 149.68, 130.08, 129.93 (q, $^2J_{CF}$=31.1 Hz), 129.51, 128.43, 124.23 (q, $^1J_{CF}$=272.5 Hz), 121.28, 120.57, 119.15, 115.64 (q, $^3J_{CF}$=3.3 Hz), 111.60 (q, $^3J_{CF}$=3.6 Hz), 108.90, 108.07, 52.66, 50.41, 44.71, 34.66.

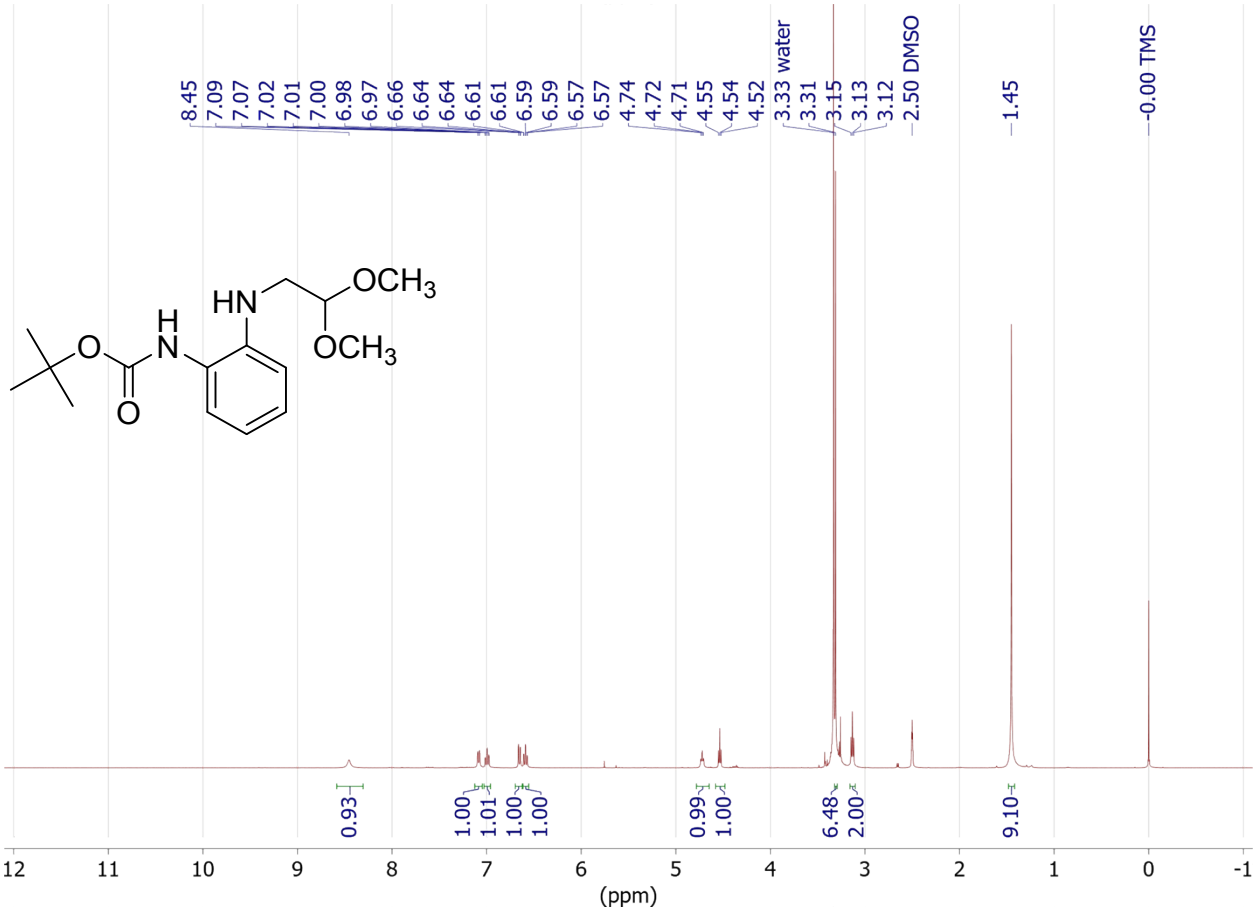
vpoe**ESI-HRMS**: calcd for $C_{20}H_{22}ON_4F_3$ [M+H]$^+$: 391.17402; found: 391.17369; delta= -0.85 ppm.

