Supporting Information for:

Continuous flow upgrading of glycerol toward oxiranes and active pharmaceutical ingredients thereof

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1. Continuous flow setups

1.1 Microfluidic setups and parts

All microfluidic setups were assembled with commercially available parts.

1.1.1 Pumps

ThalesNano microHPLC® pumps (wetted parts: SS 316, ruby and sapphire) or Chemyx Fusion 6000® High Force syringe pumps equipped with stainless steel syringes (6 or 20 mL) with Dupont™ Kalrez® Spectrum™ AS-568 O-rings (0.549 x 0.103”) were utilized to handle the liquid feeds.

1.1.2 SS packed-bed reactor (glass beads)

Packed-bed reactors were assembled from SS columns (12.5 cm × 7 mm o.d. × 4 mm i.d.) with coned PEEK fittings.

1.1.3 PFA tubing and coils

Feed lines, PFA coil reactors and collection lines were constructed from PFA tubing (high purity PFA; 1.58 mm outer diameter, 800 µm internal diameter).

1.1.4 Connectors, ferrules and mixers

Capillaries were assembled with coned PEEK fittings or Super Flangeless PEEK nuts, ETFE ferrules and SS rings. Mixers consisted of PEEK T-mixers (0.02” through hole) or PEEK cross-junctions (0.02” trough hole). Connectors, ferrules, unions and mixers were purchased from IDEX/Upchurch (details in Table S1).

1.1.5 Check-valves

The check-valves inserted between the pumps and the reactors were purchased from IDEX/Upchurch Scientific (PEEK check-valve holder).

1.1.6 Back-pressure regulators

Spring-loaded BPRs were purchased from IDEX/Upchurch Scientific (PEEK or SS check-valve holder). Dome-type BPRs were purchased from Zaiput Flow Technologies (BPR-10). The dome-type BPR was connected to a compressed gas cylinder (nitrogen) to set the working pressure. Low volume adjustable BPRs were purchased from Future Chemistry.

1.1.7 In-line liquid-liquid separator

The in-line liquid-liquid separator was obtained from Zaiput Flow Technologies (SEP-10) and equipped with a hydrophobic OB-900 membrane.

1.1.8 Thermoregulatory devices

PFA coils were thermoregulated in oil baths (Heidolph™ MR Hei-Tec® equipped with Pt-1000 temperature sensors).

1.2 Mesofluidic setups and parts

1.2.1 Pumps

The liquid feeds were handled with Corning dosing lines (HMP gear pump and FLOM PTFE intelligent pump).

1.2.2 Mesofluidic reactor

The mesofluidic setup utilized for the neutralization/dechlorination step was manufactured by Corning SAS (Corning® Advanced-Flow™ G1 SiC reactor) and equipped with 6 fluidic modules connected in series (60 mL total internal volume).

1.2.3 Thermoregulatory device

The reactor was maintained at reaction temperature with a LAUDA Integral XT 280 thermostat (LAUDA Therm 180 silicone oil).

1.2.4 Back-pressure regulator

A dome-type BPR from Zaiput Flow Technologies (BPR-1000) connected to a compressed gas cylinder (nitrogen) was utilized to set the working pressure.

1.3 Part numbers & vendors

Standard fluidic elements and connectors were purchased from IDEX/Upchurch Scientific, Valco Instruments Co. Inc, Future Chemistry and Zaiput Flow Technologies (Table S1).

Table S1. Connectors, ferrules and unions.

Item	Details	Vendor	Reference
Connectors	One-Piece Fingertight, PEEK, 10-32 Coned, for 1/16” OD	IDEX/ Upchurch Scientific	F-120X
	Super Flangeless Nuts, natural PEEK 1/4-28 thread for 1/16” OD tubing	IDEX/ Upchurch Scientific	P-255X
	Super Flangeless Ferrule Tefzel (ETFE) and SS ring 1/4-28 thread for 1/16” OD tubing	IDEX/ Upchurch Scientific	P-259X
Unions	Natural polypropylene standard low pressure union 1/4-28	IDEX/ Upchurch Scientific	P-620

Mixers	T-mixer, natural PEEK 1/4-28 thread for 1/16" o.d. tubing, 0.02" through hole	IDEX/ Upchurch Scientific	P-712
	Cross Assembly, natural PEEK, 1/4-28 thread for 1/16" o.d. tubing, 0.02" through hole	IDEX/ Upchurch Scientific	P-722
Check-valve	Check-valve inline cartridge 1.5 psi and cartridge holder, PEEK	IDEX/ Upchurch Scientific	CV-3000
Spring-loaded BPR	BPR cartridge with gold coating (various set points)	IDEX/ Upchurch Scientific	P-763
Cartridge holder	BPR holder assembly for spring-loaded cartridge, PEEK	IDEX/ Upchurch Scientific	P-465
Dome-type BPR	Dome-type BPR, metal-free, with adjustable set point	Zaiput Flow Techn.	BPR-10
			BPR-1000
Liquid-liquid separator	Continuous separator, metal-free wetted parts	Zaiput Flow Techn.	SEP-10
Low volume adjustable BPR	Adjustable BPR by turning the bottom screw, Kalrez® and PEEK wetted parts	Future Chemistry	Included in B-480
Tubing	High-purity PFA tubing, 1.58 mm outer diameter, 800 µm internal diameter	VICI (Valco Ins. Co. Inc.)	JR-T-4002-M25

1.4 Detailed continuous flow setups

1.4.1 Hydrochlorination of glycerol (**1**)

See manuscript for experimental details (Scheme 1, Tables 1 and 2).

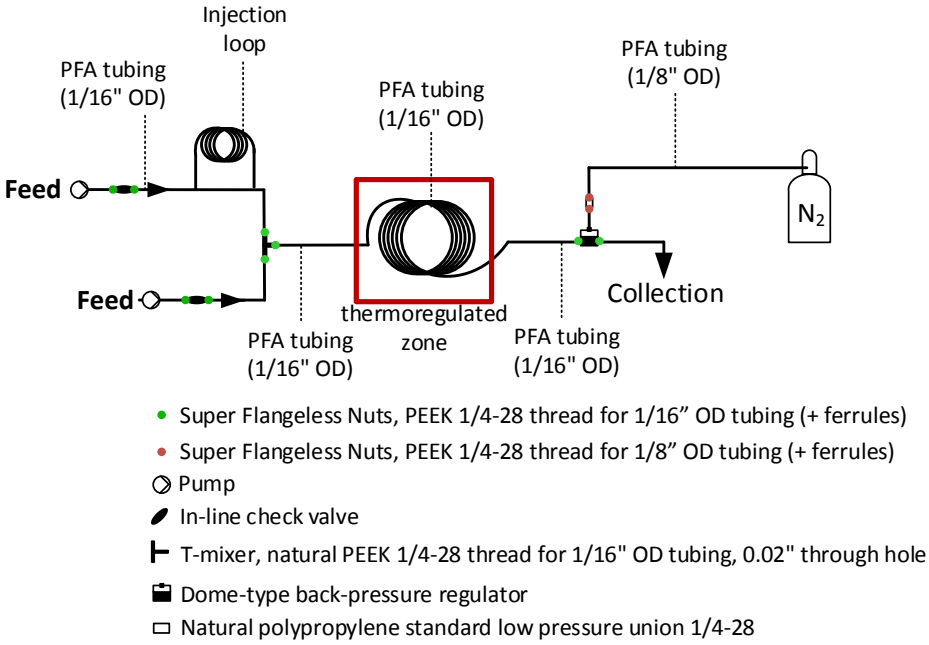


Figure S1. Detailed setup for the continuous flow hydrochlorination of glycerol (**1**).

1.4.2 Hydrochlorination of glycerol (**1**) in presence of an organic carrier

See Section 2.2.4 for experimental details.

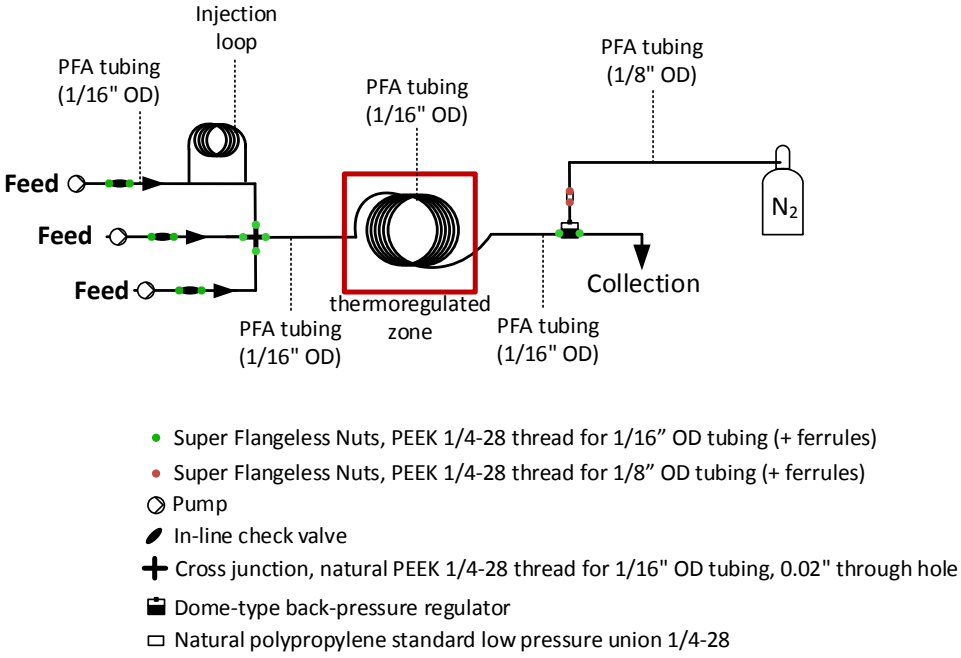


Figure S2. Detailed setup for the continuous flow hydrochlorination of glycerol (**1**) in presence of an organic carrier.

1.4.3 Hydrochlorination/dechlorination sequence for the preparation of glycidol (**4**) and epichlorohydrin (**5**) starting from glycerol (**1**)

See manuscript for experimental details (Scheme 2, Table 3).

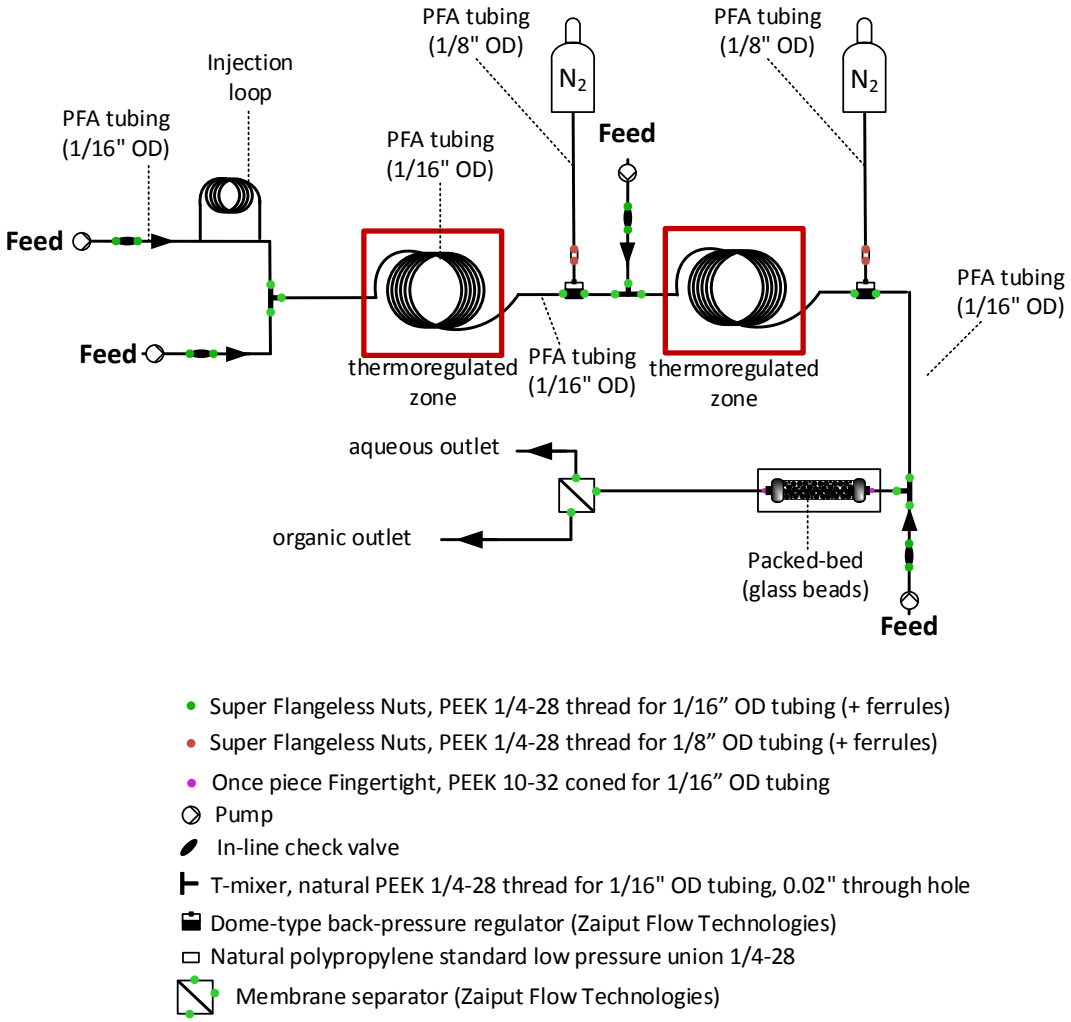


Figure S3. Detailed setup for the concatenated hydrochlorination/dechlorination sequence of glycerol (**1**) featuring the in-line extraction module (pressure regulation downstream the membrane separator is omitted for clarity).

