

Supporting information for:

Diaryl diamines with dual inhibition of the histamine H₃ receptor and the norepinephrine transporter, and the efficacy of 4-(3-(methylamino)-1-phenylpropyl)-6-(2-(pyrrolidin-1-yl)ethoxy)naphthalen-1-ol in pain.

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Analogs of Compounds 4, 5 and 8

Table S1. Binding affinity for the rat NET and H₃R.^a

Cmpd	Rat NET ^b K _i (nM)		Rat H ₃ R ^c K _i (nM)		Human H ₃ R ^c K _i (nM)	
4	230	(200, 260) ^d	48	(47, 48) ^d	ND ^e	
5	14	(11, 19)	37	(32, 43)	7.4	(6.2, 8.9)
A	410	(150,1100) ^d	8.3	(7.4,9.4) ^d	ND ^e	
B	180	(80,440)	22	(18,27)	2.2	(1.8,2.7)
C	4900	(4700,5100) ^d	48	(43,53) ^d	ND ^e	
D	100	(80,130) ^d	29	(27,31) ^d	13	(12,14) ^d
6	89	(50, 150) ^d	5.4	(4.8, 6.0) ^d	1.6	(1.6, 1.6) ^d
7	110	(85, 150) ^d	0.72	(0.58, 0.91) ^d	0.28	(0.26, 0.30) ^d
8	4.3	(3.3, 5.5)	5.1	(4.4, 6.0)	1.3	(0.9, 2.0)
9	14	(12, 17)	2.9	(2.2, 3.7)	0.89	(0.73, 1.08)
E	110	(100,130) ^d	8.3	(7.1,9.8) ^d	2.0	(1.9,2.1) ^d
F	51	(46,57) ^d	13	(10,17) ^d	5.0	(4.7,5.3) ^d
G	4000	(3400,4600) ^d	26	(23,29) ^d	3.9	(3.8,3.9) ^d

^an₃. Values in parentheses are the upper and lower limits derived as a result of the standard deviation.; ^bAssessed by displacement of [³H]-nisoxetine from cell membranes isolated from rat cerebral cortex.²⁷; ^cAssessed by displacement of [³H]-N-R-methyl histamine from cell membranes isolated from C6 cells expressing cloned rat H₃R.²¹; ^dn = 2; ^eND = not determined

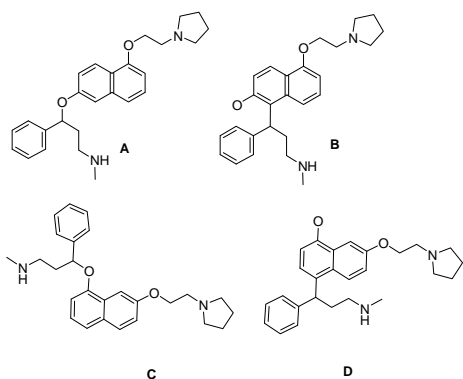


Figure 3. Analogs of compounds **4** and **5**.

Four derivatives of compounds **4** and **5** were synthesized to explore the SAR of these types of molecules. As can be seen from Table S1, the compounds similar to **4**, wherein a phenyl-propyl-methylamine moiety is connected to the naphthalene ring through an ether linkage (compounds **A** and **C**), had lower potency for the NET site than those connected directly to the naphthalene ring (compounds **B** and **D**). Of note was the observation the compound **B** was over 4 fold more potent at the H₃ receptor. Overall, compound **5** was the still most potent for the NET site among this group of compounds.

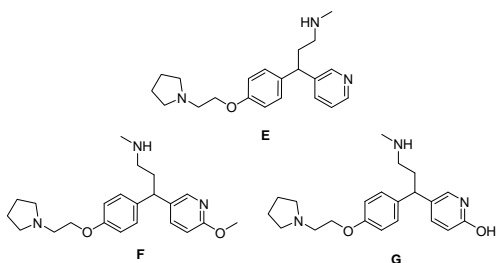


Figure 4. Analogs of compound **8**.

Several analogs of compound **8** were synthesized to explore the unsubstituted phenyl portion of the molecule. Introduction of more polar heterocycles resulted in a significant (> 10 fold) reduction of the NET activity.

Human functional antagonism of compounds 4-9

As can be seen in Table 2, antagonism of the human H₃R was demonstrated for compounds 4-9 through blockade of agonist-induced (RAMH) stimulation of GTP γ S binding.

Table S2. In Vitro Human H₃R Functional Antagonism of Cmpds 4-7 and 9 in GTP γ S Binding^{a,b}

Cmpd	inhibition of [³⁵ S]GTP γ S binding K _b (nM)	
4	67	(49,91)
5	8.3	(7.6,9.1)
6	2.4	(1.5,3.9)
7	0.79	(0.28,2.27)
9	2.1	(1.0,4.5)

^an \geq 2. Inhibition of RAMH-induced binding of [³⁵S]GTP γ S.²³ Values in parentheses are the upper and lower limits derived as a result of the standard deviation. ^bCompound 8 has been excluded from the table because this compound will be published in a pharmacology manuscript in which compound 8 will be described in more detail.

Estimated receptor occupancy calculation of compound **5**

In the “free drug principle”, compounds that are permeable and that are not transporter substrates (such as PgP) have equal concentrations of free drug in all compartments. At steady-state equilibrium under passive diffusion, the concentration of free drug in the plasma is equal to the concentration of free drug in the brain.^{28,40}

The concentration in nM of free drug for compound **5** for a given dose was calculated using the measured plasma levels, the free fraction of drug (33 %) from the measured plasma protein binding (67 %) and the molecular weight (404 ng/nmol):

$$\text{Free concentration (nM)} = [(\text{plasma level ng/mL}) * (1000 \text{ mL/L}) / (404 \text{ ng/nmol})] * 0.33$$

The receptor occupancy³⁹ of compound **5** was calculated using the free concentration and the K_i (NET = 14 nM, rat H₃R = 37 nM):

$$\text{Receptor occupancy} = \text{Free concentration (nM)} / [\text{Free concentration (nM)} + K_i \text{ (nM)}]$$

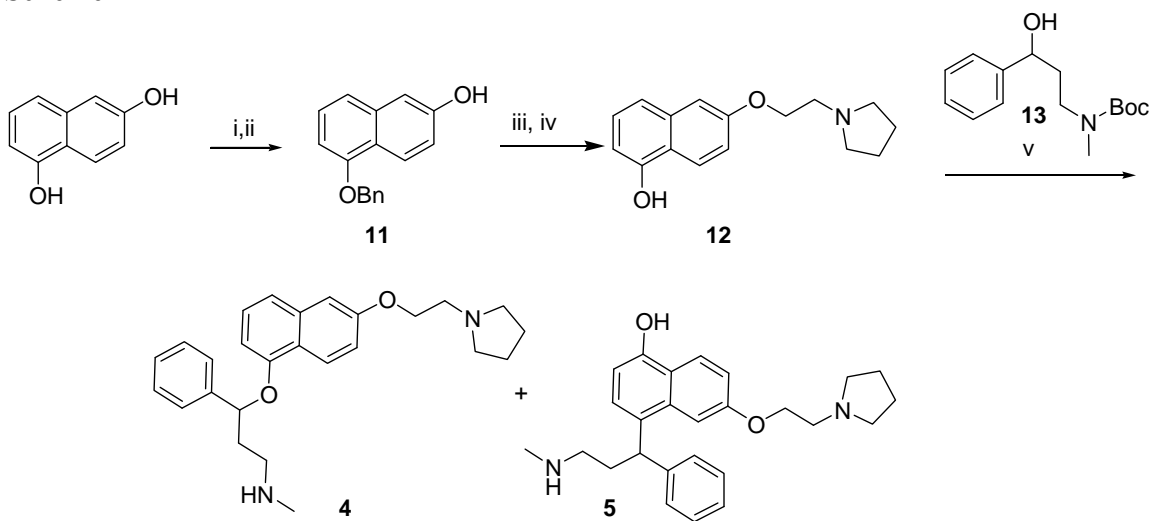
Table S3. Estimated receptor occupancy of compound **5** at the H₃R and NET in rats at 1, 3 and 10 mg/kg i.p.

Dose (mg/kg)	Measured plasma level (ng/mL)	Free concentration (nM)	H ₃ R receptor occupancy	NET receptor occupancy
1	129	105	74	88
3	382	311	89	96
10	1239	1010	97	99

Complete experimental section: This section contains the experimentals included in the main document as well as experimentals for known intermediates (compounds **11**, **16** and **17**) not included in the main document.

General. Proton NMR spectra were obtained on a Varian Mercury plus 300 or Varian UNITY plus 300 MHz instrument with chemical shifts (δ) reported relative to tetramethylsilane as an internal standard. Melting points were determined on a Stanford Research Systems MPA100 Automated Melting Point System and are uncorrected. All target compounds possess a purity of at least 95% based on combustion analysis (± 0.4), performed by QTI (Quantitative Technologies, Inc.). Column chromatography was carried out either with an Analogix IntelliFlash 280 chromatography apparatus using SuperFlashTM Compound Purification Columns or on silica gel 60 (230-400 mesh). Thin-layer chromatography (TLC) was performed using 250 mm silica gel 60 glass-backed plates with F254 as indicator.