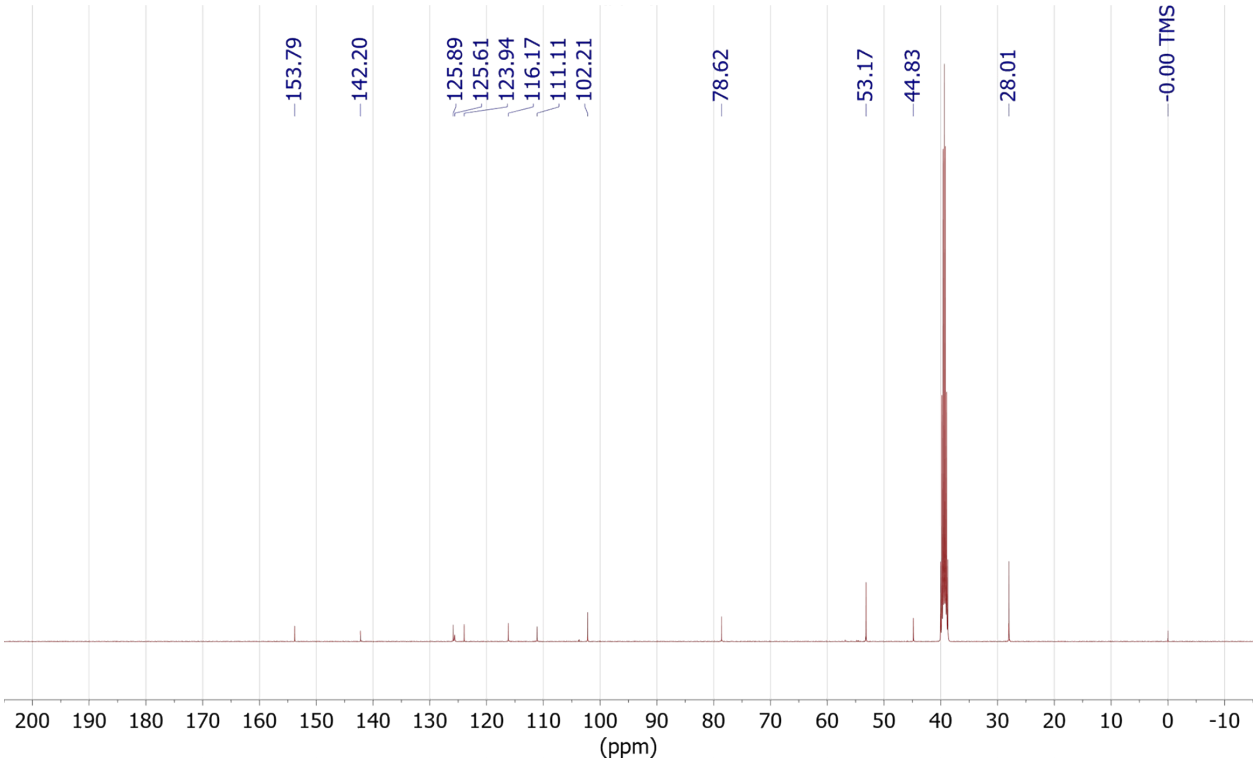
NMR spectra of intermediates 2, 4-6, and product 1 · HCl

tert-butyl (2-aminophenyl)carbamate (2) ^{1}H NMR (DMSO)