1.4.4 Dechlorination of chlorohydrin **2b** and **3b** toward oxiranes **4**,**5** (mesofluidic system)
See manuscript for experimental details (Figure 5, Table 4).

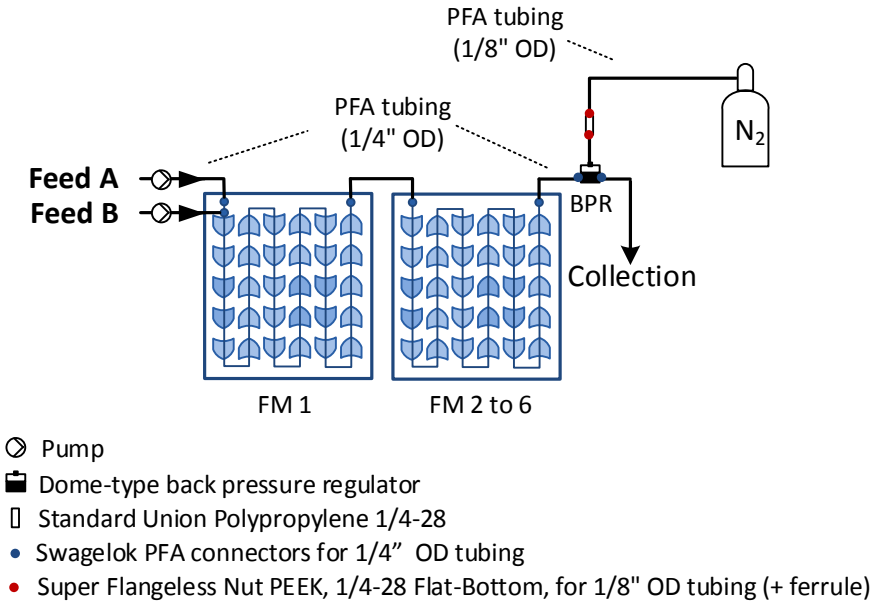


Figure S4. Detailed setup for the dechlorination step toward oxiranes **4,5** from chlorohydrin **2b** and **3b** under mesofluidic conditions.

1.4.5 Etherification of aryl alcohols **7a**,**b**
See manuscript for experimental details (Scheme 3, Table 5).

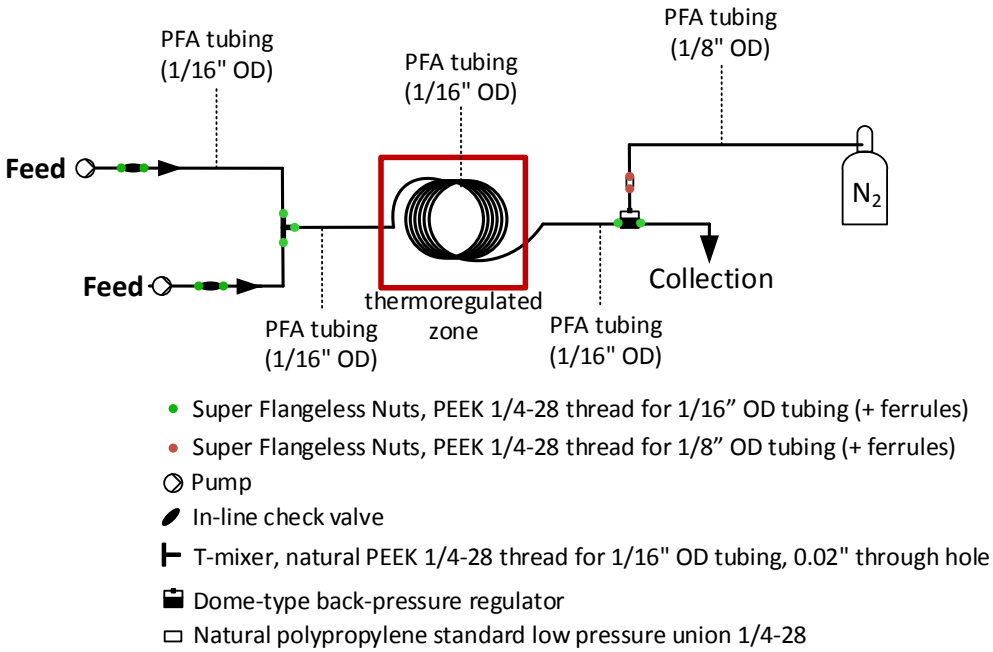


Figure S5. Detailed setup for the continuous flow etherification of aryl alcohols **7a,b** toward glycidyl derivatives **8a,b**.

1.4.6 Aminolysis of glycidyl derivatives **8a,b** (catalyst-free)
See manuscript for experimental details (Scheme 4, Table 6).

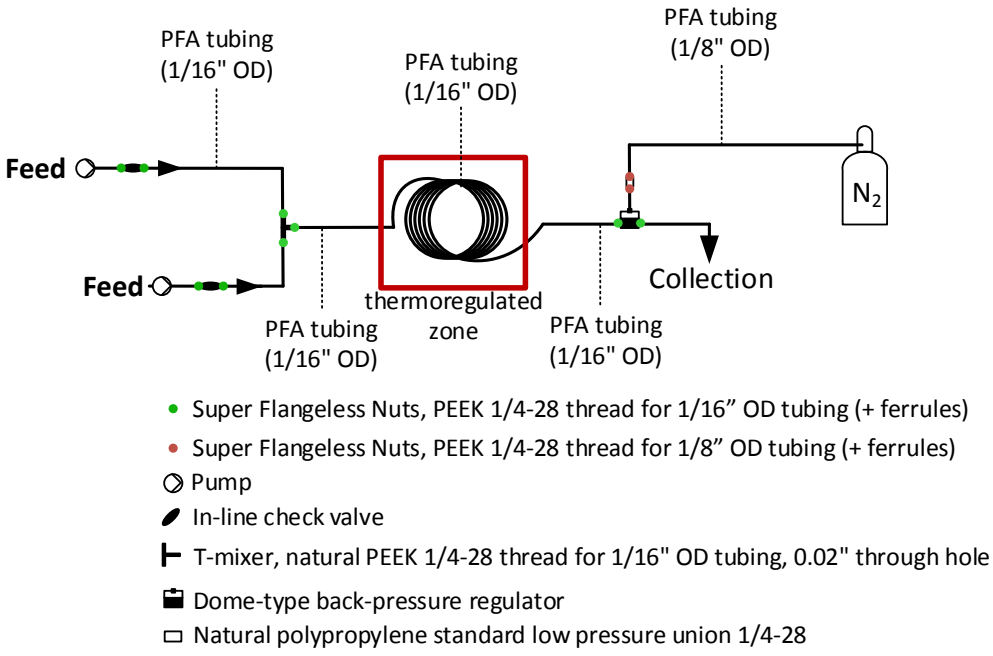


Figure S6. Detailed setup for the catalyst-free continuous flow aminolysis of glycidyl derivatives **8a,b** toward propranolol **10a**.

1.4.7 Aminolysis of glycidyl derivatives **8a,b** (catalyzed)
See manuscript for experimental details (Scheme 4, Table 6).

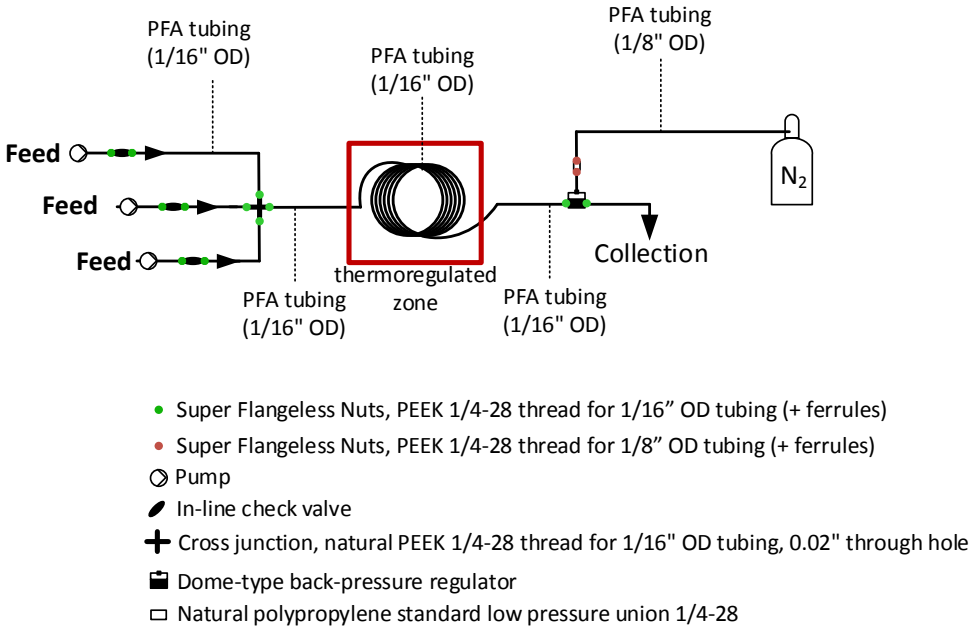


Figure S7. Detailed setup for the catalyzed continuous flow aminolysis of glycidyl derivatives **8a,b** toward APIs **10a-d**.

1.4.8 Catalyst-free concatenated system for the preparation of APIs **10a,b** from epichlorohydrin (**5**)

See manuscript for experimental details (Scheme 5).

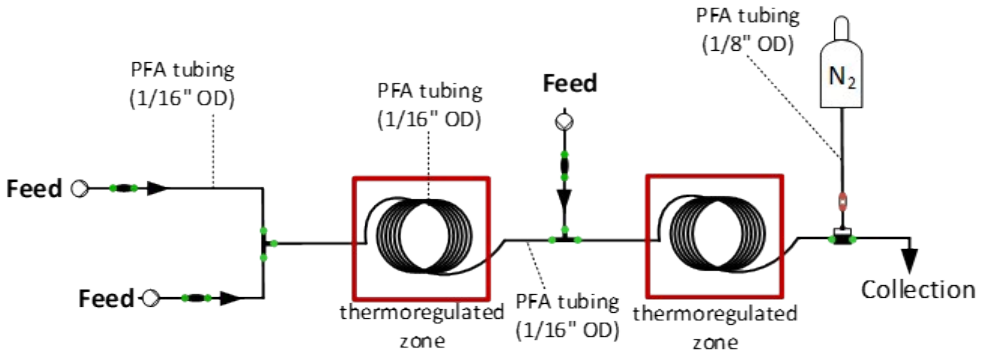


Figure S8. Detailed setup for the catalyst-free continuous flow etherification/aminolysis sequence toward APIs **10a,b**.