Scheme 1^a



^a i. BnBr, NaH, DMF; ii. chromatography; iii. N-(2-chloroethyl)pyrrolidine·HCl, NaH, DMF, 70 °C; iv. H₂, 10 % Pd/C, MeOH; v. **13**, DEAD, Ph₃P, THF; TFA

5-(Benzyloxy)naphthalen-2-ol (11).¹⁷ A solution of 1,6-dihydroxynaphthalene (70 g, 437 mmol) in dry DMF (700 mL) under nitrogen was treated in portions with NaH (60 % suspension in mineral oil, 17.5 g, 437 mmol) over 15 minutes, stirred at room temperature for 30 minutes, treated all at once with benzyl bromide (51.9 ml, 437 mmol), stirred over night at room temperature, diluted with water (1.5 L) and extracted with Et₂O (2 x 500 mL). The Et₂O extractions were combined, washed with brine, dried (MgSO₄), filtered, concentrated and chromatographed on silica gel using a 6 x 45 cm column

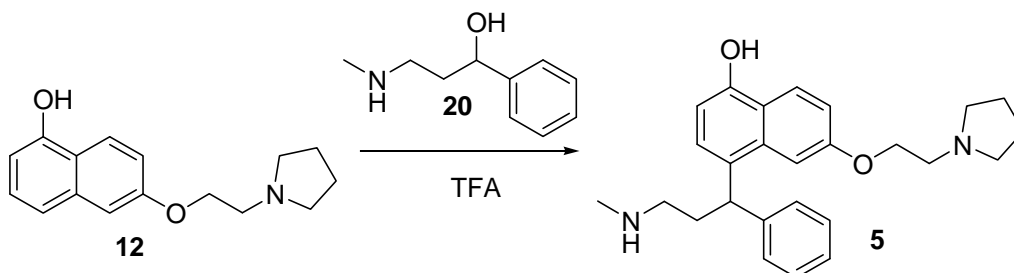
eluting with 5:1 (4 L), 4:1 (2 L), 3:1 (2 L), 2:1 (6 L) and 1:1 (3 L) hexane:(9:1 CH₂Cl₂:EtOAc) to provide 6-(benzyloxy)naphthalen-1-ol as the faster moving isomer (¹H NMR (CDCl₃) δ 5.12 (s, 1H), 5.18 (s, 2H), 6.67 (dd, *J*=7.14, 1.19 Hz, 1H), 7.17 - 7.45 (m, 7H), 7.47 - 7.52 (m, 2H), 8.10 (d, *J*=9.12 Hz, 1H); MS (DCI/NH₃) *m/z* 251 (M+H)⁺), mixed fractions containing 6-(benzyloxy)naphthalen-1-ol and the desired product and pure desired product as the slower moving isomer. The mixed fractions were rechromatographed under similar conditions to provide more of the desired product. Total yield of the pure desired product, 5-(benzyloxy)naphthalen-2-ol, was 16 g (14.6 %). ¹H NMR (CDCl₃) δ 4.96 (s, 1H), 5.22 (s, 2H), 6.74 (dd, *J*=7.14, 1.59 Hz, 1H), 7.06 (dd, *J*=8.92, 2.58 Hz, 1H), 7.11 (d, *J*=2.38 Hz, 1H), 7.16 - 7.45 (m, 5H), 7.49 - 7.55 (m, 2H), 8.25 (d, *J*=9.12 Hz, 1H); MS (DCI/NH₃) *m/z* 251 (M+H)⁺.

6-(2-(pyrrolidin-1-yl)ethoxy)naphthalen-1-ol (12). Step 1. In a 500 mL round bottomed flask, a solution of **11** (1.12 g, 4.47 mmol) in DMF (20 mL) under N₂ was treated with NaH (60 % suspension in mineral oil, 1.07 g, 26.8 mmol), stirred for 15 minutes, treated with *N*-(2-chloroethyl)pyrrolidine hydrochloride (1.52 g, 8.95 mmol), stirred for 15 minutes, heated to 70°C for 1 hour, cooled, treated with water (50 mL) and extracted with Et₂O (3 times, 150 mL, 50 mL and 50 mL). The combined Et₂O layers were washed with brine, dried (MgSO₄), filtered, concentrated and chromatographed eluting with 2 % -10 % (9:1 MeOH:ammonium hydroxide) in CH₂Cl₂ to provide the intermediate product, 1-(2-(5-(benzyloxy)naphthalen-2-yloxy)ethyl)pyrrolidine (1.27 g, 81 % yield). ¹H NMR (CDCl₃) δ 1.82 (m, 4H), 2.66 (m, 4H), 2.97 (t, *J*=5.9 Hz, 2H), 4.23 (t, *J*=6.1 Hz, 2H), 5.23 (s, 2H), 6.76 (m, 1H), 7.11 - 7.18 (m, 2H), 7.30 - 7.46 (m, 5H), 7.50 - 7.55 (m, 2H), 8.23 (d, *J*=9.1 Hz, 1H); MS (DCI/NH₃) *m/z* 348 (M+H)⁺. **Step 2.** A mixture of 1-(2-(5-(benzyloxy)naphthalen-2-yloxy)ethyl)pyrrolidine (1.26 g, 3.63 mmol) and 10% Pd/C (250 mg) in MeOH (5 mL) was stirred under H₂ (1 atm) for 2 hours, diluted to ~100 mL with CH₂Cl₂, stirred under N₂ for 15 minutes and filtered to remove the solids. The filtrate was concentrated and chromatographed eluting with 2 % -10 % (9:1 MeOH:ammonium hydroxide) in CH₂Cl₂ to provide the title compound (0.92 g, 98 %), which solidified on standing. ¹H NMR (CDCl₃) δ 1.85 (m, 4H), 2.72 (m, 4H), 2.99 (t, *J*=5.8 Hz, 2H), 4.21 (t, *J*=5.9 Hz, 2H), 6.64 (dd, *J*=6.3, 2.0 Hz, 1H), 7.02 - 7.07 (m, 2H), 7.18 - 7.24 (m, 2H), 8.00 - 8.06 (m, 1H); MS (DCI/NH₃) *m/z* 258 (M+H)⁺.

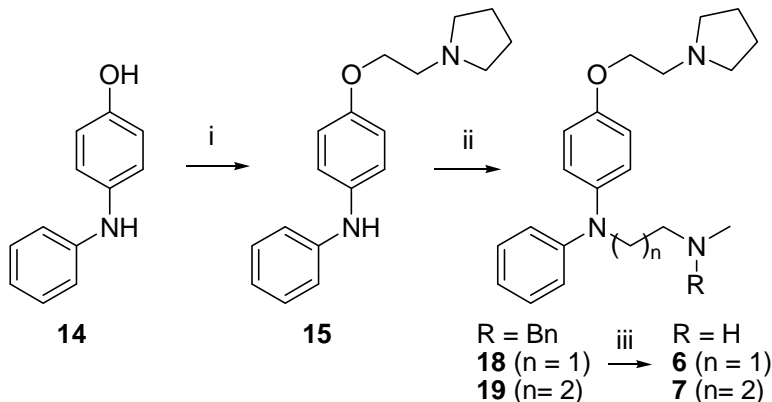
Mitsunobu conditions for formation of *N*-methyl-3-phenyl-3-(6-(2-(pyrrolidin-1-yl)ethoxy)naphthalen-1-yloxy)propan-1-amine (4) and 4-(3-(methylamino)-1-phenylpropyl)-6-(2-(pyrrolidin-1-yl)ethoxy)naphthalen-1-ol (5). Step 1. In a 250 mL flask, a solution of **12** (127 mg, 0.49 mmol), *tert*-butyl 3-hydroxy-3-phenylpropyl(methyl)carbamate (**13**) (170 mg, 0.64 mmol) and Ph₃P (168 mg, 0.64 mmol) in THF (2 mL) under N₂ at 0 °C was treated in portions over 45 minutes with a solution of DEAD (102 μl, 0.64 mmol) in THF (2 mL). The mixture was then stirred at room temperature for over night. The mixture was concentrated and chromatographed eluting with 2 % -10 % (9:1 MeOH:ammonium hydroxide) in CH₂Cl₂ to provide the desired Boc-protected intermediates. **Step 2.** The residue from above was treated with TFA (2 mL), heated to 60 °C for 2 minutes, concentrated and directly chromatographed eluting with 2 % -10 % (9:1 MeOH:ammonium hydroxide) in CH₂Cl₂ to provide compound **5** (5 mg, 12 % yield) as the slower moving isomer (¹H NMR (CDCl₃) δ 1.85 (m, 5H), 2.13 - 2.28 (m, 1H), 2.37 - 2.48 (m, 2H), 2.49 (s, 3H), 2.69 - 2.83 (m, 5H), 3.01 (t, *J*=5.9 Hz, 2H), 4.24 (t, *J*=5.9 Hz, 2H), 4.79 (dd, *J*=13.1, 2.9 Hz, 1H), 6.74 (d, *J*=8.5

Hz, 1H), 7.01 (d, $J=2.4$ Hz, 1H), 7.07 (d, $J=8.5$ Hz, 1H), 7.13 (dd, $J=9.2, 2.7$ Hz, 1H), 7.18 - 7.25 (m, 1H), 7.28 - 7.33 (m, 4H), 8.30 (d, $J=9.2$ Hz, 1H); MS (DCI/NH₃) m/z 405 (M+H)⁺ and compound **4** (20 mg, 48 % yield) (¹H NMR (CDCl₃) δ 1.83 (m, 4H), 2.04 - 2.20 (m, 1H), 2.25 - 2.39 (m, 1H), 2.43 (s, 3H), 2.66 (m, 4H), 2.78 - 2.89 (m, 2H), 2.97 (t, $J=5.9$ Hz, 2H), 4.23 (t, $J=6.1$ Hz, 2H), 5.44 (dd, $J=8.3, 4.8$ Hz, 1H), 6.48 (d, $J=7.5$ Hz, 1H), 7.07 - 7.43 (m, 9H), 8.32 (d, $J=9.5$ Hz, 1H); MS (DCI/NH₃) m/z 405 (M+H)⁺; Anal. (C₂₆H₃₂N₂O₂•0.1 H₂O) C, H, N.