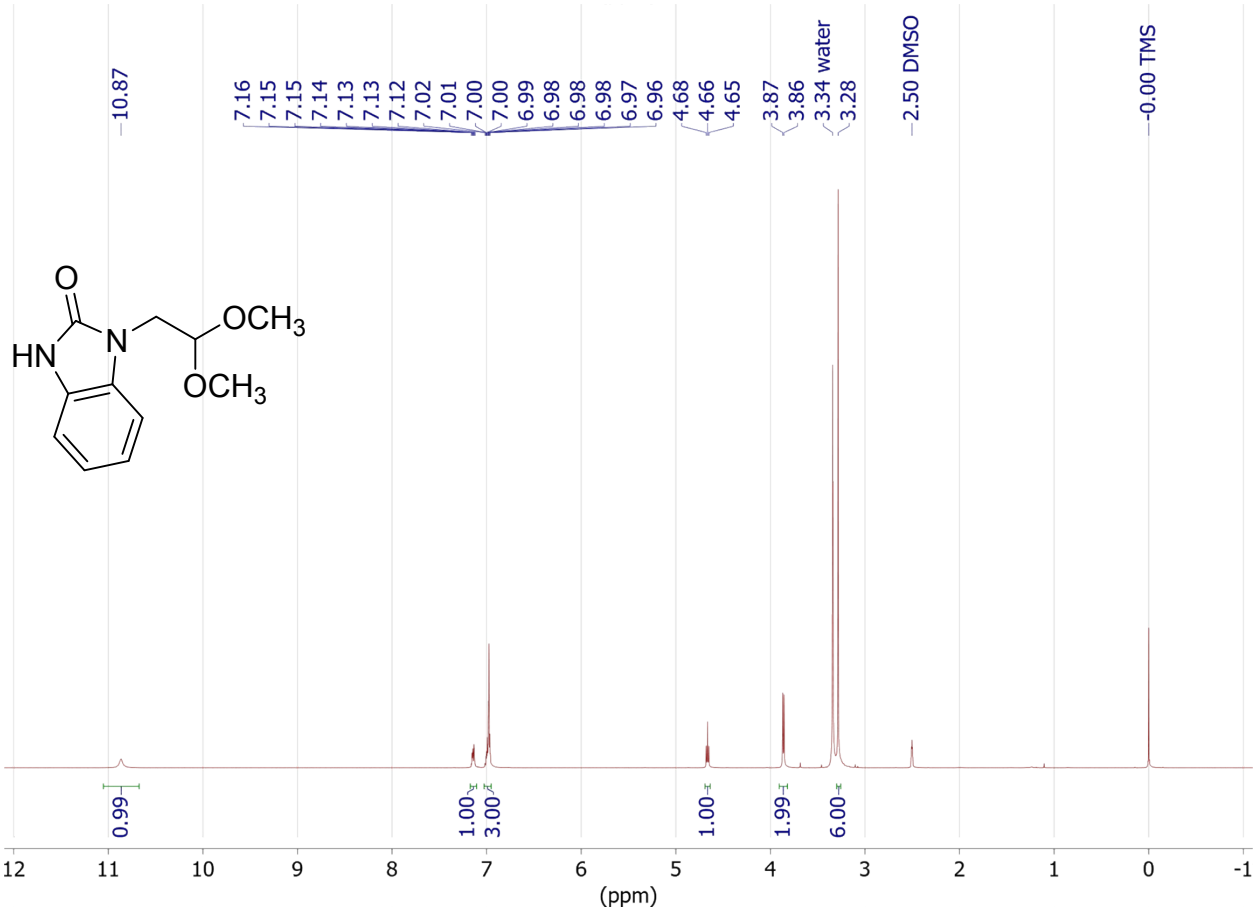


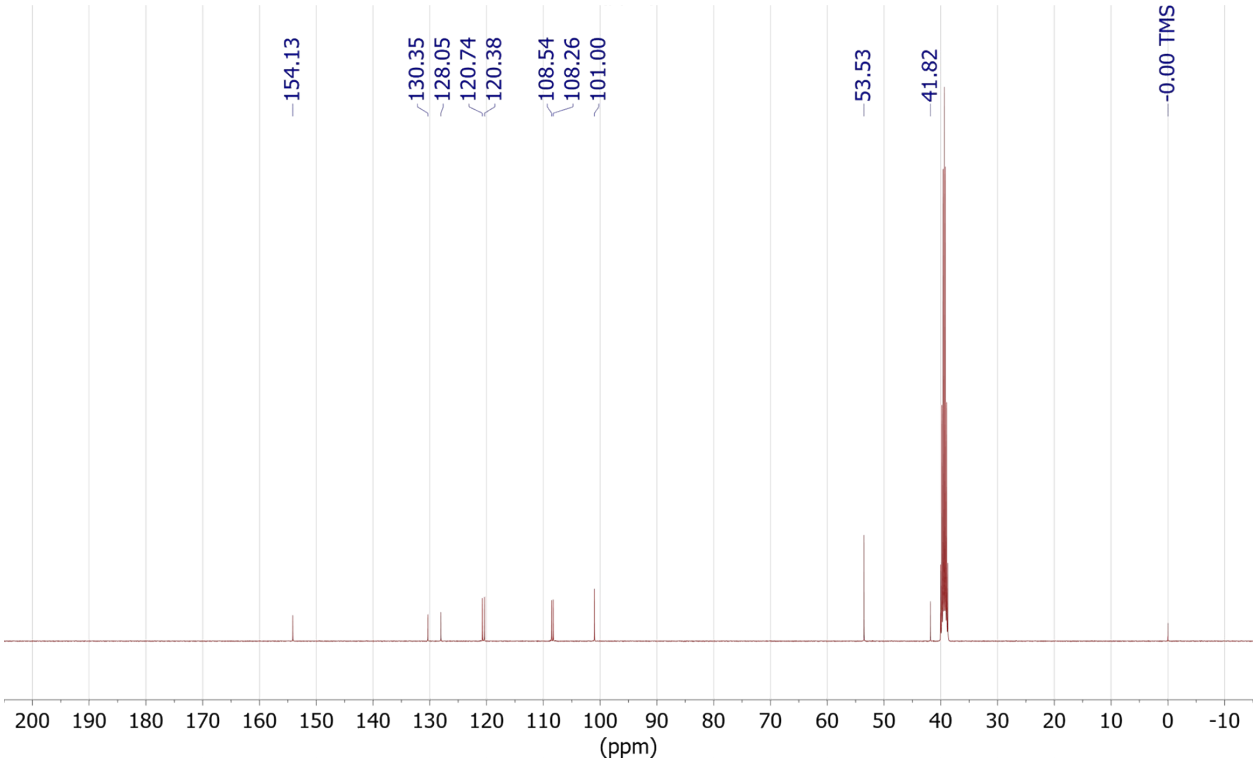
tert-butyl (2-((2,2-dimethoxyethyl)amino)phenyl)carbamate (4) ^{1}H and ^{13}C NMR (DMSO)