2 Additional experimental details

2.1 Chemicals

Chemicals, purity, CAS numbers and suppliers are provided in Table S2. Unrefined glycerin specifications are provided in Table S3.

Table S2. Solvents, chemicals and suppliers.

Solvents	Purity (%)	CAS Number	Supplier
Dimethylsulfoxide	>99%	67-68-5	VWR
Ethanol (absolute)	>99%	64-17-5	VWR
Ethyl acetate	≥99.5 %	141-78-6	Merck - Sigma Aldrich
2-Methyltetrahydrofuran	≥99%	96-47-9	Merck
Methyl *tert*-butyl ether	>99%	1634-04-4	VWR
Di-*n*-butyl ether	99%	142-96-1	Alfa Aesar
Diethyl ether	>99%	60-29-7	VWR
Petroleum spirit 40-60 °C	/	8032-32-4	VWR
Methyl ethyl ketone	>99%	78-93-3	VWR
n-Heptane	99.4%	142-82-5	VWR
Chemicals	**Purity (%)**	**CAS number**	**Supplier**
1,2,3-Propanetriol (glycerol)	99%	56-81-5	ABCR
Hydrochloric acid 36 wt.-%	/	7647-01-0	Merck
2-Chloropropane-1,3-diol	≥97%	497-04-1	Carbosynth Ltd.
3-Chloropropane-1,2-diol	99%	96-24-2	Acros Organics
1,3-Dichloropropan-2-ol	99%	96-23-1	Acros Organics
2,3-Dichloropropan-1-ol	≥98%	616-23-9	TCI
Glycidol	96%	556-52-5	Acros Organics
Epichlorohydrin	99%	106-89-8	Acros Organics
Formic acid	99%	64-18-6	Janssen
Acetic acid	99%	64-19-7	Baker
Glycolic acid	>98%	79-14-1	TCI
Succinic acid	>99%	110-15-6	TCI
Malic acid	>99%	6915-15-7	Acros Organics
L-(+)-tartaric acid	99%	87-69-4	Aldrich
Oxalic acid	98%	144-62-7	Sigma-Aldrich
Malonic acid	99%	141-82-2	Aldrich Europe
Glutaric acid	>99%	110-94-1	TCI
Adipic acid	>99%	124-04-09	TCI

Pimelic acid	>98%	111-16-0	TCI
γ-Butyrolactone	99%	96-48-0	Janssen
ε-Caprolactone	>99%	502-44-3	TCI
Hydrochloric acid 4 mol L^{-1} in cyclopentyl methyl ether	/	7647-01-0	TCI
Sodium hydroxide	98.5%	1310-73-2	Acros Organics
1-(2-Methoxyphenyl)piperazine	98%	35386-24-4	Acros Organics
Isopropylamine	99%	75-31-0	Acros Organics
1-Naphthol	>99%	90-15-3	Acros Organics
2-Allylphenol	>98%	1745-81-9	Alfa Aesar
Propranolol hydrochloride	>99%	318-98-9	TCI
Naftopidil	98%	57149-07-2	Acros Organics
Potassium *tert*-butoxide	>98%	865-47-4	Acros Organics
Zinc perchlorate hexahydrate	/	10025-64-6	Alfa Aesar
Zinc trifluoromethanesulfonate	>98%	54010-75-2	TCI

Table S3. Specifications of the unrefined glycerin.

Property	Range (%)	Supplier
Glycerin content	Min 80.0	Cargill™
Water content	Max 15.0	
MONG (Matter Organic Non Glycerin)	Max 2.5	
Salts (NaCl, as ash)	Max 7.0	
Methanol content	Max 0.2	

2.2 Additional experimental data

2.2.1 Analytical methods

Yield, conversion and partition coefficient values were determined by GC-FID or by HPLC-DAD using the following methods:

GC method A: The GC-FID oven program consisted of the following steps: a 3 min hold at 40 °C, a 20 °C/min ramp to 100 °C, a 40 °C/min ramp to 220°C °C, and a 3 min hold at 220 °C. The temperature of the injector was set at 250 °C and the temperature of the FID was set at 240 °C. Prior to analysis unless specified otherwise, the sample was homogenized, 50 µL of the sample was diluted with 1 mL of EtOH in a 1.5 mL Eppendorf® vial. If necessary, the sample was then centrifuged during 5 min at 10,000 rpm. The supernatant was finally collected and injected for analysis. Conversions, yields and/or partition coefficients of compounds **1**, **2a**, **2b**, **3a**, **3b**, **4** and **5** were determined using this method.

GC method B: The GC-FID oven program consisted of the following steps: a 3 min hold at 40 °C, a 20 °C/min ramp to 100 °C, a 40 °C/min ramp to 220 °C, and a 6 min hold at 220 °C. The temperature of the injector was set at 250 °C and the temperature of the FID was set at 240 °C. Prior to analysis unless specified otherwise, the sample was homogenized, 50 µL of the sample was diluted with 1 mL of EtOH in a 1.5 mL Eppendorf® vial. Conversions and/or yields of compounds **5**, **7a**, **7b**, **8a** and **8b** were determined using this method.

GC method C: The GC-FID oven program consisted of the following steps: a 3 min hold at 40 °C, a 30 °C/min ramp to 280 °C and a 5 min hold at 280 °C. The temperature of the injector was set at 300 °C and the temperature of the FID was set at 300 °C. Prior to analysis unless specified otherwise, the sample was homogenized, 50 µL of the sample was diluted with 1 mL of EtOH in a 1.5 mL Eppendorf® vial. Conversions and/or yields of compounds **8a**, **8b**, **10a** and **10c** were determined using this method.

HPLC method A:

Eluent: A: Water + 0.1% CF_3COOH (v:v)
B: Acetonitrile

Gradient Table:

Time [min]	A [%]	B [%]
0	100	0
20	20	80
23	20	80
25	100	0
31	100	0

Flow: 1 mL min^{-1}

Injection Volume: 10-20 µL

Column: C18, 100 × 4.6 mm, 3 µm

Oven Temperature: 40 °C

Diode Array Detector: 180-800 nm (processed either at 280 nm (**10b**) or at 275 nm (**10d**))

2.2.2 Representative GC and HPLC traces

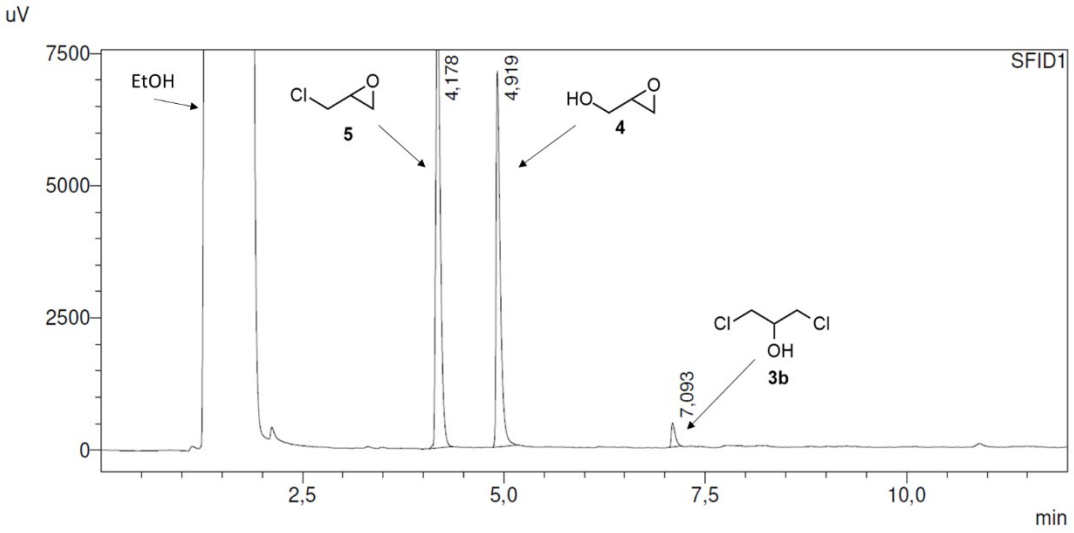


Figure S9. GC trace of the effluent obtained from the dechlorination of **2b** and **3b** toward **4** and **5** under mesofluidic conditions (see Table 4, entry 1 of the manuscript, GC method A).

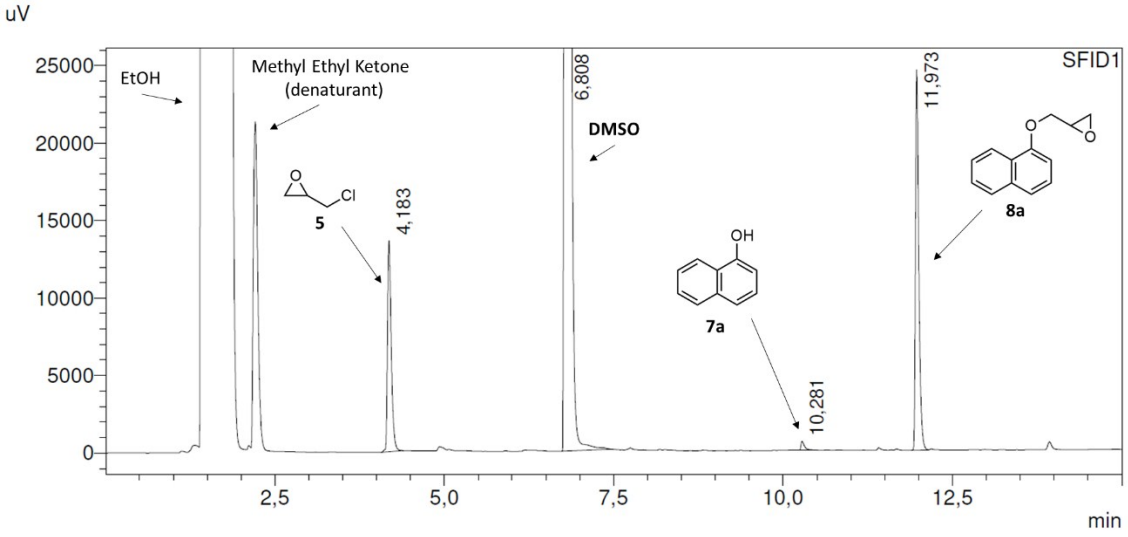


Figure S10. GC trace of the effluent obtained from the glycidyl ether synthesis of **8a** from aryl alcohol **7a** under microfluidic conditions (see Table 5, entry 6 of the manuscript, GC method B).

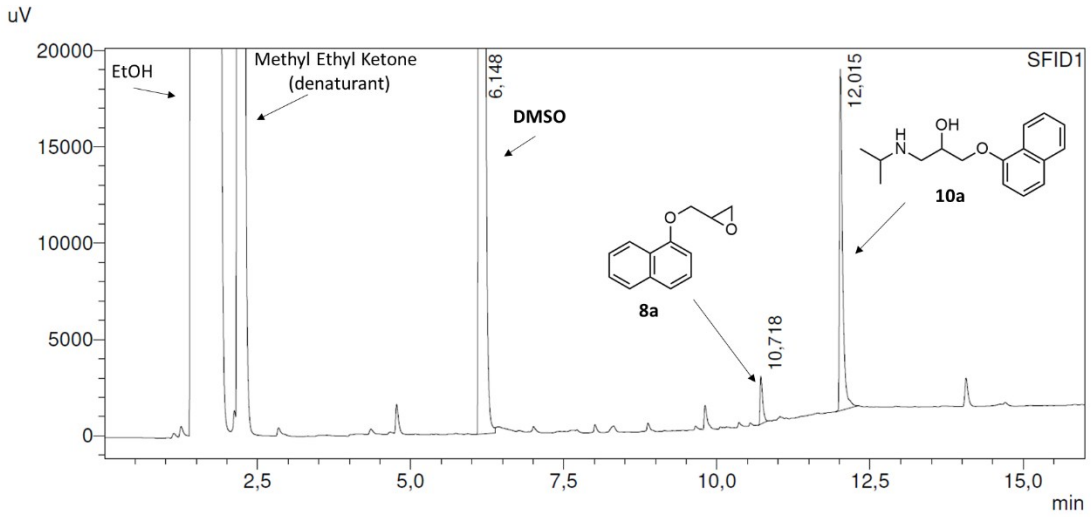


Figure S11. GC trace of the effluent obtained from the aminolysis of **8a** toward **10a** under microfluidic conditions (see Table 6, entry 7 of the manuscript, GC method C).