Scheme 1A



TFA conditions. 4-(3-(methylamino)-1-phenylpropyl)-6-(2-(pyrrolidin-1-yl)ethoxy)naphthalen-1-ol (5). A solution of compound **12** (5.40 g, 21.0 mmol) in TFA (45 mL) was treated with α -[2-(methylamino)ethyl]benzyl alcohol (**20**) (3.47 g, 21.0 mmol) and stirred over night at room temperature. The mixture was concentrated to an oil, dissolved in CH₂Cl₂ (150 mL) and washed with 1 M NaOH. The aqueous layer was extracted with CH₂Cl₂ (100 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered, concentrated and chromatographed eluting with a gradient of 10:1:1 to 4:1:1 EtOAc:HCOOH:H₂O. The fractions containing product were combined, concentrated to an oil, transferred to a separatory funnel with water (100 mL), basified with 50 weight % NaOH to pH ~9 and extracted with CH₂Cl₂ (3 x 100 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered, concentrated, suspended on silica gel and chromatographed eluting with 2 % -10 % (9:1 MeOH:ammonium hydroxide) in CH₂Cl₂ to provide 1.95 g (23 %) of compound **5**. **Salt formation:** A flask containing compound **5** (1.19 g, 2.95 mmol) was treated with 1.11 M H₃PO₄ in water (2.66 ml, 2.95 mmol), treated with some CH₃CN (~ 5 mL) and water (~2 mL) and swirled to insure that all of the components were dissolved. The mixture was slowly treated with CH₃CN (250 mL) to allow the salt to slowly precipitate instead of all at once. After standing for 2 hours, the salt was collected by filtration, washed with CH₃CN and dried over night with heating (~70 °C) under house vacuum to provide the mono-phosphoric acid salt of **5** (1.18 g, 79 % yield). ¹H NMR (DMSO-d₆) δ 1.70 (m, 4H), 2.24 - 2.41 (m, 2H), 2.42 (s, 3H), 2.54 - 2.75 (m, 6H), 2.87 (t, $J=5.8$ Hz, 2H), 4.15 (t, $J=5.9$ Hz, 2H), 4.79 (t, $J=8$ Hz, 2H), 7.05 (dd, $J=9.2, 2.7$ Hz, 1H), 7.11 (d, $J=8.5$ Hz, 1H), 7.13 - 7.21 (m, 3H), 7.24 - 7.31 (m, 2H), 7.33 - 7.38 (m, 2H), 8.12 (d, $J=9.2$ Hz, 1H); MS (ESI⁺) m/z 405 (M+H)⁺; Anal. (C₂₆H₃₂N₂O₂•H₃PO₄•1.5 H₂O) C, H, N.

Scheme 2^a

^a i. N-(2-chloroethyl)pyrrolidine-HCl, NaH, DMF, 70 °C; ii. Cmpd **18**: Cl(CH₂)₂NMeBn-HCl (**16**), NaH, DMF, 70 °C; Cmpd **19**: Cl(CH₂)₃NMeBn-HCl (**17**), NaH, DMF, 70 °C; iii. H₂, 20 % Pd(OH)₂/C, IPA, 80 °C.

N-phenyl-4-(2-(pyrrolidin-1-yl)ethoxy)aniline (15). In a 250 mL round bottomed flask, a solution of 4-(phenylamino)phenol (**14**) (3.27 g, 17.64 mmol) in DMF (20 mL) was treated with NaH (60 % suspension in mineral oil, 0.705 g, 17.6 mmol), stirred for 30 minutes, treated with N-(2-chloroethyl)pyrrolidine hydrochloride (1 g, 5.88 mmol), stirred at 70 °C for 1 hour, stirred at room temperature over night and partitioned between 1 M NaOH (100 mL) and Et₂O (50 mL). The layers were separated and the aqueous layer was extracted with Et₂O (2 x 50 mL). The combined Et₂O layers were washed with 0.1 M NaOH (50 mL), washed with brine, dried (MgSO₄), filtered, concentrated and chromatographed 3:1 to 0:1 EtOAc:[4:1:1 EtOAc:H₂O:HCOOH]. The fractions containing product were concentrated, basified with 50 % NaOH solution and extracted with CH₂Cl₂ (3 x 50 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered and concentrated to provide the desired product (1.66 g, 100 % yield). ¹H NMR (CDCl₃) δ 1.81 (m, 4H), 2.63 (m, 4H), 2.89 (t, *J*=5.9 Hz, 2H), 4.09 (t, *J*=6.1 Hz, 2H), 5.48 (bs, 1H), 6.79 - 6.93 (m, 5H), 7.02 - 7.09 (m, 2H), 7.17 - 7.24 (m, 2H); MS (DCI/NH₃) *m/z* 283 (M+H)⁺.

N-benzyl-2-chloro- N-methylethanamine hydrochloride (16).¹⁹ A flask containing N-benzyl- N-methylethanolamine (4.9 ml, 30 mmol) in CHCl₃ (15 mL) was treated dropwise with a solution of SOCl₂ (2.69 ml, 36.9 mmol) in CHCl₃ (5 mL). The mixture was stirred over the weekend. The mixture was concentrated to dryness and treated with acetone. The crystals were collected by filtration, washed with acetone and dried under vacuum to provide the title compound (4.4 g, 65 % yield). ¹H NMR (DMSO-d₆) δ 2.18 - 2.30 (m, 2H), 2.64 (d, *J*=4.8 Hz, 3H), 2.99 - 3.12 (m, 1H), 3.14 - 3.27 (m, 1H), 3.73 (t, *J*=6.3 Hz, 2H), 4.25 (dd, *J*=12.7, 5.6 Hz, 1H), 4.38 (dd, *J*=13.1, 5.2 Hz, 1H), 7.43 - 7.49 (m, 3H), 7.62 (m, 2H), 10.99 (bs, 1H); MS (DCI/NH₃) *m/z* 184 (M+H)⁺.

N-benzyl-3-chloro- N-methylpropan-1-amine hydrochloride (17). A flask containing a solution of N-methyl-1-phenylmethanamine (1 g, 8.25 mmol), 1-bromo-3-chloropropane (0.894 ml, 9.08 mmol) and Et₃N (1.50 ml, 10.7 mmol) in dioxane (8 mL) was heated to

80 °C for 4 hours, cooled, concentrated, diluted with Et₂O (100 mL), washed with 50 mL of NaHCO₃ sln, washed with brine, dried (MgSO₄), filtered, concentrated and chromatographed eluting with 6:1 to 0:1 hexane: Et₂O to provide the free base of the product. This free base in Et₂O was treated with a stream of HCl gas for ~30 seconds providing a non-crystalline residue. The supernatant was disposed of and the residue was washed with Et₂O (30 mL) and treated again with Et₂O (30 mL) from which crystallization occurred. The hygroscopic crystals were collected by filtration, washed with Et₂O and quickly transferred to a vacuum chamber and dried under vacuum to provide the title compound (0.9 g, 47 %). ¹H NMR (DMSO-d₆) δ 2.24 (m, 2H), 2.64 (d, *J*=4.8 Hz, 3H), 3.07 (m, 1H), 3.20 (m, 1H), 3.73 (t, *J*=6.3 Hz, 2H), 4.25 (dd, *J*=12.7, 5.6 Hz, 1H), 4.38 (dd, *J*=13.1, 5.2 Hz, 1H), 7.46 (m, 3H), 7.61 (m, 2H), 10.99 (s, 1H); MS (DCI/NH₃) *m/z* 198 (M+H)⁺.

N¹-benzyl-N¹-methyl-N²-phenyl-N²-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)ethane-1,2-diamine (18). In a 100 mL round bottomed flask, a mixture of compound **15** (170 mg, 0.60 mmol) and NaH (60 % suspension in mineral oil, 240 mg, 6.0 mmol) under nitrogen was treated with DMF (3 mL), stirred for 5 minutes, treated with compound **16** (199 mg, 0.903 mmol), stirred for 10 minutes, heated to 130 °C for 1 hour, cooled and partitioned between Et₂O (75 mL) and 0.1 M NaOH (25 mL). The Et₂O layer was washed with brine, dried (MgSO₄), filtered, concentrated and chromatographed eluting with 2 % -10 % (9:1 MeOH:ammonium hydroxide) in CH₂Cl₂ to provide the title compound (250 mg, 98 % yield). ¹H NMR (CDCl₃) δ 1.82 (m, 4H), 2.24 (s, 3H), 2.58 - 2.70 (m, 6H), 2.91 (t, *J*=5.9 Hz, 2H), 3.52 (s, 2H), 3.74 - 3.83 (m, 2H), 4.10 (t, *J*=6.1 Hz, 2H), 6.65 - 6.75 (m, 3H), 6.85 - 6.93 (m, 2H), 7.00 - 7.07 (m, 2H), 7.09 - 7.16 (m, 2H), 7.21 - 7.33 (m, 5H); MS (DCI/NH₃) *m/z* 430 (M+H)⁺.