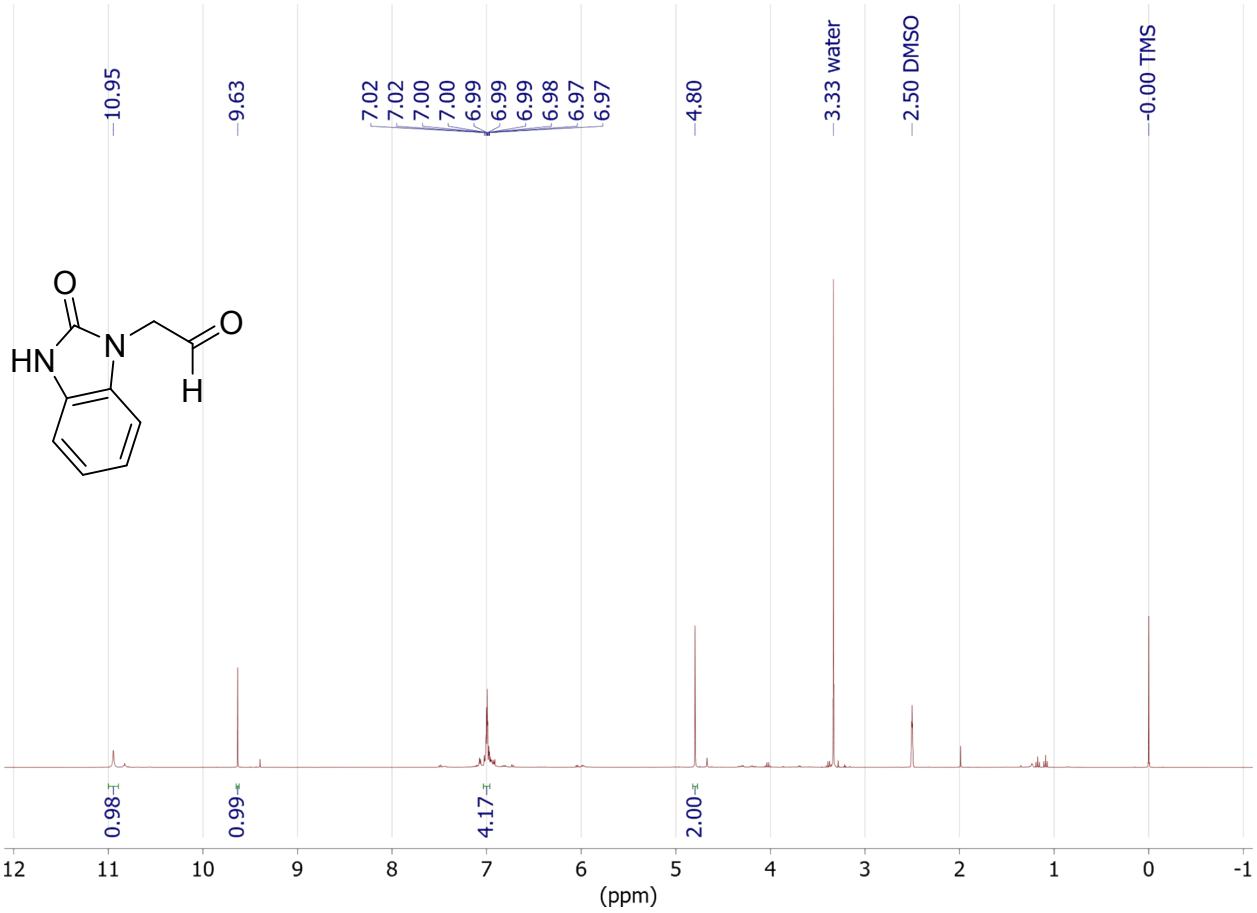
1-(2,2-dimethoxyethyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (5) ^{1}H and ^{13}C NMR (DMSO)