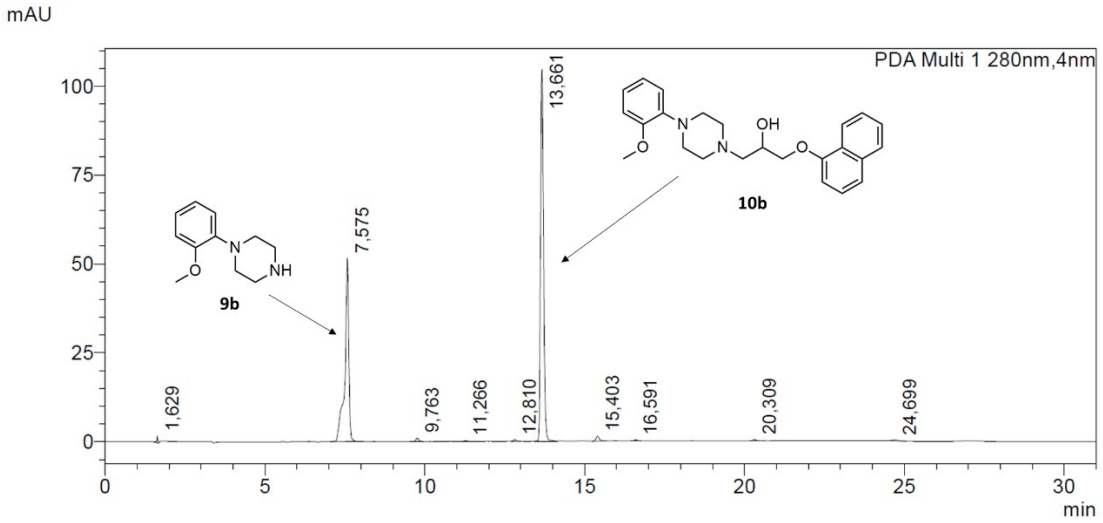


Figure S12. HPLC trace of the effluent obtained from the aminolysis of **9b** toward **10b** under microfluidic conditions (see Table 6, entry 16 of the manuscript, HPLC method A, 280 nm).

2.2.3 Impact of the HCl/**1** ratio on the formation of chlorohydrins **2b** and **3a,b** under continuous flow conditions

Pimelic acid (**6k**, 10 mol% with respect to **1**) was solubilized in HCl 36 wt.-% and inserted in a PFA injection loop prior to processing. The pumps used to deliver the solution of HCl/catalyst and neat **1** were set according to Table S4 for specific HCl/**1** ratios. Both streams were mixed through a PEEK T-mixer and reacted in a PFA capillary coil (1.5 mL internal volume, estimated 20 min residence time) at 140 °C under 8 bar of counterpressure. The reactor effluent was collected at steady state, neutralized, diluted with water and ethanol, and analyzed by GC-FID (Table S4).

Table S4. Impact of the HCl/**1** ratio for the generation of chlorohydrins **2b** and **3a,b** under continuous flow conditions[a].

Entry	Flow rate HCL/Catalyst (µL min^{-1})	Flow rate neat **1** (µL min^{-1})	HCl/**1** ratio	Conv. (%)[b]	**2b** yield (%)[b]	**3a** yield (%)[b]	**3b** yield (%)[b]	Cumulated yield (%)
1	8.4	68	6:1	>99	35	2	44	81
2	6.9	70	7.5:1	>99	27	2	47	76
3	5.8	71	9:1	>99	30	2	47	79

[a]Conditions: Pimelic acid 10 mol%, 20 minutes of residence time, 140 °C, 8 bar of counterpressure (see also Figure S1). [b]Determined by GC-FID.

2.2.4 Introduction of a co-solvent for the formation of chlorohydrins **2b** and **3a,b** under continuous flow conditions

Pimelic acid (**6k**, 10 mol% with respect to **1**) was solubilized in HCl 36 wt.-% and inserted in a PFA injection loop prior to processing. The pumps used to deliver the solution of HCl/catalyst, neat **1** and the organic co-solvent were set at 68 µL min^{-1}, 8.4 µL min^{-1} and 75 µL min^{-1} respectively. The streams were mixed through a PEEK cross-junction and reacted in a PFA capillary coil (3 mL internal volume, estimated 20 min residence time) at 140 °C under 8 bar of counterpressure. The reactor effluent was collected at steady state, neutralized, diluted with water and ethanol, and analyzed by GC-FID (Table S5).

Table S5. Impact of an organic co-solvent for the generation of chlorohydrins **2b** and **3a,b** under continuous flow conditions[a].

Entry	Co-solvent	Pressure (bar)	Conv. (%)[b]	**2b** yield (%)[b]	**3a** yield (%)[b]	**3b** yield (%)[b]	Cumulated yield (%)
1	*n*-Butyl acetate	8	>99	27	1	43	71
2[c]	MIBK	8	79	50	0	6	56
3[d]	1-Butanol	8	>99	27	0	34	61
4	Dichloroethane	10	11	9	0	<1	10
5	Toluene	8	99	47	1	22	70

MIBK = Methyl isobutyl ketone. [a]Conditions: Pimelic acid 10 mol%, 20 minutes of residence time, 140 °C (see also Figure S2). [b]Determined by GC-FID. [c]HCl 28 wt.-% was used to keep two immiscible feeds. [d]Immiscible side-products were obtained.

2.2.5 Use of HCl in an organic solvent as chlorination agent for the formation of chlorohydrins **2b** and **3a,b** under continuous flow conditions

Pimelic acid (**6k,** 10 mol% with respect to **1**) was solubilized in a solution of HCl 4 mol L^{-1} in cyclopentyl methyl ether (CPME) and inserted in a PFA injection loop prior to processing. The pumps used to deliver the solution of HCl in CPME/catalyst and neat **1** were set at 72 µL min^{-1} and 4.6 µL min^{-1}, respectively. Both streams were mixed through a PEEK T-mixer and reacted in a PFA capillary coil (1.5 mL internal volume, estimated 20 min residence time) at 140 °C under 10 bar of counterpressure. The reactor effluent was collected at steady state, neutralized, diluted with ethanol, and analyzed by GC-FID (Table S6).

Table S6. Impact of the use of HCl 4 mol L^{-1} in CPME as chlorination agent for the generation of chlorohydrins **2b** and **3a,b** under continuous flow conditions[a].

Entry	Conv. (%)[b]	**2b** yield (%)[b]	**3a** yield (%)[b]	**3b** yield (%)[b]	Cumulated yield (%)
1	78	6	0	0	6

[a]Conditions: Pimelic acid 10 mol%, 20 minutes of residence time, 140 °C and 10 bar of counterpressure (see also Figure S1). [b]Determined by GC-FID.

2.2.6 Semi-continuous concentration of epichlorohydrin (**5**)

A solution of epichlorohydrin (0.18 M in MTBE) was introduced into a two-neck round-bottom flask through a septum, using a HPLC pump set at 0.32 mL min^{-1}. The round-bottom flask was equipped with a magnetic stir bar, a Vigreux column and a condenser. The flask was heated at 105 °C under stirring. After 6 hours of continuous operation, the distillate consisted of 109 mL of pure MTBE, and 3.3 mL of epichlorohydrin 5.5 M was obtained in the flask. This solution was next utilized for the preparation of 2-(naphthalen-1-yloxymethyl)oxirane (**8a**, 74% yield) according to the general procedure described in the manuscript (see also Scheme 3).

2.2.7 Batch procedure for the synthesis of 2-(naphthalen-1-yloxymethyl)oxirane (**8a**)

The general procedure was adapted from reference.[S1] A magnetic stir bar, a 40 wt.-% solution of NaOH in water (100 mL), epichlorohydrin (22.20 g, 240 mmol, 4 equiv.) and tetrabutylammonium bromide (0.96 g, 3 mmol) were added in a round-bottom flask placed in an ice bath. 1-Naphthol (8.65 g, 60 mmol, 1 equiv.) was added over a period of 30 minutes to the stirred solution of epichlorohydrin. The mixture was allowed to stir and evolve to room temperature during 16 hours. The mixture was then diluted with 100 mL of water and extracted with 3 x 50 mL of diethyl ether. The organic phases were combined, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The resulting crude material was purified by column chromatography on silica gel (eluent: 95:5 mixture of petroleum ether 40-60 °C/ethyl acetate), affording 2-(naphthalen-1-yloxymethyl)oxirane as a transparent oil (7.88 g, 66%).

2.2.8 Batch procedure for the synthesis of 2-[(2-prop-2-enylphenoxy)methyl]oxirane (**8b**)

The general procedure was adapted from reference.[S1] A magnetic stir bar, a 40 wt.-% solution of NaOH in water (100 mL), epichlorohydrin (22.20 g, 240 mmol, 4 equiv.) and tetrabutylammonium bromide (0.96 g, 3 mmol) were added in a round-bottom flask placed in an ice bath. 2-Allylphenol (8.05 g, 60 mmol, 1 equiv.) was added over a period of 30 minutes to the stirred solution of epichlorohydrin. The mixture was allowed to stir and evolve to room temperature during 16 hours. The mixture was then diluted with 100 mL of water and extracted with 3 x 50 mL of diethyl ether. The organic phases were combined, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The resulting crude material was purified by column chromatography on silica gel (eluent: 95:5 mixture of petroleum ether 40-60 °C/ethyl acetate), affording 2-[(2-prop-2-enylphenoxy)methyl]oxirane as a transparent oil (9.34 g, 82%).

2.2.9 Batch procedure for the preparation of propranolol free-base (**10a**)

Propranolol hydrochloride was solubilized in deionized water and the pH of the mixture was adjusted to 10-11 with a NaOH solution. The resulting mixture was extracted with diethyl ether three times. The organic phases were combined, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure affording pure propranolol free-base as a white solid.

2.2.10 Batch procedure for the synthesis of alprenolol (**10c**)

The general procedure was adapted from reference.[S2] A magnetic stir bar, 2-[(2-prop-2-enylphenoxy)methyl]oxirane (2.00 g, 10.5 mmol, 1 equiv.), isopropylamine (0.93 g, 15.8 mmol, 1.5 equiv.) and dimethylformamide (70 mL) were added in a septum-sealed round-bottom flask. The mixture was heated at 60 °C and stirred for 12 hours. The mixture was then diluted with 50 equiv. of water (9.5 mL) and was allowed to stir at room temperature for 12 additional hours. Then, 50 mL of brine were added and the resulting mixture was extracted with 3 x 50 mL of diethyl ether. The organic phases were combined, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The resulting crude material was purified by recrystallization in *n*-heptane, affording pure alprenolol as white crystals (0.71 g, 27%).

2.2.11 Batch procedure for the synthesis of 1-(2-allylphenoxy)-3-[4-(2-methoxyphenyl)-1-piperazinyl]-2-propanol (**10d**)

The general procedure was adapted from reference.[S2] 2-((2-Allylphenoxy)methyl)oxirane (2 g, 1 mmol, 1 equiv.) and 1-(2-methoxyphenyl)piperazine (2.37 g, 1.2 mmol, 1.2 equiv.) were dissolved in 70 mL of DMSO. The solution was transferred into a round-bottom flask equipped with a magnetic stir bar and sealed with a septum. The mixture was heated at 60°C

for 10 hours. It was then cooled to room temperature and 10 mL of water were added. The medium was transferred into a dropping funnel, diluted with 50 mL of brine and extracted with 3 x 50 mL of diethyl ether. The organic phases were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting crude material was purified by silica gel column chromatography (eluent: 85:15 mixture of dichloromethane/methanol), affording 1-(2-allylphenoxy)-3-(4-(2-methoxyphenyl)piperazin-1-yl)propan-2-ol as a white solid (0.82 g, 21%).

2.2.12 Purification procedures for the APIs and analog **10a-d**

The volume of reactor effluent used in the purification methods is *ca.* 10 mL (see also Scheme 4 and Table 6, entries 12 and 16-18 of the manuscript).