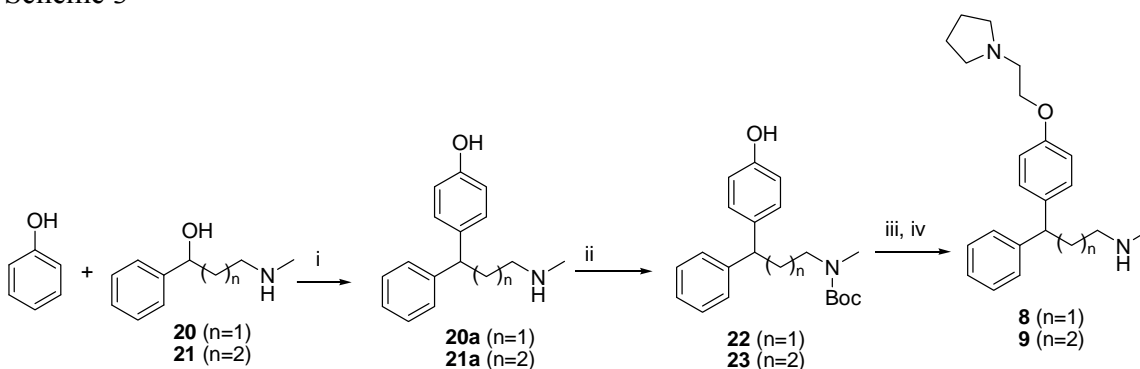
N¹-benzyl-N¹-methyl-N³-phenyl-N³-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)propane-1,3-diamine (19). A solution of compound **15** (65 mg, 0.230 mmol) in DMF (2 mL) under nitrogen was treated with NaH (60 % suspension in mineral oil, 55.2 mg, 1.38 mmol), stirred for 10 minutes, treated with compound **17** (108 mg, 0.460 mmol), treated with more 60 % suspension of NaH (60 % suspension in mineral oil, 55 mg, 1.4 mmol), stirred for 5 minutes at room temperature, stirred for 1 hour at 70 °C, cooled, diluted with Et₂O (75 mL), washed with 0.1 M NaOH (20 mL), washed with brine, dried (MgSO₄), filtered, concentrated and chromatographed eluting with 2 % -10 % (9:1 MeOH:ammonium hydroxide) in CH₂Cl₂ to provide the title compound (107 mg, 105 % yield). ¹H NMR (CDCl₃) δ 1.73 - 1.89 (m, 6H), 2.16 (s, 3H), 2.42 (t, *J*=6.9 Hz, 2H), 2.64 (m, 4H), 2.91 (t, *J*=6.1 Hz, 2H), 3.45 (s, 2H), 3.69 (t, *J*=7.1 Hz, 2H), 4.10 (t, *J*=5.9 Hz, 2H), 6.69 - 6.79 (m, 3H), 6.85 - 6.93 (m, 2H), 7.01 - 7.08 (m, 2H), 7.11 - 7.19 (m, 2H), 7.20 - 7.35 (m, 5H); MS (DCI/NH₃) *m/z* 444 (M+H)⁺.

N¹-methyl-N²-phenyl-N²-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)ethane-1,2-diamine (6). A solution of compound **18** (245 mg, 0.570 mmol) and Pearlman's Catalyst (145 mg) in IPA (3 mL) under H₂ was heated to 80 °C for 4 hours, stirred at room temperature over night, diluted with CH₂Cl₂ (50 mL), stirred for 5 minutes under N₂, and filtered. The filtrate was concentrated and chromatographed eluting with 4 % - 20 % (9:1 MeOH:ammonium hydroxide) in CH₂Cl₂ to provide recovered starting material followed by the title compound (111 mg, 57 % yield). ¹H NMR (CDCl₃) δ 1.81 (m, 4H), 2.43 (s, 3H), 2.63 (m, 4H), 2.82 (t, *J*=6.6 Hz, 2H), 2.90 (t, *J*=5.9 Hz, 2H), 3.78 (t, *J*=6.6 Hz, 2H),

4.10 (t, $J=5.9$ Hz, 2H), 6.72 - 6.81 (m, 3H), 6.87 - 6.94 (m, 2H), 7.04 - 7.10 (m, 2H), 7.13 - 7.20 (m, 2H); MS (DCI/NH₃) m/z 340 (M+H)⁺; Anal. (C₂₁H₂₉N₃O•0.3 H₂O) C, H, N.

N¹-methyl-N³-phenyl-N³-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)propane-1,3-diamine (7). A mixture of compound **19** (100 mg, 0.225 mmol) and Pearlman's Catalyst (45.0 mg) in IPA (3 mL) under H₂ was stirred at 80 °C for 4 hours, cooled, diluted with CH₂Cl₂ (50 mL), stirred for 5 minutes under N₂ and filtered to remove the solids. The filtrate was concentrated and chromatographed eluting with 2 % - 20 % (9:1 MeOH:ammonium hydroxide) in CH₂Cl₂ to provide recovered starting material and the title compound (49 mg, 61 % yield). ¹H NMR (CDCl₃) δ 1.75 - 1.87 (m, 6H), 2.41 (s, 3H), 2.63 (m, 6H), 2.90 (t, $J=6.1$ Hz, 2H), 3.69 (t, $J=7.5$ Hz, 2H), 4.10 (t, $J=5.9$ Hz, 2H), 6.70 - 6.77 (m, 3H), 6.86 - 6.94 (m, 2H), 7.02 - 7.09 (m, 2H), 7.12 - 7.20 (m, 2H); MS (DCI/NH₃) m/z 354 (M+H)⁺; Anal. (C₂₂H₃₁N₃O•0.3 H₂O) C, H, N.

Scheme 3^a



^a i. TFA; ii. Boc₂O, CH₃CN, Δ; iii. N-(2-chloroethyl)pyrrolidine·HCl, NaH, DMF, 70 °C; iv. TFA

4-(3-(methylamino)-1-phenylpropyl)phenol (20a). A solution of α-[2-(methylamino)ethyl]benzyl alcohol (**20**) (1.76 g, 10.6 mmol) in TFA (5 mL) was treated with phenol (1 g, 10.63 mmol), stirred at room temperature for over the weekend, concentrated to an oil and partitioned between aqueous NaOH solution and CH₂Cl₂ (50 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 25 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered, concentrated and chromatographed eluting with 2 % - 10 % (9:1 MeOH:ammonium hydroxide) in CH₂Cl₂ to provide 2 products, the less polar 2-(3-(methylamino)-1-phenylpropyl)phenol (708 mg, 28 % yield) (¹H NMR (CDCl₃) δ 2.09 - 2.21 (m, 1H), 2.28 - 2.51 (m, 3H), 2.48 (s, 3H), 2.75 - 2.82 (m, 1H), 4.62 (dd, $J=12.7, 3.6$ Hz, 1H), 6.65 - 6.73 (m, 2H), 6.90 - 6.95 (m, 1H), 7.01 - 7.08 (m, 1H), 7.18 - 7.24 (m, 1H), 7.27 - 7.39 (m, 4H); MS (DCI/NH₃) m/z 242 (M+H)⁺) and the title compound as the more polar isomer (351 mg, 13.7 % yield). ¹H NMR (CDCl₃) δ 2.13 - 2.35 (m, 3H), 2.40 (s, 3H), 2.62 (t, $J=7.7$ Hz, 2H), 3.85 (dd, $J=8.9, 6.5$ Hz, 1H), 6.55 (d, $J=8.7$ Hz, 2H), 7.00 (d, $J=8.3$ Hz, 2H), 7.11 - 7.18 (m, 1H), 7.18 - 7.28 (m, 4H); MS (DCI/NH₃) m/z 242 (M+H)⁺.

tert-butyl 3-(4-hydroxyphenyl)-3-phenylpropyl(methyl)carbamate (22). A flask containing compound **20a** (343 mg, 1.42 mmol) was treated with a solution of Boc₂O

(0.37 g, 1.7 mmol) in CH₃CN (5 mL), swirled until the starting material was in solution, heated to near reflux for 1 minute, cooled, concentrated and directly chromatographed eluting with 5:1 to 1:1 hexane:EtOAc to provide compound **22** (462 mg, 95 % yield). ¹H NMR (CDCl₃) δ 1.41 (s, 9H), 2.22 (q, *J*=7.8 Hz, 2H), 2.80 (s, 3H), 3.06 - 3.22 (m, 2H), 3.81 (t, *J*=7.8 Hz, 1H), 6.74 (d, *J*=7.8 Hz, 2H), 7.08 (d, *J*=8.5 Hz, 2H), 7.21 (d, 5H); MS (DCI/NH₃) *m/z* 342 (M+H)⁺.