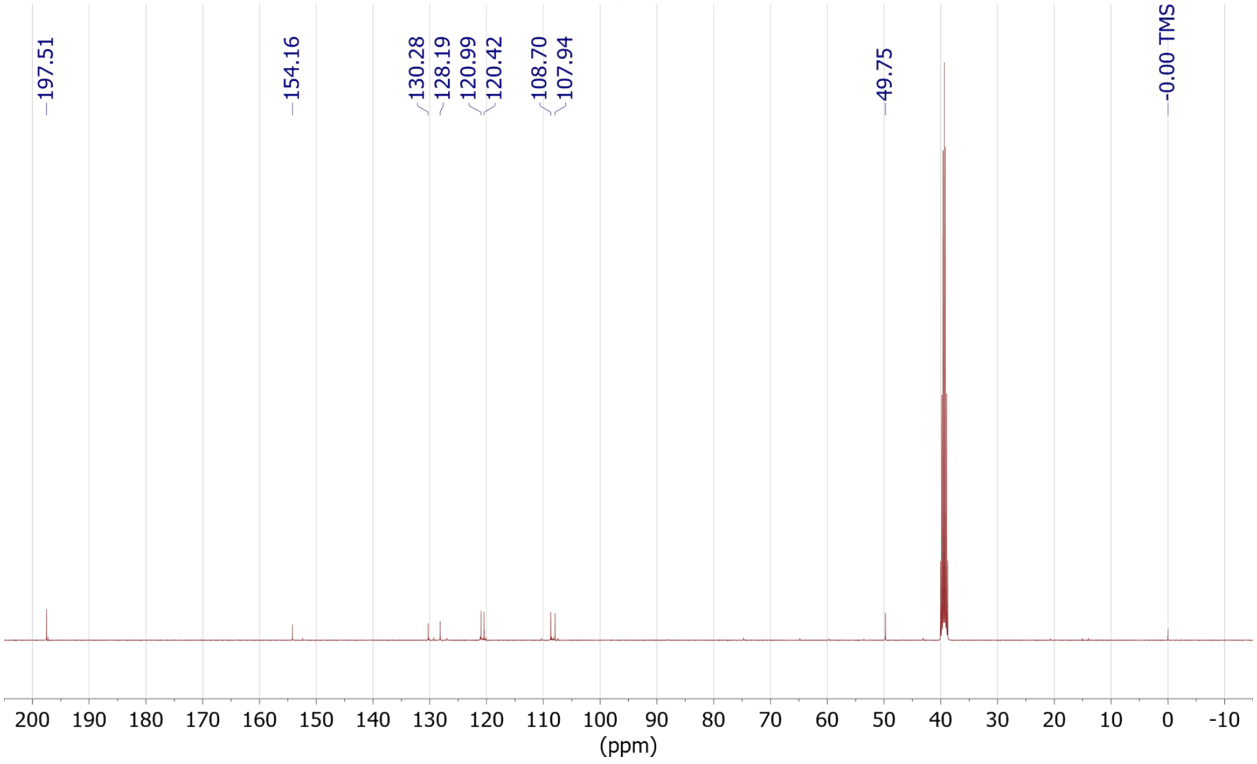




2-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)acetaldehyde (6) ^{1}H and ^{13}C NMR (DMSO)