- Propranolol (**10a**) and alprenolol (**10c**):

The excess of isopropylamine (**9a**) was removed under reduced pressure. The resulting solution was diluted with 20 mL of brine and extracted with 4 x 20 mL of diethyl ether. The organic phases were combined, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The resulting crude material was purified by recrystallization in *n*-heptane, affording pure propranolol (**10a**, 63% isolated yield, white crystals) or alprenolol (**10c**, 69% isolated yield, white crystals).

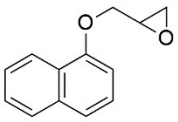
- Naftopidil (**10b**):

The effluent was diluted with 10 mL of brine and extracted with 5 x 10 mL of diethyl ether. The organic phases were combined, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The resulting crude material was purified by column chromatography on silica gel (eluent: 60:35:5 mixture of ethyl acetate/petroleum ether 40-60/triethylamine), affording pure naftopidil (**10b**) as a white solid (66% isolated yield).

- Analog (**10d**):

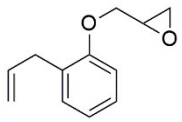
The effluent was diluted with 20 mL of brine and extracted with 4 x 20 mL of diethyl ether. The organic phases were combined, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The resulting crude material was purified by column chromatography on silica gel (eluent: 70:25:5 mixture of ethyl acetate/petroleum ether 40-60/triethylamine), affording pure 1-(2-allylphenoxy)-3-[4-(2-methoxyphenyl)-1-piperazinyl]-2-propanol (**10d**) as a white solid (85% isolated yield).

2.3 Characterization of compounds



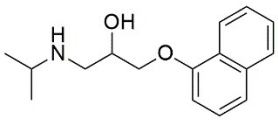
$C_{13}H_{12}O_2$
MW 200.23

2-(Naphthalen-1-yloxymethyl)oxirane (8a). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.40 – 8.29 (m, 1 H), 7.88 – 7.80 (m, 1H), 7.57 – 7.44 (m, 3H), 7.38 (t, *J* = 7.9 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 4.40 (dd, *J* = 11.0, 3.1 Hz, 1H), 4.14 (dd, *J* = 11.0, 5.6 Hz, 1H), 3.54 – 3.44 (m, 1H), 2.97 (t, *J* = 4.5 Hz, 1H), 2.86 (dd, *J* = 5.0, 2.7 Hz, 1H) ppm. The NMR data match those reported in the literature.[S3] **^{13}C NMR ($CDCl_3$, 100.6 MHz):** δ = 154.3, 134.6, 127.6, 126.6, 125.8, 125.7, 125.4, 122.1, 120.9, 105.1, 69.0, 50.3, 44.8 ppm. **ESI HRMS** *m/z* $C_{13}H_{12}O_2Na^+$ $[M+Na]^+$: calcd 223.0730; found 223.0730.



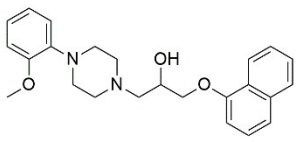
$C_{12}H_{14}O_2$
MW190.24

2-[(2-Prop-2-enylphenoxy)methyl]oxirane (8b). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.23 – 7.12 (m, 2H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.08 – 5.92 (m, 1H), 5.13 – 5.01 (m, 2H), 4.23 (dd, *J* = 11.0, 3.1 Hz, 1H), 4.00 (dd, *J* = 11.0, 5.4 Hz, 1H), 3.43 (d, *J* = 6.6 Hz, 2H), 3.40 – 3.33 (m, 1H), 2.91 (t, *J* = 4.5 Hz, 1H), 2.78 (dd, *J* = 5.0, 2.7 Hz, 1H) ppm. **^{13}C NMR ($CDCl_3$, 100.6 MHz):** δ = 156.2, 137.0, 130.0, 129.1, 127.4, 121.2, 115.5, 111.7, 68.8, 50.4, 44.7, 34.4 ppm. The NMR data match those reported in the literature.[S4] **ESI HRMS** *m/z* $C_{12}H_{14}O_2Na^+$ $[M+Na]^+$: calcd 213.0886; found 213.0887.



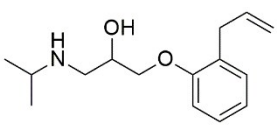
$C_{16}H_{21}NO_2$
MW 259.34

1-Naphthalen-1-yloxy-3-(propan-2-ylamino)propan-2-ol (10a). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.30 – 8.19 (m, 1H), 7.86 – 7.75 (m, 1H), 7.55 – 7.41 (m, 3H), 7.37 (t, *J* = 7.9 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 4.26 – 4.09 (m, 3H), 3.01 (dd, *J* = 12.2, 3.4 Hz, 1H), 2.94 – 2.79 (m, 2H), 1.12 (d, *J* = 6.3 Hz, 6H) ppm. **^{13}C NMR ($CDCl_3$, 100.6 MHz):** δ = 154.5, 134.6, 127.7, 126.6, 126.0, 125.7, 125.4, 122.0, 120.8, 105.1, 70.8, 68.7, 49.6, 49.1, 23.4, 23.2 ppm. The NMR data match those reported in the literature.[S5] **ESI HRMS** *m/z* $C_{16}H_{22}NO_2^+$ $[M+H]^+$: calcd 260.1645; found 260.1644.



$C_{24}H_{28}N_2O_3$
MW 392.49

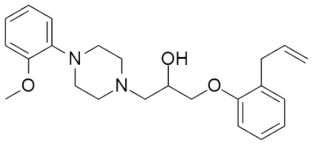
1-[4-(2-Methoxyphenyl)piperazin-1-yl]-3-naphthalen-1-yloxypropan-2-ol (10b). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.33 – 8.23 (m, 1H), 7.86 – 7.75 (m, 1H), 7.56 – 7.42 (m, 3H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.07 – 6.91 (m, 3H), 6.92 – 6.82 (m, 2H), 4.36 – 4.13 (m, 3H), 3.88 (s, 3H), 3.65 (br s, 1H), 3.14 (br s, 4H), 3.01 – 2.87 (m, 2H), 2.79 – 2.64 (m, 4H) ppm. The NMR data match those reported in the literature.[S6] **^{13}C NMR ($CDCl_3$, 100.6 MHz):** δ = 154.6, 152.4, 141.3, 134.6, 127.6, 126.6, 126.0, 125.8, 125.4, 123.2, 122.1, 121.2, 120.7, 118.4, 111.4, 105.0, 70.7, 65.8, 61.1, 55.5, 53.8, 50.9 ppm. **ESI HRMS** *m/z* $C_{24}H_{29}N_2O_3^+$ $[M+H]^+$: calcd 393.2173; found 393.2171.



$C_{15}H_{23}NO_2$
MW 249.35

1-(Propan-2-ylamino)-3-(2-prop-2-enylphenoxy)propan-2-ol (10c). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.23 – 7.10 (m, 2H), 6.92 (t, *J* = 7.4 Hz, 1H),

6.85 (d, *J* = 8.1 Hz, 1H), 6.06 – 5.91 (m, 1H), 5.10 – 4.97 (m, 2H), 4.09 – 3.92 (m, 3H), 3.40 (d, *J* = 6.5 Hz, 2H), 2.94 – 2.71 (m, 3H), 1.09 (d, *J* = 6.3 Hz, 6H). **^{13}C NMR ($CDCl_3$, 100.6 MHz):** δ = 156.5, 137.4, 130.2, 128.6, 127.6, 121.1, 115.4, 111.5, 70.7, 68.8, 49.5, 49.0, 34.8, 23.3, 23.2. The NMR data match those reported in the literature.[S5] **ESI HRMS** *m/z* $C_{15}H_{24}NO_2$ $[M+H]^+$: calcd 250.1802; found 250.1800.



$C_{23}H_{30}N_2O_3$
MW 382.50

1-(2-Allylphenoxy)-3-[4-(2-methoxyphenyl)-1-piperazinyl]-2-propanol (10d). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.24 – 7.11 (m, 2H), 7.07 – 6.82 (m, 6H), 6.08 – 5.92 (m, 1H), 5.13 – 4.99 (m, 2H), 4.24 – 4.11 (m, 1H), 4.09 – 3.96 (m, 2H), 3.87 (s, 3H), 3.42 (d, *J* = 6.5 Hz, 2H), 3.13 (br s, 5H), 2.95 – 2.82 (m, 2H), 2.77 – 2.59 (m, 4H). **^{13}C NMR ($CDCl_3$, 100.6 MHz):** δ = 156.5, 152.4, 141.3, 137.3, 130.1, 128.8, 127.5, 123.2, 121.1, 121.0, 118.3, 115.5, 111.5, 111.3, 70.5, 65.9, 61.0, 55.5, 53.8, 50.8, 34.7. **ESI HRMS** *m/z* $C_{23}H_{31}N_2O_3^+$ $[M+H]^+$: calcd 383.2329; found 383.2329.

2.4 Copies of NMR spectra

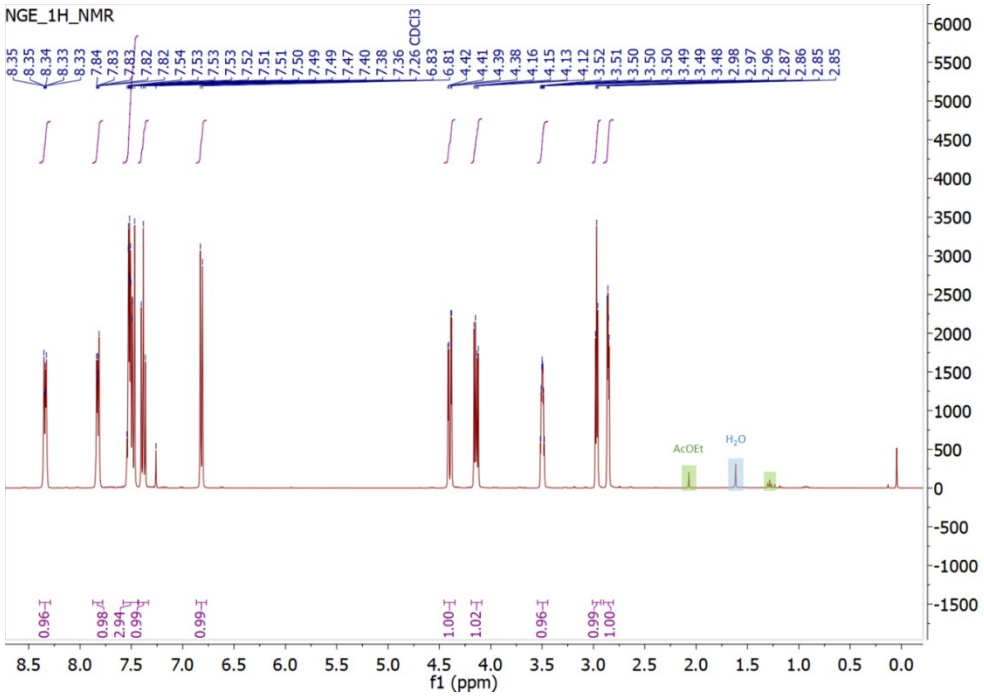


Figure S13. ^{1}H NMR spectrum (400 MHz) of 2-(naphthalen-1-yloxymethyl)oxirane (**8a**) in $CDCl_3$.