***N*-methyl-3-phenyl-3-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)propan-1-amine (8). Step**

1. A solution of compound **22** (455 mg, 1.333 mmol) in DMF (5 mL) under nitrogen was treated with NaH (60 % suspension in mineral oil, 320 mg, 8.00 mmol), stirred for 10 minutes, treated with *N*-(2-chloroethyl)pyrrolidine hydrochloride (453 mg, 2.67 mmol), heated to 70 °C for 1 hour, cooled to room temperature, diluted with Et₂O (100 mL), washed with washed with 0.1 M NaOH (100 mL and 50 mL), washed with brine, dried (MgSO₄), filtered, concentrated and chromatographed eluting with 2 % (10 minutes), 2-10 % (over 20 minutes) (9:1 MeOH:ammonium hydroxide) in CH₂Cl₂ to provide the desired product, *tert*-butyl methyl(3-phenyl-3-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)propyl)carbamate (420 mg, 72 % yield). ¹H NMR (CDCl₃) δ 1.41 (s, 9H), 1.79 (m, 4H), 2.23 (q, *J*=7.9 Hz, 2H), 2.60 (m, 4H), 2.80 (bs, 3H), 2.87 (t, *J*=6.1 Hz, 2H), 3.14 (m, 2H), 3.83 (t, *J*=7.7 Hz, 1H), 4.06 (t, *J*=6.1 Hz, 2H), 6.83 (d, *J*=8.7 Hz, 2H), 7.13 (d, *J*=8.7 Hz, 2H), 7.16 - 7.32 (m, 5H); MS (DCI/NH₃) *m/z* 439 (M+H)⁺. **Step 2.** A solution of *tert*-butyl methyl(3-phenyl-3-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)propyl)carbamate (410 mg, 0.930 mmol) in TFA (4 mL) was heated to 60 °C for 2 minutes, concentrated partitioned between 1 M NaOH and CH₂Cl₂ (25 mL). The aqueous layer was not basic, so it was treated with ~ 0.5 mL of 50 % NaOH solution. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 25 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered, concentrated and chromatographed eluting with 4 % - 20 % (9:1 MeOH:ammonium hydroxide) in CH₂Cl₂ to provide the compound **8** (300 mg, 96 % yield). ¹H NMR (CDCl₃) δ 1.79 (m, 4H), 2.19 (q, *J*=7.5 Hz, 2H), 2.37 (s, 3H), 2.52 (t, *J*=7.1 Hz, 2H), 2.60 (m, 4H), 2.86 (t, *J*=6.1 Hz, 2H), 3.94 (t, *J*=7.7 Hz, 1H), 4.06 (t, *J*=5.9 Hz, 2H), 6.83 (d, *J*=8.7 Hz, 2H), 7.14 (d, *J*=8.3 Hz, 2H), 7.16 - 7.31 (m, 5H); MS (DCI/NH₃) *m/z* 339 (M+H)⁺.

Note from authors on the synthesis of 4-(Methylamino)-1-phenylbutan-1-ol (21): We recommend not using the following procedure for the synthesis of compound **21** due to the low yield of step 2. The authors of this manuscript suggest using the alternate procedure described in footnote 35.

4-(Methylamino)-1-phenylbutan-1-ol (21). Step 1.³³ A solution of 3-benzoylpropionic acid (3.5 g, 20 mmol) and Et₃N (9.6 ml, 69 mmol) in THF (100 mL) was cooled to -40 °C, treated dropwise with ethyl chloroformate (2.1 ml, 22 mmol), stirred at -20 °C for 30 minutes, treated with 40 wt. % methylamine in water (8.5 ml, 98 mmol), stirred at room temperature over night, concentrated to remove the majority of the THF and partitioned between 1 M HCl (100 mL) and Et₂O (400 mL). The Et₂O layer was washed with brine. On standing before drying with MgSO₄, a solid precipitated. This solid was collected by filtration and washed with a small amount of Et₂O to provide some of the desired product. The filtrate was dried (MgSO₄), filtered and concentrated to provide additional

desired product (total of 3.7 g, 99%). ¹H NMR (CDCl₃) δ 1.41 (s, 9H), 1.79 (m, 4H), 2.23 (q, *J*=7.9 Hz, 2H), 2.60 (m, 4H), 2.80 (s, 3H), 2.87 (t, *J*=6.1 Hz, 2H), 3.14 (dd, *J*=8.7, 6.7 Hz, 2H), 3.83 (t, *J*=7.7 Hz, 1H), 4.06 (t, *J*=6.1 Hz, 2H), 6.83 (d, *J*=8.7 Hz, 2H), 7.13 (d, *J*=8.7 Hz, 2H), 7.16 - 7.32 (m, 5H); MS (DCI/NH₃) *m/z* 192 (M+H)⁺. **Step 2.**³⁴ A solution of 1 M LAH in THF (100 mL, 100 mmol) was treated with a solution of *N*-methyl-4-oxo-4-phenylbutanamide (3.7 g, 19.35 mmol), in THF (10 mL) dropwise over 15 minutes and the mixture was stirred at room temperature over night. The mixture was carefully poured onto ice (very exothermic) and the resulting mixture was extracted with Et₂O (2 x 250 mL). The combined Et₂O layers were washed with brine, dried (MgSO₄), filtered, concentrated and purified by chromatographed eluting with 2 % - 20 % (9:1 MeOH:ammonium hydroxide) in CH₂Cl₂ to provide the title compound (0.15 g, 4 %).³⁵ ¹H NMR (CDCl₃) δ 1.52 - 1.74 (m, 2H), 1.75 - 1.88 (m, 1H), 1.91 - 2.00 (m, 1H), 2.45 (s, 3H), 2.54 - 2.64 (m, 1H), 2.74 (ddd, *J*=11.9, 6.3, 4.0 Hz, 1H), 3.54 (bs, 2H), 4.68 (dd, *J*=8.1, 3.0 Hz, 1H), 7.18 - 7.25 (m, 1H), 7.28 - 7.40 (m, 4H).

4-(4-(methylamino)-1-phenylbutyl)phenol (21a). A mixture of phenol (102 mg, 1.09 mmol) and compound **21** (65 mg, 0.36 mmol) was treated with TFA (1 mL), stirred at room temperature over night, concentrated to dryness and partitioned between 1 M NaOH (5 mL) and CH₂Cl₂ (25 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 25 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered, concentrated and chromatographed eluting with 2 % - 20 % (9:1 MeOH:ammonium hydroxide) in CH₂Cl₂ to provide a mixture of the title compound as the minor product and major isomer, 2-(4-(methylamino)-1-phenylbutyl)phenol, which was not separated but carried onto the next step. MS (DCI/NH₃) *m/z* 256 (M+H)⁺.

tert-butyl 4-(4-hydroxyphenyl)-4-phenylbutyl(methyl)carbamate (23). A mixture of compound **21a** and 2-(4-(methylamino)-1-phenylbutyl)phenol (36.6 mg, 0.143 mmol) was treated with a solution of Boc₂O (38 mg, 0.17 mmol) in CH₃CN (2 mL), heated for 2 minutes at reflux, cooled, concentrated and directly chromatographed eluting with a gradient of 1:1 to 0:1 hexane:[9:1 CH₂Cl₂:EtOAc] to provide 2 products, *tert*-butyl 4-(2-hydroxyphenyl)-4-phenylbutyl(methyl)carbamate as the less polar undesired isomer (37.7 mg) (MS (DCI/NH₃) *m/z* 356 (M+H)⁺) and the desired *tert*-butyl 4-(4-hydroxyphenyl)-4-phenylbutyl(methyl)carbamate (16.1 mg, 12% for 2 steps) as the more polar isomer. ¹H NMR (CDCl₃) δ 1.34 - 1.53 (m, 11H), 1.96 (q, *J*=7.5 Hz, 2H), 2.76 (s, 3H), 3.21 (bs, 2H), 3.84 (t, *J*=7.7 Hz, 1H), 4.94 (bs, 0.4H), 5.06 (bs, 0.5H), 6.74 (d, *J*=8.3 Hz, 2H), 7.08 (d, *J*=8.7 Hz, 2H), 7.12 - 7.30 (m, 5H); MS (DCI/NH₃) *m/z* 356 (M+H)⁺.

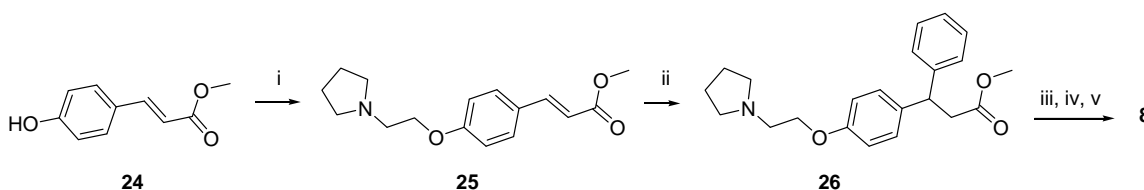
***N*-methyl-4-phenyl-4-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)butan-1-amine (9).**

Step 1. Compound **23** (16 mg, 0.045 mmol) in DMF (1 mL) was treated with NaH (60 % suspension in mineral oil, 11 mg, 0.27 mmol), stirred for 10 minutes, treated with *N*-(2-chloroethyl)pyrrolidine hydrochloride (15 mg, 0.09 mmol), stirred for 5 minutes, treated with more NaH (60 % suspension in mineral oil, 10.8 mg, 0.270 mmol), stirred at 70 °C for 1 hour, cooled, diluted with Et₂O (50 mL), washed with 0.1 M NaOH (2 x 25 mL), washed with brine, dried (MgSO₄), filtered, concentrated, and chromatographed eluting with 2 % -10 % (9:1 MeOH:ammonium hydroxide) in CH₂Cl₂ to provide the desired product, *tert*-butyl methyl(4-phenyl-4-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)butyl)carbamate (18.4 mg, 90 % yield). ¹H NMR (CDCl₃) δ 1.36 - 1.52

(m, 11H), 1.79 (m, 4H), 1.97 (q, $J=7.8$ Hz, 2H), 2.60 (m, 4H), 2.76 (s, 3H), 2.87 (t, $J=5.9$ Hz, 2H), 3.21 (bs, 2H), 3.85 (t, $J=7.5$ Hz, 1H), 4.06 (t, $J=6.1$ Hz, 2H), 6.82 (d, $J=8.8$ Hz, 2H), 7.12 (d, $J=8.8$ Hz, 2H), 7.14 - 7.30 (m, 5H); MS (DCI/NH₃) m/z 453 (M+H)⁺. **Step 2.** *tert*-Butyl methyl(4-phenyl-4-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)butyl)carbamate (18 mg, 0.041 mmol) was treated with TFA (1.5 mL), heated to 60 °C for 2 minutes, concentrated and partitioned between 1 M NaOH (5 mL) and CH₂Cl₂ (25 mL). The aqueous layer was extracted with CH₂Cl₂ (25 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered and concentrated to provide the desired product, *N*-methyl-4-phenyl-4-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)butan-1-amine (12.5 mg, 87 % yield). ¹H NMR (CDCl₃) δ 1.26 - 1.51 (m, 2H), 1.79 (m, 4H), 2.04 (q, $J=7.8$ Hz, 2H), 2.39 (s, 3H), 2.61 (m, 6H), 2.87 (t, $J=5.9$ Hz, 2H), 3.83 (t, $J=7.8$ Hz, 1H), 4.06 (t, $J=6.1$ Hz, 2H), 6.82 (d, $J=8.8$ Hz, 2H), 7.13 (d, $J=8.8$ Hz, 2H), 7.15 - 7.30 (m, 5H); MS (DCI/NH₃) m/z 353 (M+H)⁺.