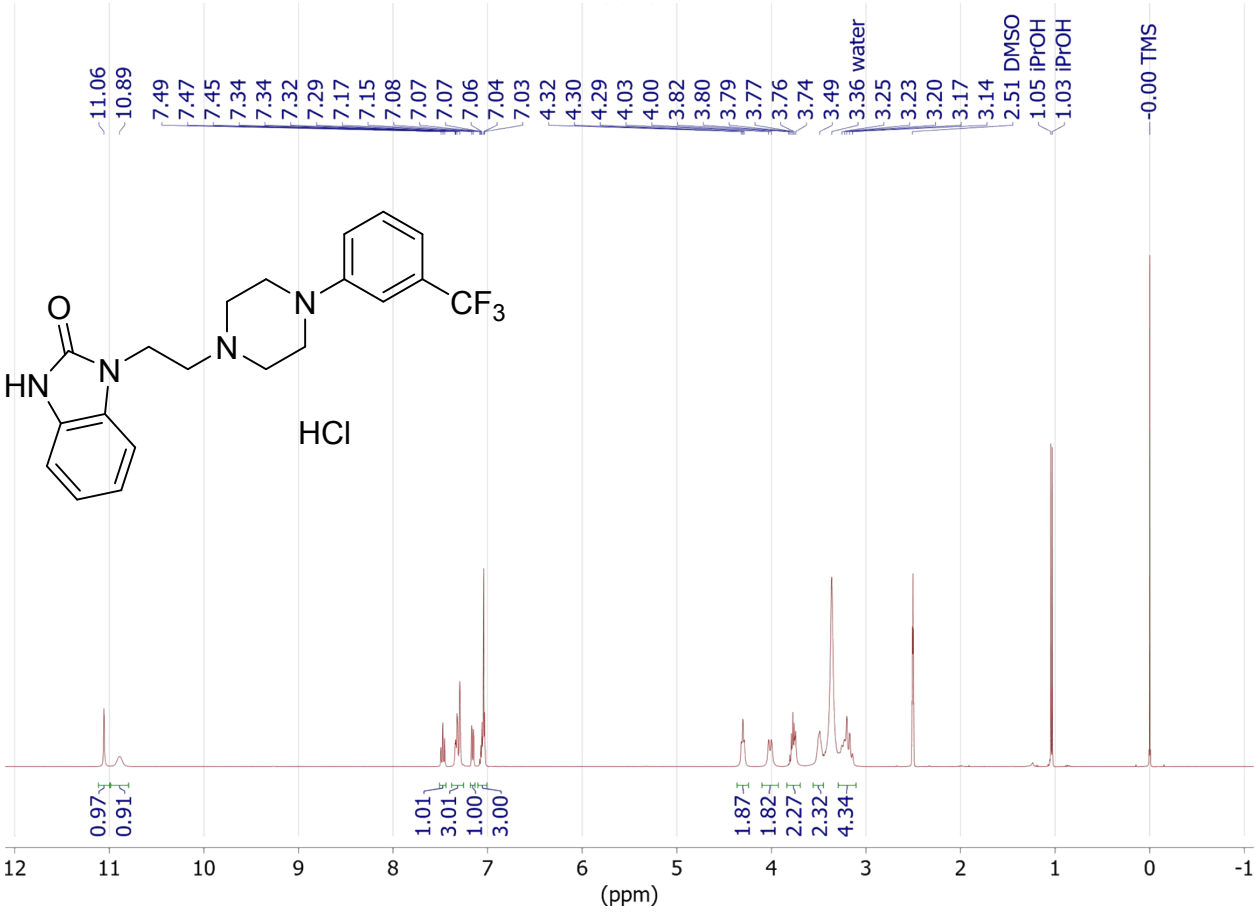
(note: impurities occur due to decomposition in DMSO-*d*6 solvent, poor solubility doesn't allow other solvents)