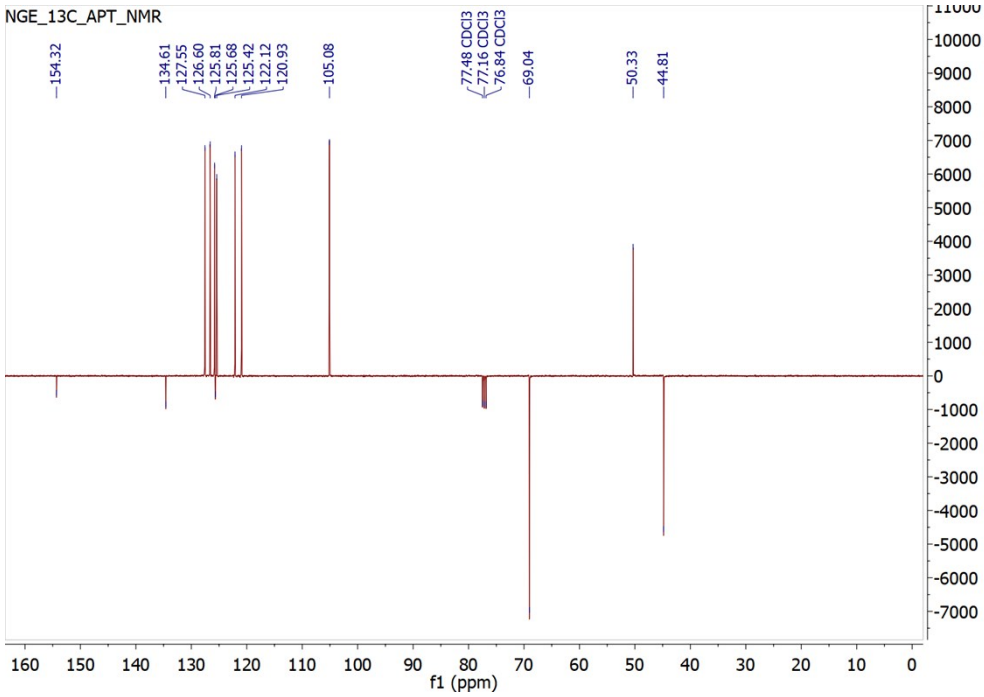


Figure S14. ^{13}C APT NMR spectrum (100.6 MHz) of 2-(naphthalen-1-yloxymethyl)oxirane (**8a**) in $CDCl_3$.

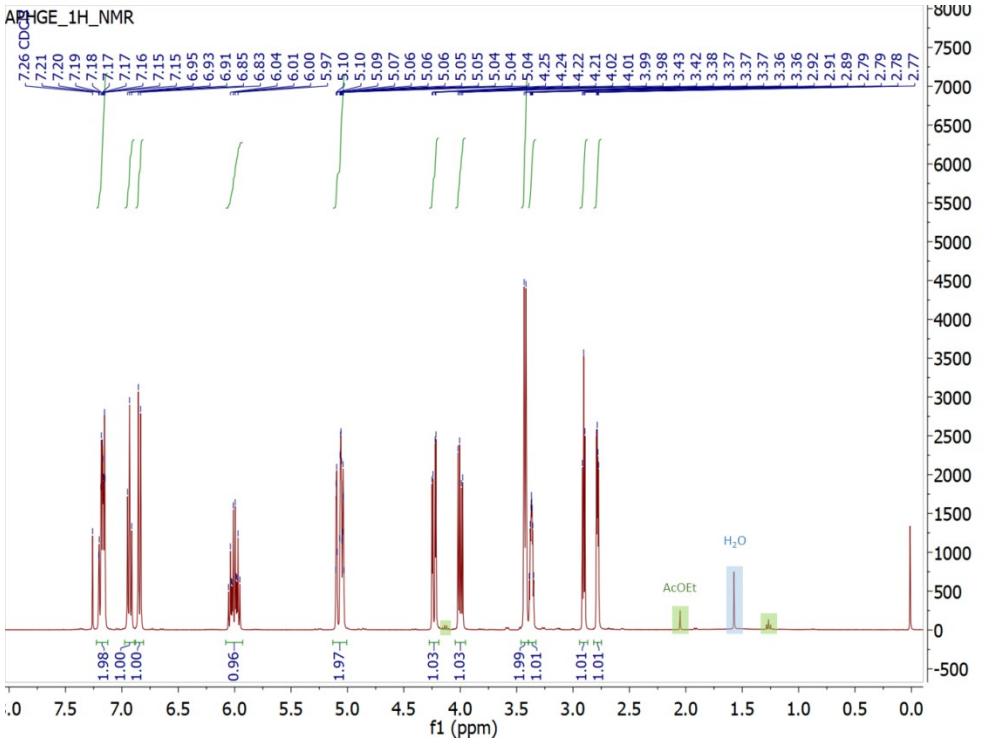


Figure S15. ^{1}H NMR spectrum (400 MHz) of 2-[(2-prop-2-enylphenoxy)methyl]oxirane (**8b**) in $CDCl_3$.

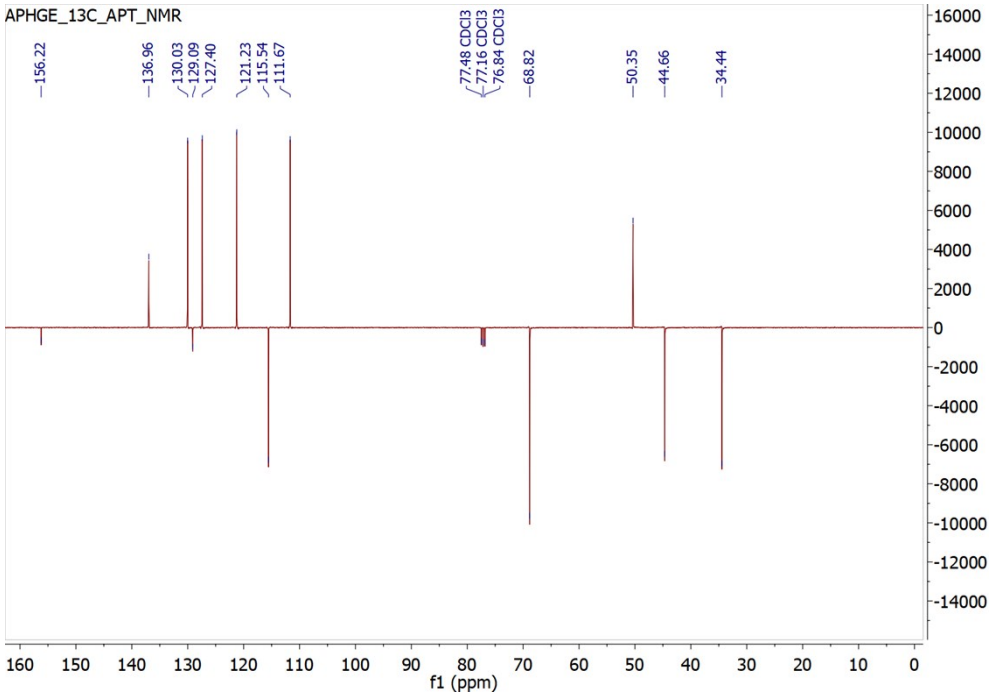


Figure S16. ^{13}C APT NMR spectrum (100.6 MHz) of 2-[(2-prop-2-enylphenoxy)methyl]oxirane (**8b**) in $CDCl_3$.

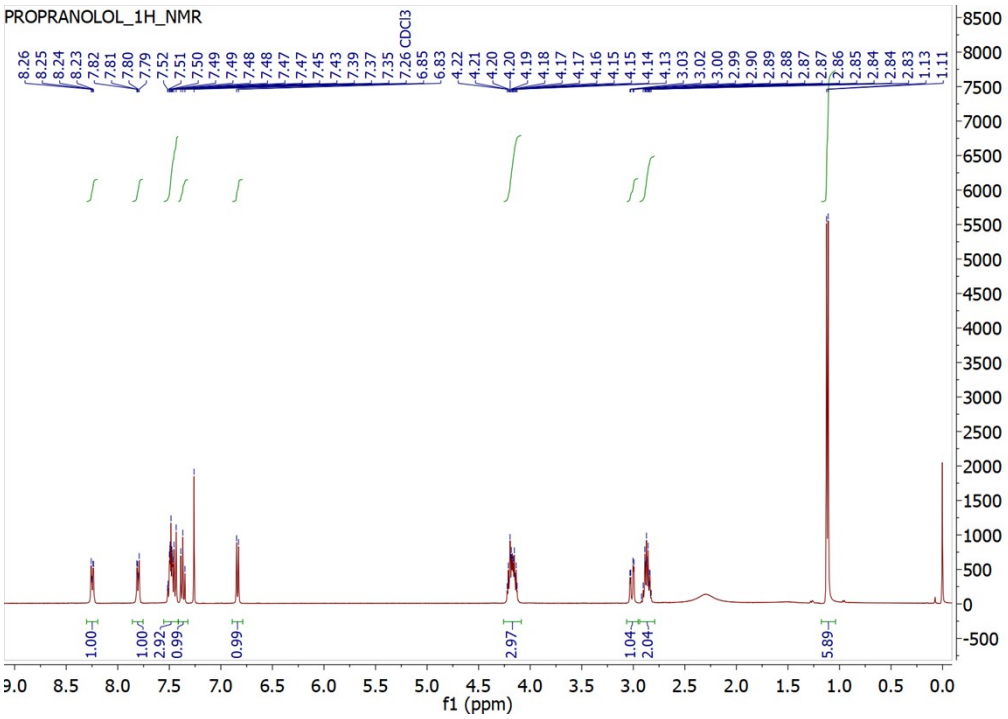


Figure S17. ^{1}H NMR spectrum (400 MHz) of 1-naphthalen-1-yloxy-3-(propan-2-ylamino)propan-2-ol (**10a**) in $CDCl_3$.

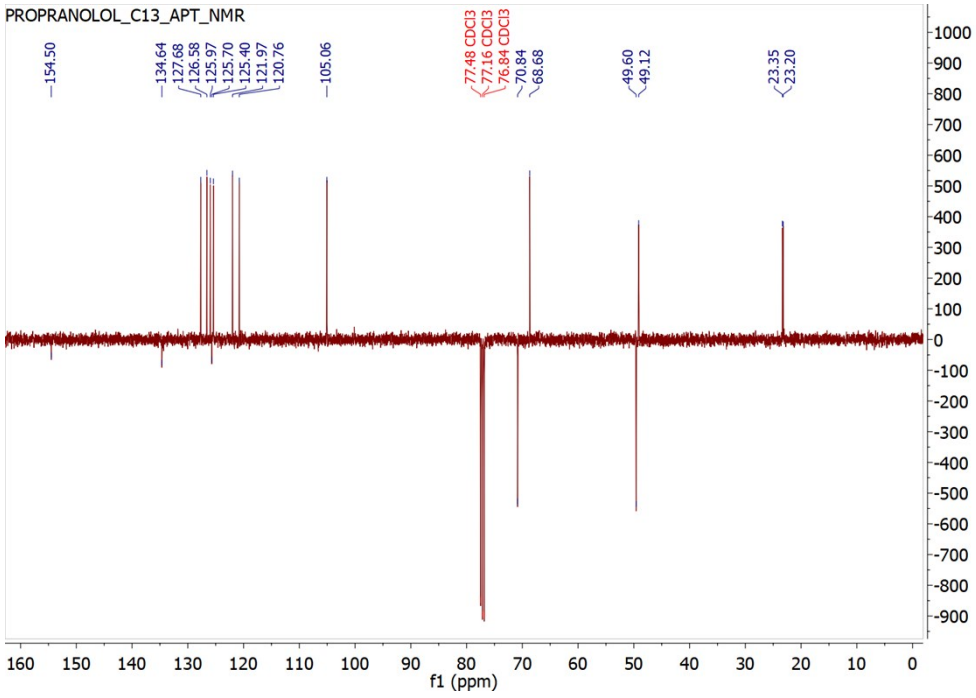


Figure S18. ^{13}C APT NMR spectrum (100.6 MHz) of 1-naphthalen-1-yloxy-3-(propan-2-ylamino)propan-2-ol (**10a**) in $CDCl_3$.