Alternate synthesis to compound 8.

Scheme 4^a



^a i. *N*-(2-chloroethyl)pyrrolidine·HCl, NaH, DMF, 70 °C; ii. PhB(OH)₂, Pd(OAc)₂, 2,2'-bipyridine, 10:5:3 AcOH:THF:H₂O; iii. LAH, THF; iv. MsCl, Et₃N, CH₂Cl₂; v. 40 % aqueous MeNH₂ in MeOH, sealed vessel, 65 °C, 3 h.

(E)-methyl 3-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)acrylate (25). A solution of (E)-methyl 3-(4-hydroxyphenyl)acrylate (compound **24**)³⁶ (5.0 g, 28 mmol) in DMF (110 mL) under N₂ was treated with NaH (60 % suspension in mineral oil, 4.49 g, 112 mmol), stirred for 5 minutes, treated with *N*-(2-chloroethyl)pyrrolidine hydrochloride (9.6 g, 56 mmol), stirred for 5 minutes, heated to 80 °C for 35 min, cooled, diluted with Et₂O (100 mL) and poured in portions and carefully into a swirled flask containing ice cold water (500 mL) and Et₂O (500 mL). The layers were separated and the aqueous was extracted with Et₂O (300 mL). The combined Et₂O layers were washed with cold 0.1 M NaOH (250 mL), washed with brine, dried (MgSO₄), filtered, concentrated and chromatographed eluting with 2 % -10 % (9:1 MeOH:ammonium hydroxide) in CH₂Cl₂ to provide the title compound (4.93 g, 64 % yield). ¹H NMR (CDCl₃) δ 1.81 (m, 4H), 2.63 (m, 4H), 2.91 (t, *J*=5.9 Hz, 2H), 3.79 (s, 3H), 4.14 (t, *J*=5.9 Hz, 2H), 6.30 (d, *J*=15.9 Hz, 1H), 6.92 (d, *J*=8.7 Hz, 2H), 7.46 (d, *J*=8.7 Hz, 2H), 7.64 (d, *J*=15.9 Hz, 1H); MS (DCI/NH₃) *m/z* 276 (M+H)⁺.

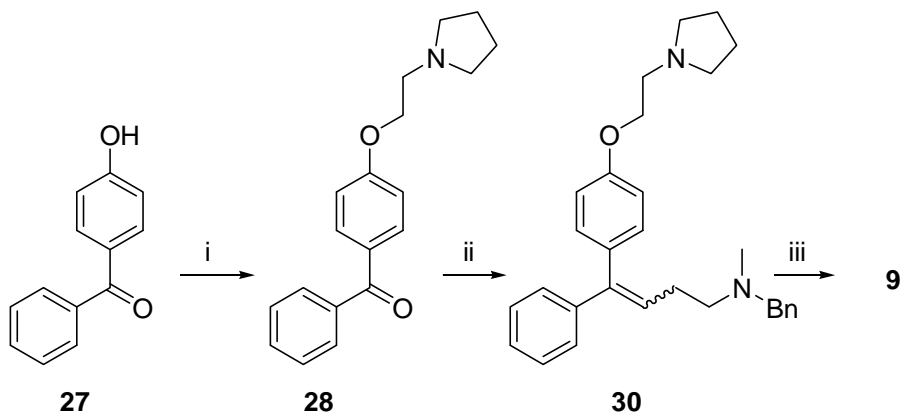
Methyl 3-phenyl-3-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)propanoate (26). A mixture of compound **25** (2.1 g, 7.63 mmol), phenylboronic acid (2.79 g, 22.88 mmol), 2,2'-bipyridine (0.238 g, 1.525 mmol)³⁷ and PdOAc₂ (0.086 g, 0.381 mmol) in 15 mL of 10:5:3 AcOH:THF:H₂O was heated to 70 °C over night, heated to 90 °C for 2 hours, cooled, concentrated to an oil, diluted with CH₂Cl₂ (100 mL) and washed with cold 1 M NaOH (25 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered, concentrated and chromatographed eluting with 2 % -10 % (9:1 MeOH:ammonium hydroxide) in CH₂Cl₂ to provide the title compound (2.41 g, 89 % yield). ¹H NMR (CDCl₃) δ 1.80 (m, 4H), 2.63 (m, 4H), 2.89 (t, *J*=6.1 Hz, 2H), 3.02 (d, *J*=8.1 Hz, 2H), 3.57 (s, 3H), 4.07 (t, *J*=6.1 Hz, 2H), 4.50 (t, *J*=8.0 Hz, 1H), 6.82 (d, *J*=8.8 Hz, 2H), 7.12 (d, *J*=8.5 Hz, 2H), 7.16 - 7.31 (m, 5H); MS (DCI/NH₃) *m/z* 354 (M+H)⁺.

***N*-Methyl-3-phenyl-3-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)propan-1-amine di-maleate (8). Step 1.** A solution of compound **26** (2.27 g, 6.42 mmol) in THF (25 mL) at 0 °C under N₂ was treated slowly with 1 M LAH in THF (19.27 mL, 19.27 mmol) and stirred over night. The mixture was cooled and carefully treated with water (50 mL), dropwise at first. This mixture was diluted with CH₂Cl₂ (200 mL) and filtered through

celite to remove the emulsion. The layers were separated and the aqueous was extracted with CH₂Cl₂ (2 x 50 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered, concentrated to provide 3-phenyl-3-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)propan-1-ol (1.93 g, 92 % yield). ¹H NMR (CDCl₃) δ 1.26 (t, *J*=5.2 Hz, 1H), 1.79 (m, 4H), 2.28 (dd, *J*=14.3, 6.3 Hz, 2H), 2.60 (m, 4H), 2.87 (t, *J*=6.1 Hz, 2H), 3.60 (q, *J*=5.9 Hz, 2H), 4.04 - 4.11 (m, 3H), 6.84 (d, *J*=8.7 Hz, 2H), 7.15 (d, *J*=8.7 Hz, 2H), 7.18 - 7.31 (m, 5H); MS (DCI/NH₃) *m/z* 326 (M+H)⁺. **Step 2.** A solution of the product from Step 1 (1.93 g, 5.93 mmol) in CH₂Cl₂ (25 mL) was treated with Et₃N (2.5 ml, 18 mmol), treated with MsCl (0.69 ml, 8.9 mmol), stirred at room temperature over night and partitioned between cold 1 M NaOH (25 mL) and CH₂Cl₂ (50 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 25 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered, concentrated and chromatographed eluting with 2 % - 10 % (9:1 MeOH:ammonium hydroxide) in CH₂Cl₂ to provide 3-phenyl-3-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)propyl methanesulfonate (2 g, 84 % yield). ¹H NMR (CDCl₃) δ 1.80 (m, 4H), 2.46 (dd, *J*=14.3, 6.3 Hz, 2H), 2.62 (m, 4H), 2.88 (t, *J*=5.9 Hz, 2H), 2.90 (s, 3H), 4.03 - 4.10 (m, 3H), 4.15 (t, *J*=6.3 Hz, 2H), 6.85 (d, *J*=8.7 Hz, 2H), 7.13 (d, *J*=8.7 Hz, 2H), 7.16 - 7.32 (m, 5H); MS (DCI/NH₃) *m/z* 404 (M+H)⁺. **Step 3.** A solution of the product from Step 2 (2 g, 4.96 mmol) in THF (20 mL) and a 40 wt. % solution of methylamine in water (20 ml, 230 mmol) was heated to 65 °C in a pressure tube for 3 hours, cooled, concentrated and chromatographed eluting with 4 % - 20 % (9:1 MeOH:ammonium hydroxide) in CH₂Cl₂ to provide the free base of compound **8** (1.39 g, 83 % yield). ¹H NMR (CDCl₃) δ 1.79 (m, 4H), 2.19 (q, *J*=7.7 Hz, 2H), 2.38 (s, 3H), 2.52 (t, *J*=7 Hz, 2H), 2.60 (m, 4H), 2.87 (t, *J*=6.1 Hz, 2H), 3.94 (t, *J*=7.9 Hz, 1H), 4.06 (t, *J*=5.9 Hz, 2H), 6.83 (d, *J*=8.3 Hz, 2H), 7.14 (d, *J*=8.7 Hz, 2H), 7.17 - 7.31 (m, 5H); MS (DCI/NH₃) *m/z* 339 (M+H)⁺. **Step 4. Salt formation.** A solution of the product from Step 3 (1.38 g, 4.08 mmol) in EtOH (5 mL) was treated with maleic acid (0.97 g, 8.36 mmol) and swirled until the maleic acid dissolved, concentrated to approximately 3 mL, treated slowly with EtOAc until about 25 mL total solution was achieved. After crystallization had started, the mixture was slowly swirled and treated with more EtOAc (10 mL). After 15 minutes EtOAc (100 mL) was added with mixing and the solid was allowed to stand at room temperature for 2 hours. The solid was collected by filtration, washed with EtOAc and dried over night under vacuum with heating to provide the title compound (2.17 g, 93 % yield). mp. 120-122 °C; ¹H NMR (CD₃OD) δ 2.10 (m, 4H), 2.35 - 2.45 (m, 2H), 2.67 (s, 3H), 2.87 - 2.95 (m, 2H), 3.45 (bs, 4H), 3.60 - 3.64 (m, 2H), 3.99 (t, *J*=8.0 Hz, 1H), 4.26 - 4.32 (m, 2H), 6.24 (s, 3.4H), 6.95 (d, *J*=8.8 Hz, 2H), 7.15 - 7.22 (m, 1H), 7.25 (d, *J*=8.5 Hz, 2H), 7.24 - 7.33 (m, 4H); MS (DCI/NH₃) *m/z* 339 (M+H)⁺; Anal. (C₂₂H₃₀N₂O•2 C₄H₄O₄) C, H, N.