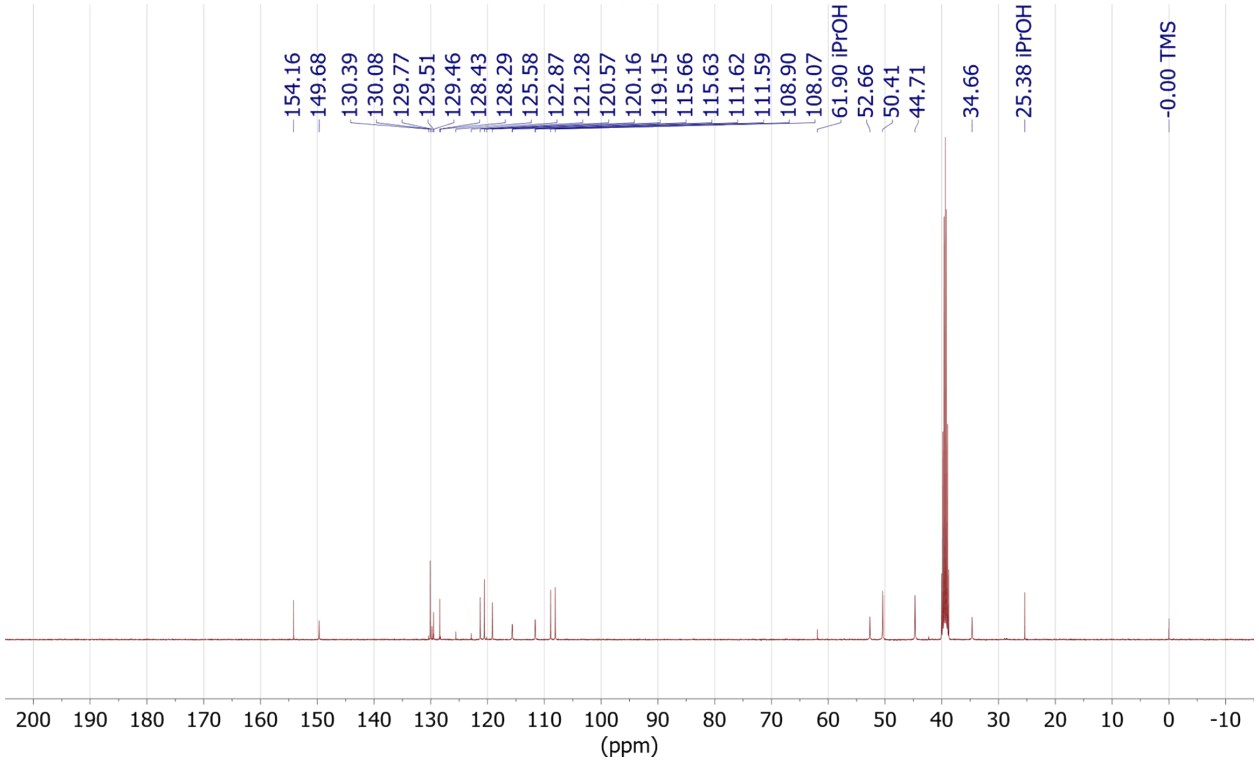




1-(2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one hydrochloride (flibanserin hydrochloride, 1 · HCl) ^{1}H and ^{13}C NMR (DMSO)

(note: contains residual 2-propanol solvent)





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7 https://syrris.com/modules/asia-heater/

8 https://www.dibaind.com/labware/omnifit-labware-connectors-adapters-valves/

9 https://www.dibaind.com/labware/omnifit-labware-glass-chromatography-columns/

10 http://www.zaiput.com/back-pressure-regulators

11 http://thalesnano.com/h-cube-series

12 http://www.sigmaaldrich.com/catalog/product/supelco/58696u

13 http://www.sigmaaldrich.com/catalog/product/supelco/58699

14 https://www.sigmaaldrich.com/catalog/product/supelco/z226955

15 http://www.knauer.net/en/product/bushing_and_sealing_ring.html

16 http://www.sigmaaldrich.com/catalog/product/supelco/57654