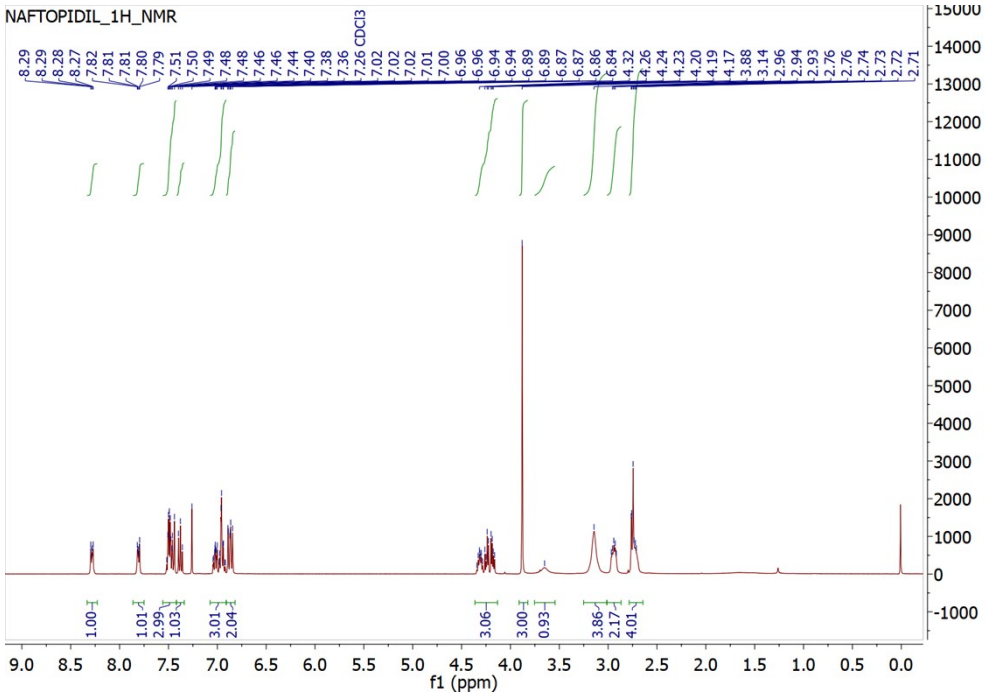


Figure S19. ^{1}H NMR spectrum (400 MHz) of 1-[4-(2-methoxyphenyl)piperazin-1-yl]-3-naphthalen-1-yloxypropan-2-ol (**10b**) in $CDCl_3$.

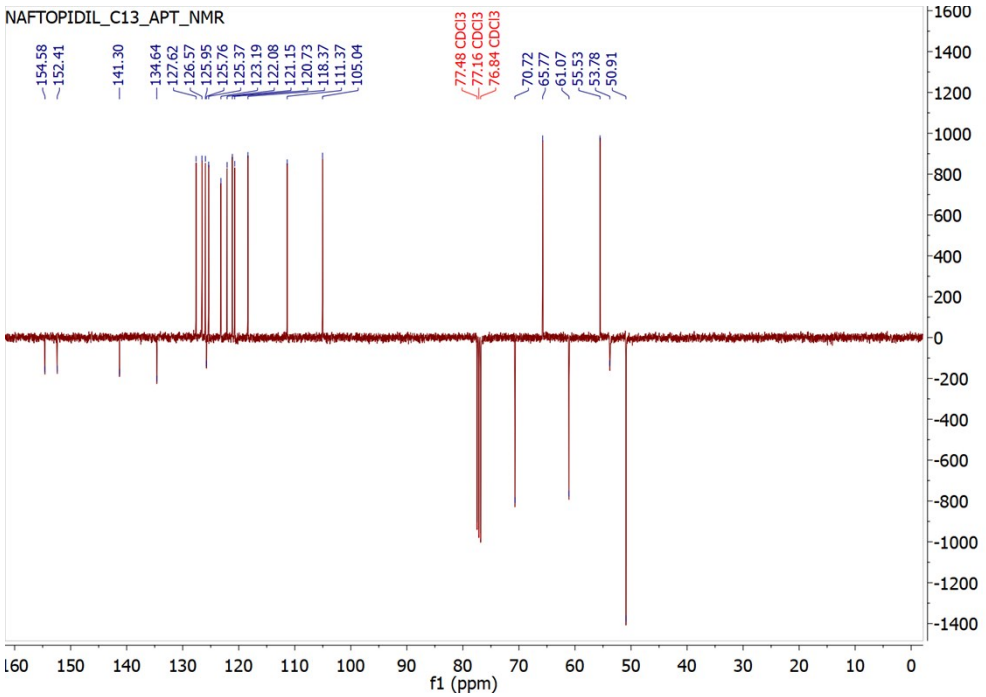


Figure S20. ^{13}C APT NMR spectrum (100.6 MHz) of 1-[4-(2-methoxyphenyl)piperazin-1-yl]-3-naphthalen-1-yloxypropan-2-ol (**10b**) in $CDCl_3$.

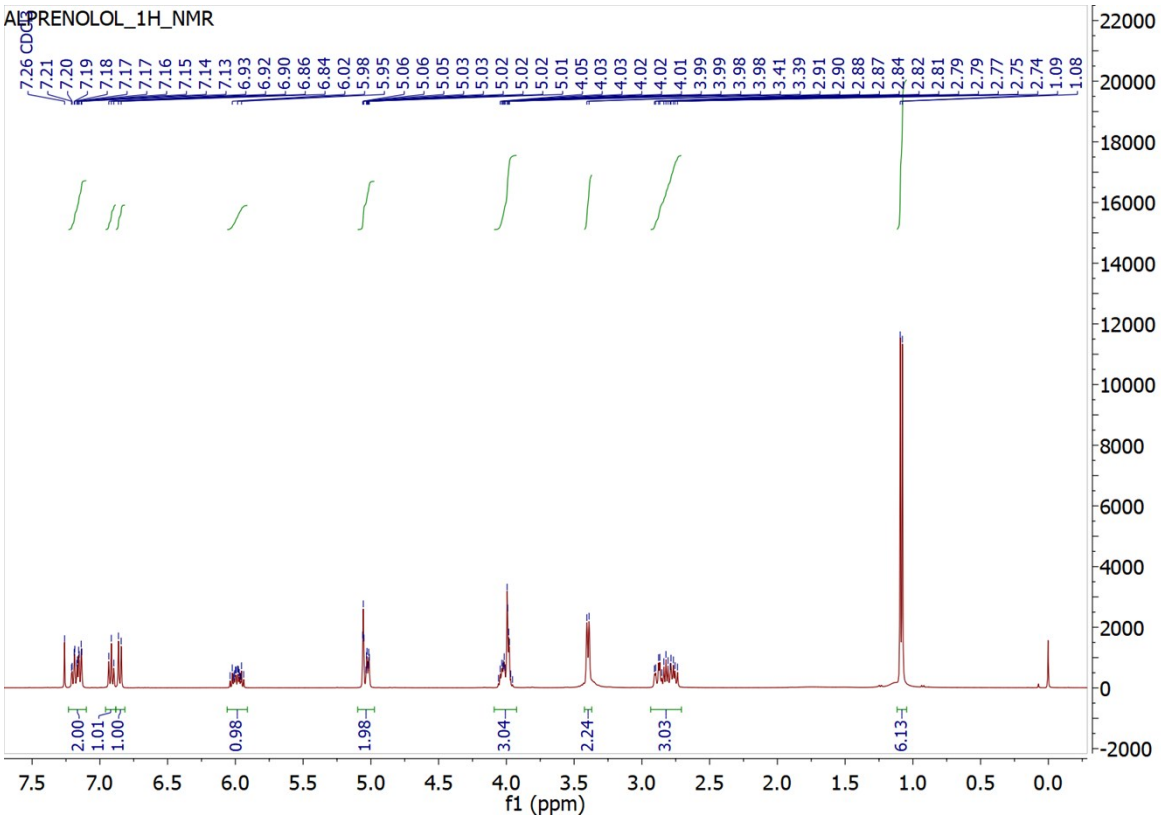


Figure S21. ^{1}H NMR spectrum (400 MHz) of 1-(propan-2-ylamino)-3-(2-prop-2-enylphenoxy)propan-2-ol (**10c**) in $CDCl_3$.

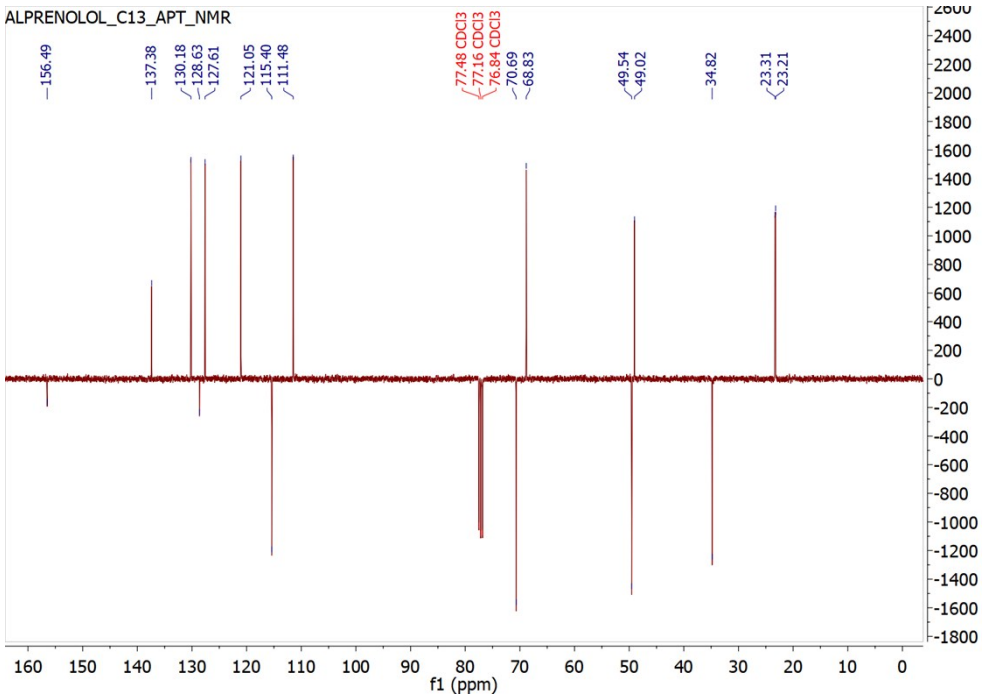


Figure S22. ^{13}C APT NMR spectrum (100.6 MHz) of 1-(propan-2-ylamino)-3-(2-prop-2-enylphenoxy)propan-2-ol (**10c**) in $CDCl_3$.

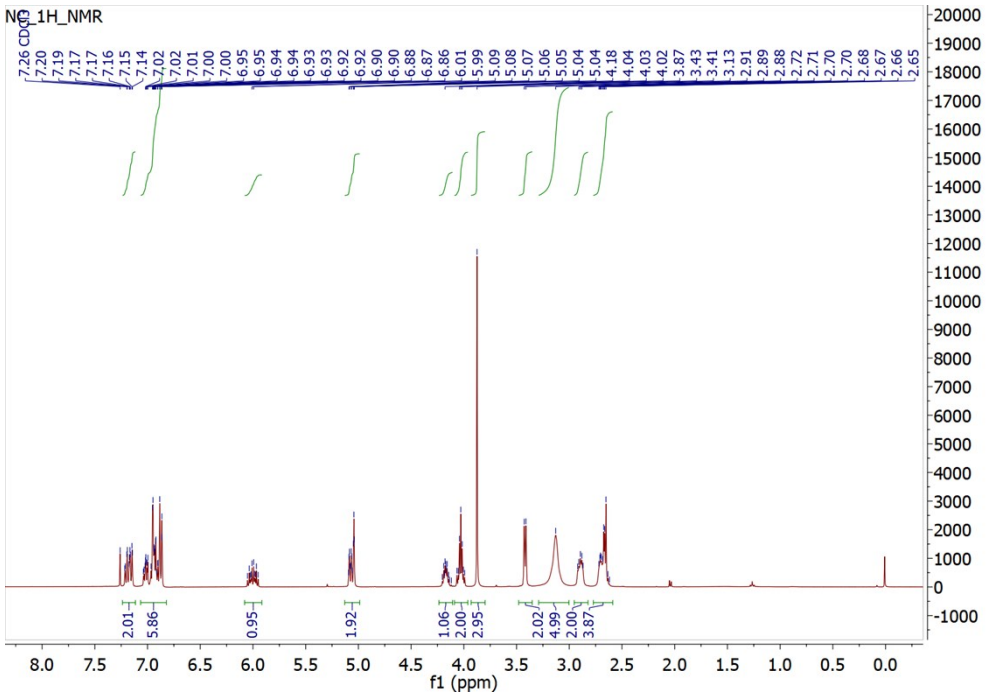


Figure S23. ^{1}H NMR spectrum (400 MHz) of 1-(2-allylphenoxy)-3-[4-(2-methoxyphenyl)-1-piperazinyl]-2-propanol (**10d**) in $CDCl_3$.