Altenate synthesis to compound 9.

Scheme 5^a



^a i. N-(2-chloroethyl)pyrrolidine·HCl, NaH, DMF, 70 °C; ii. BnMeN(CH₂)₃P⁺Ph₃·Br⁻ (29), n-BuLi; iii, H₂, 20 % Pd(OH)₂/C, MeOH, 30 psi, 48 h.

Phenyl(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)methanone (28). A mixture of 4-hydroxybenzophenone (27) (5 g, 25 mmol) and 1-(2-chloroethyl)pyrrolidine hydrochloride (5.2 g, 30 mmol) in DMF (70 mL) under N₂ was treated with NaH (60 % suspension in mineral oil, 2.2 g, 55 mmol), stirred at room temperature for 10 minutes, heated to 80 °C for 1 hour, cooled, diluted with water (350 mL), and extracted with Et₂O (2 x 100 mL). The combined Et₂O layers were washed with 0.1 M NaOH (100 mL), washed with brine, dried (MgSO₄), filtered, concentrated and chromatographed eluting with 2 % - 10 % (9:1 MeOH:ammonium hydroxide) in CH₂Cl₂ to provide the title compound (7.0 g, 94 % yield). ¹H NMR (CDCl₃) δ 1.82 (m, 4H), 2.64 (m, 4H), 2.94 (t, *J*=5.9 Hz, 2H), 4.19 (t, *J*=5.9 Hz, 2H), 6.98 (d, *J*=9.2 Hz, 2H), 7.42 - 7.51 (m, 2H), 7.52 - 7.60 (m, 1H), 7.72 - 7.77 (m, 2H), 7.82 (d, *J*=9.2 Hz, 2H); MS (ESI+) *m/z* 296 (M+H)⁺.
(3-(benzyl(methyl)amino)propyl)triphenylphosphonium bromide (29).³⁸ A mixture of *N*-methylbenzylamine (3.06 ml, 23.7 mmol), (3-bromopropyl)triphenylphosphonium bromide (10.0 g, 21.5 mmol) and Et₃N (9.0 ml, 65 mmol) in CH₃CN (21 mL) was heated to 80 °C over the weekend, cooled, concentrated, treated with 1 M NaOH (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered and concentrated. This residue was treated with EtOAc and allowed to crystallize. The resulting solid was collected by filtration and washed with EtOAc. The solid was recrystallized by dissolved in hot CHCl₃ (~10 mL) and slowly treated with EtOAc (~25 mL). More EtOAc was slowly added as the crystals started to form. After about 2 hours, the solid was collected by filtration, washed with EtOAc, crushed in a mortar and pestle and dried under vacuum at 70 °C to provide the title compound (9.94 g, 91 % yield). ¹H NMR (CDCl₃) δ 1.77 - 1.90 (m, 2H), 2.11 (s, 3H), 2.71 (t, *J*=5.9 Hz, 2H), 3.44 (s, 2H), 3.85 - 3.97 (m, 2H), 7.18 - 7.31 (m, 5H), 7.62 - 7.71 (m, 6H), 7.73 - 7.87 (m, 9H); MS (ESI+) *m/z* 424 (M+H)⁺.

***N*-benzyl-*N*-methyl-4-phenyl-4-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)but-3-en-1-amine (30).** A suspension of compound 29 (6.40 g, 12.7 mmol) in THF (30 mL) at 0 °C

under nitrogen was treated dropwise over 5 minutes with 2.5 M BuLi (4.4 ml, 11 mmol), stirred for 45 minutes at 0 °C, treated with a solution of compound **28** (2.5 g, 8.5 mmol) in THF (30 mL) stirred over night at room temperature, concentrated to an oil and partitioned between Et₂O (75 mL) and 1 M HCl (75 mL). The layers were separated and the aqueous was washed with Et₂O (75 mL). The aqueous layer was basified to pH 14 with 50 % NaOH solution and extracted with CH₂Cl₂ (3 x 50 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered and concentrated. This residue which had started to crystallize on standing was diluted with EtOAc (150 mL) and, after fully crystallizing, the solid was collected by filtration and identified as recovered compound **29**. The EtOAc filtrate was concentrated and chromatographed eluting with 2 % - 10 % (9:1

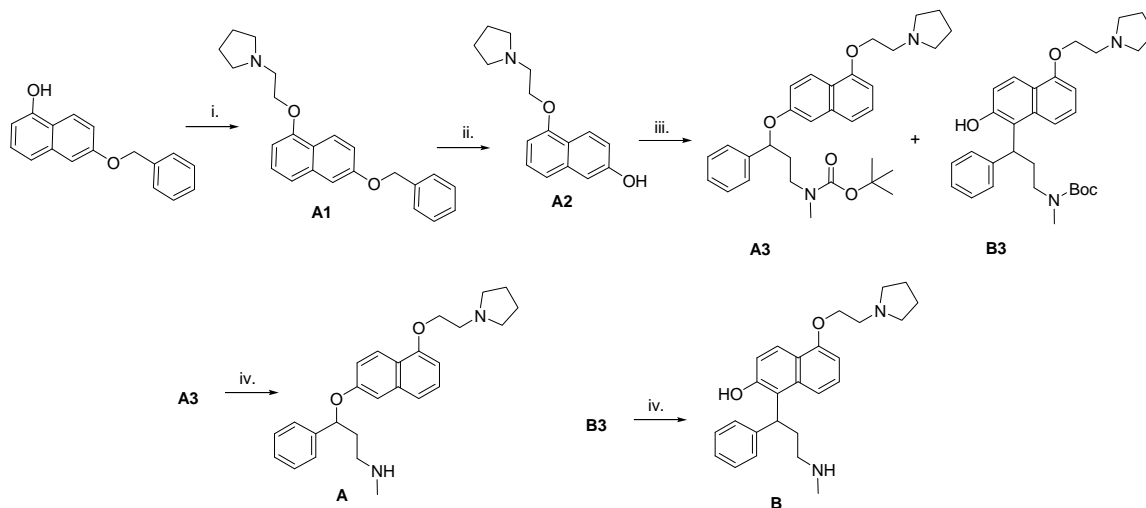
MeOH:ammonium hydroxide) in CH₂Cl₂ to provide the title compound (3.39 g, 91 % yield) as a mixture of cis and trans isomers. ¹H NMR (CDCl₃) δ 1.76 - 1.86 (m, 4H), 2.15 and 2.17 (s and s, 3H), 2.24 - 2.38 (m, 2H), 2.40 - 2.53 (m, 2H), 2.58 - 2.67 (m, 4H), 2.88 and 2.92 (t and t, *J*=5.9 Hz, 2H), 3.44 and 3.46 (s and s, 2H), 4.08 and 4.13 (t and t, *J*=6 Hz, 2H), 5.99 and 6.03 (t and t, *J*=7.3 Hz, 1H), 6.80 and 6.90 (d and d, *J*=9 Hz, 2H), 7.03 - 7.17 (m, 3H), 7.18 - 7.38 (m, 9H); MS (ESI+) *m/z* 441 (M+H)⁺.