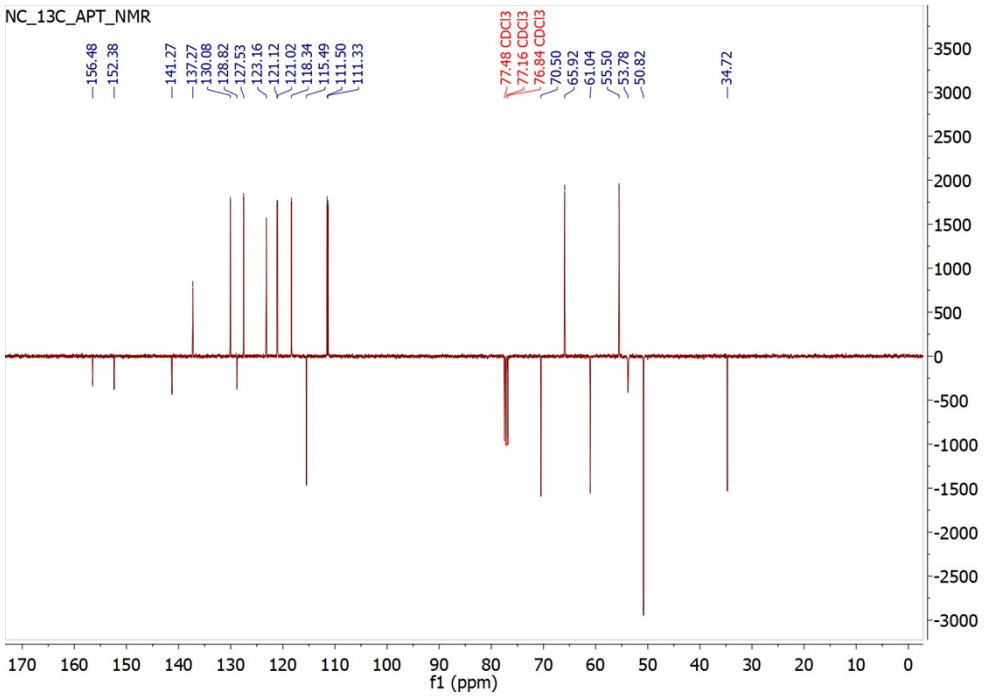


Figure S24. ^{13}C APT NMR spectrum (100.6 MHz) of 1-(2-allylphenoxy)-3-[4-(2-methoxyphenyl)-1-piperazinyl]-2-propanol (**10d**) in $CDCl_3$.

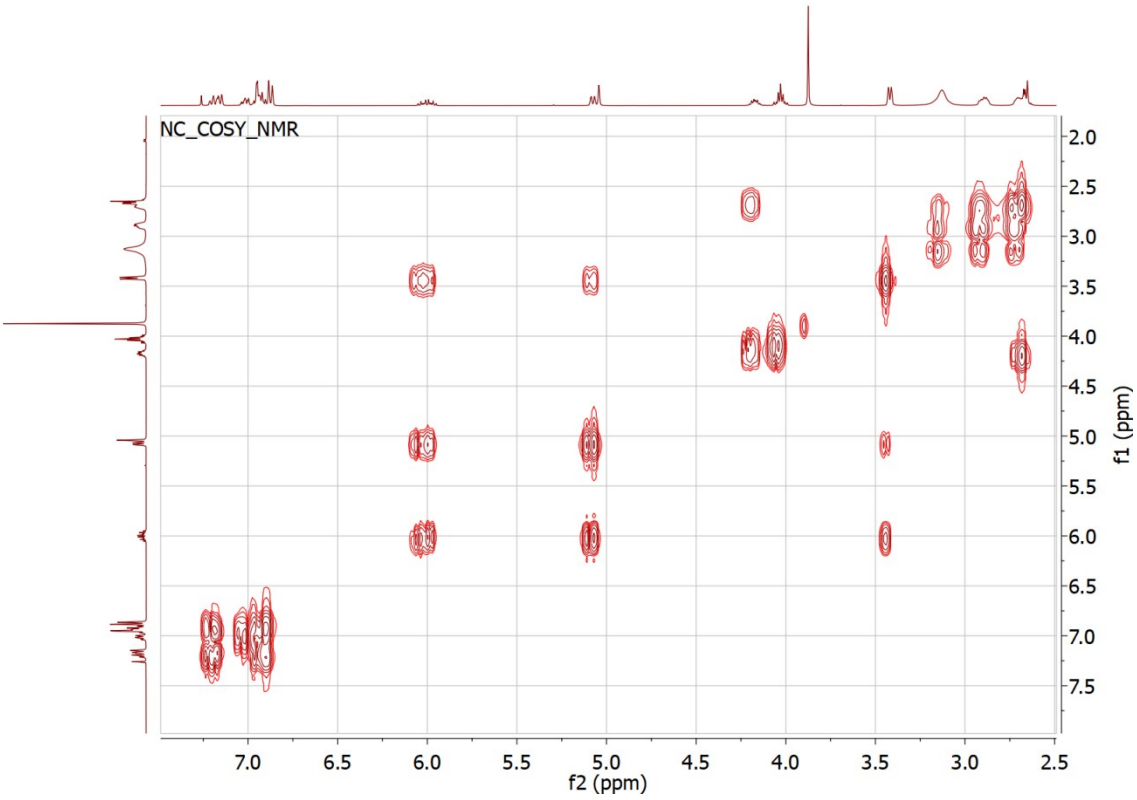


Figure S25. COSY NMR spectrum of 1-(2-allylphenoxy)-3-[4-(2-methoxyphenyl)-1-piperazinyl]-2-propanol (**10d**) in $CDCl_3$.

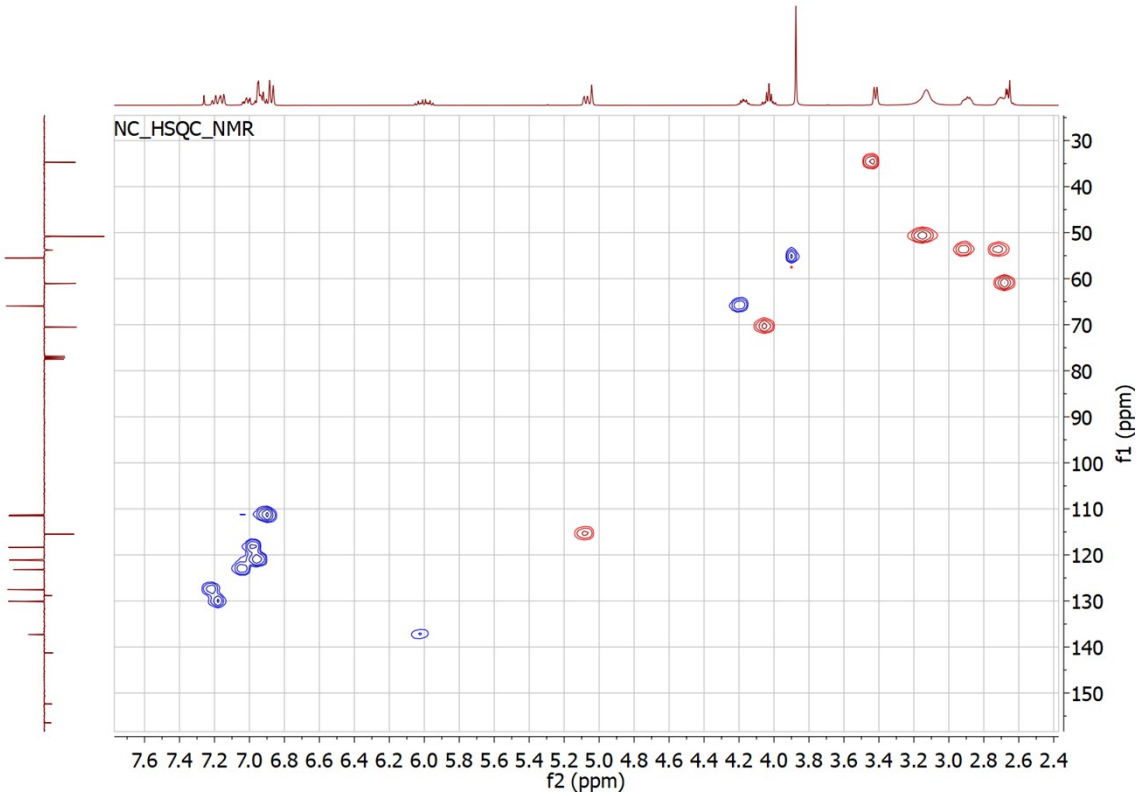


Figure S26. HSQC NMR spectrum of 1-(2-allylphenoxy)-3-[4-(2-methoxyphenyl)-1-piperazinyl]-2-propanol (**10d**) in $CDCl_3$.

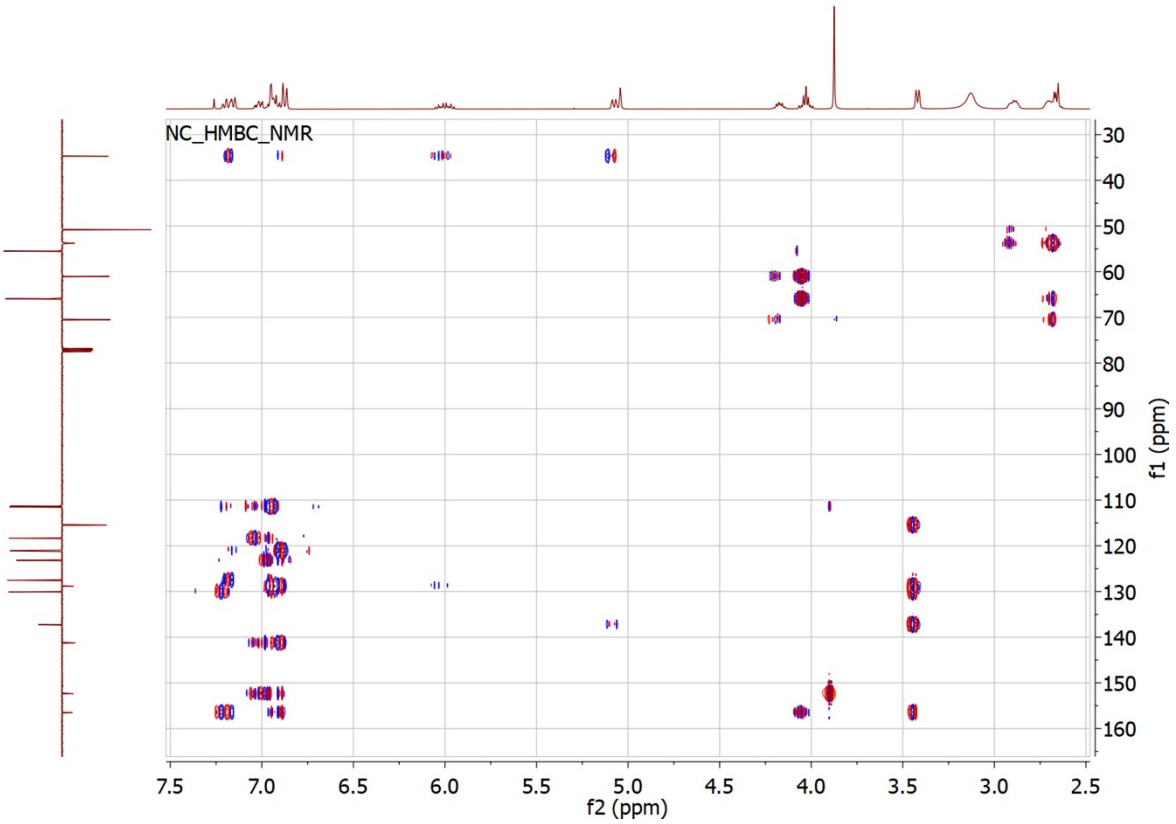


Figure S27. HMBC NMR spectrum of 1-(2-allylphenoxy)-3-[4-(2-methoxyphenyl)-1-piperazinyl]-2-propanol (**10d**) in $CDCl_3$.

3 References

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