***N*-methyl-4-phenyl-4-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)butan-1-amine dimaleate (9)**. A solution of compound **30** (3.32 g, 7.54 mmol) in MeOH (40 ml) was added to 20% Pd(OH)₂ (0.33 g, 2.4 mmol) in a 250 mL stainless steel pressure bottle and shaken under H₂ for 48 hr at 30 psi and room temperature. The mixture was filtered, concentrated and chromatographed eluting with 2 % - 10 % (9:1 MeOH:ammonium hydroxide) in CH₂Cl₂ to provide 1.71 g (88% yield) of the free base of compound **9**. ¹H NMR (CDCl₃) δ 1.37 - 1.49 (m, 2H), 1.79 (m, 4H), 1.99 - 2.09 (m, 2H), 2.38 (s, 3H), 2.54 - 2.63 (m, 6H), 2.87 (t, *J*=6.1 Hz, 2H), 3.83 (t, *J*=7.7 Hz, 1H), 4.06 (t, *J*=6.1 Hz, 2H), 6.82 (d, *J*=8.7 Hz, 2H), 7.13 (d, *J*=8.7 Hz, 2H), 7.15 - 7.29 (m, 5H); MS (ESI+) *m/z* 353 (M+H)⁺. **Salt**

Formation. A solution of compound **9** (1.71 g, 4.85 mmol) was dissolved in EtOH (10 mL), treated with maleic acid (1.18 g, 10.2 mmol), heated until the solution became homogeneous, filtered and concentrated to ~ 10 mL total volume, treated with treated with EtOAc (100 mL) and set aside over night. The solution was decanted off and the oil was treated with EtOAc. This process was repeated until crystallization. The crystals were collected by filtration, washed with EtOAc and dried to provide 1.80 g (63 %) the title compound. ¹H NMR (DMSO-d₆) δ 1.38 - 1.52 (m, 2H), 1.82 - 2.11 (m, 6H), 2.90 (t, *J*=7.6 Hz, 2H), 2.98 - 3.46 (m, 7H), 3.52 (bs, 2H), 3.90 (t, *J*=7.8 Hz, 1H), 4.22 (t, *J*=4.7 Hz, 2H), 6.02 (s, 3.1H), 6.92 (d, *J*=8.8 Hz, 2H), 7.13 - 7.21 (m, 1H), 7.21 - 7.32 (m, 4H), 7.25 (d, *J*=8.8 Hz, 2H), 8.19 (s, 1.5H), 9.59 (s, 0.5H); MS (ESI+) *m/z* 353 (M+H)⁺; Anal. (C₂₃H₃₂N₂O•2 C₄H₄O₄) C, H, N.

Schemes and experimental section for compounds A-G

Scheme 6. Synthesis of compounds A and B.^a



^a i. N-(2-chloroethyl)pyrrolidine·HCl, NaH, DMF, 70 °C; ii. Pd/C, H₂, MeOH; iii. compound **13**, PPh₃, DEAD, THF; iv. TFA

1-(2-(6-(Benzyloxy)naphthalen-1-yloxy)ethyl)pyrrolidine (A1). A sln of 6-(benzyloxy)naphthalen-1-ol¹⁷ (0.42 g, 1.7 mmol) in DMF (5 mL) under N₂ was treated with 60 % sodium hydride (0.40 g, 10 mmol), stirred at room temp for 15 min, treated with N-(2-chloroethyl)pyrrolidine hydrochloride (0.57 g, 3.4 mmol), stirred at 70 °C for 1 h, stirred at room temp over night, treated with water (10 mL) and partitioned between water (50 mL) and Et₂O (100 mL). The layers were separated and the aqueous layer was extracted with Et₂O (50 mL). The combined Et₂O layers were washed with 0.1 M NaOH (60 mL), washed with brine, dried (MgSO₄), filtered, concd and chromatographed on silica gel eluting with a gradient of 1-10 % (9:1 MeOH:NH₄OH sln) in CH₂Cl₂ to provide the title compound (0.46 g, 79 % yield). ¹H NMR (300 MHz, CDCl₃) δ 1.87 – 1.77 (m, 4H), 2.75 – 2.64 (m, 4H), 3.04 (t, *J* = 5.9 Hz, 2H), 4.28 (t, *J* = 6.0 Hz, 2H), 5.18 (s, 2H), 6.69 (dd, *J* = 6.6, 2.0 Hz, 2H), 7.22 – 7.16 (m, 1H), 7.44 – 7.24 (m, 5H), 7.52 – 7.46 (m, 2H), 8.21 – 8.16 (m, 1H); MS (DCI/NH₃) *m/z* 348 (M+H)⁺.

5-(2-(Pyrrolidin-1-yl)ethoxy)naphthalen-2-ol (A2). A sln of compound **A1** (460 mg, 1.3 mmol) in MeOH (5 mL) was purged N₂. 10% Pd/C (100 mg) was added and the atmosphere was exchanged with N₂ and then with H₂, and the mixture was stirred under H₂ for 2 h. The atmosphere was exchanged with N₂ and the sln was diluted with MeOH (100 mL) and stirred for 10 min. The mixture was filtered to remove the solids and the filtrate was concd to and chromatographed on silica gel eluting with a gradient of 2 % to 10 % (9:1 MeOH:NH₄OH sln) in CH₂Cl₂ to provide the desired product (272 mg, 80 %

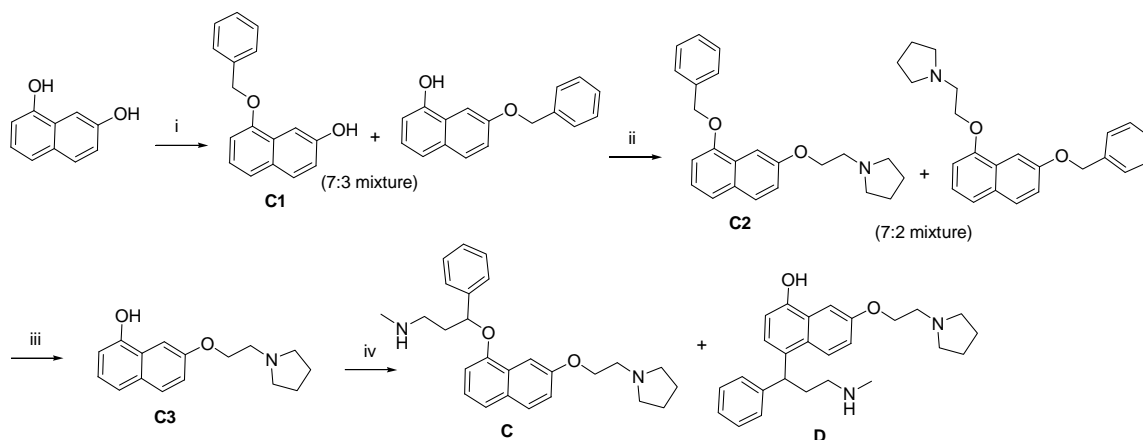
yield). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.92 – 1.80 (m, 4H), 2.81 – 2.71 (m, 4H), 3.08 (t, $J = 5.8$ Hz, 2H), 4.29 (t, $J = 5.8$ Hz, 2H), 6.62 (d, $J = 6.9$ Hz, 1H), 6.98 (dd, $J = 9.0, 2.5$ Hz, 1H), 7.04 (d, $J = 2.5$ Hz, 1H), 7.17 (d, $J = 8.2$ Hz, 1H), 7.29 – 7.22 (m, 1H), 8.09 (d, $J = 9.0$ Hz, 1H); MS (DCI/ NH_3) m/z 258 (M+H) $^+$.

tert-Butyl methyl(3-phenyl-3-(5-(2-(pyrrolidin-1-yl)ethoxy)naphthalen-2-yloxy)propyl)carbamate (A3) and **tert-butyl 3-(2-hydroxy-5-(2-(pyrrolidin-1-yl)ethoxy)naphthalen-1-yl)-3-phenylpropyl(methyl)carbamate (B3)**. A sln of compound B2 (270 mg, 1.1 mmol) and Ph_3P (360 mg, 1.4 mmol) in THF (5 mL) under N_2 was cooled to 0 °C, treated over 5 min with DEAD (40 wt. % in toluene, 0.62 mL, 1.4 mmol), stirred at room temp over the weekend, concd and chromatographed on silica gel eluting with a gradient of 2 % to 10 % (9:1 MeOH: NH_4OH sln) in CH_2Cl_2 to provide the major product, compound A3 ((325 mg, 61.3 % yield) $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.39 (s, 9H), 1.87 – 1.74 (m, 4H), 2.27 – 2.06 (m, 2H), 2.74 – 2.62 (m, 4H), 2.85 (s, 3H), 3.01 (t, $J = 5.9$ Hz, 2H), 3.45 (bs, 2H), 4.24 (t, $J = 5.9$ Hz, 2H), 5.27 (dd, $J = 8.3, 4.4$ Hz, 1H), 6.62 (d, $J = 7.6$ Hz, 1H), 6.94 (d, $J = 2.2$ Hz, 1H), 7.17 – 7.10 (m, 2H), 7.42 – 7.19 (m, 6H), 8.12 (d, $J = 9.2$ Hz, 1H); MS (DCI/ NH_3) m/z 505 (M+H) $^+$) and the more polar product, compound B3 ($^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.37 (s, 9H), 1.85 – 1.76 (m, 4H), 2.75 – 2.46 (m, 6H), 2.78 (s, 3H), 3.01 – 2.89 (m, 1H), 3.04 (t, $J = 5.9$ Hz, 2H), 3.56 – 3.24 (m, 1H), 4.26 (t, $J = 5.9$ Hz, 2H), 4.98 (t, $J = 7.3$ Hz, 1H), 6.64 (d, $J = 7.6$ Hz, 1H), 7.09 – 6.99 (m, 1H), 7.16 (dd, $J = 12.1, 4.9$ Hz, 1H), 7.28 – 7.20 (m, 3H), 7.34 (d, $J = 7.6$ Hz, 2H), 7.56 – 7.40 (m, 1H), 8.15 (d, $J = 9.1$ Hz, 1H); MS (DCI/ NH_3) m/z 505 (M+H) $^+$.)

N-methyl-3-phenyl-3-(5-(2-(pyrrolidin-1-yl)ethoxy)naphthalen-2-yloxy)propan-1-amine (A). Compound A3 was treated with TFA at 60 °C for 5 min, concd and chromatographed on silica gel eluting with a gradient of 2 % to 10 % (9:1 MeOH: NH_4OH sln) in CH_2Cl_2 to provide the title compound as the faster moving product ($^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.85 – 1.76 (m, 4H), 2.12 – 1.97 (m, 1H), 2.23 (dq, $J = 10.2, 6.6$ Hz, 1H), 2.43 (s, 3H), 2.71 – 2.64 (m, 4H), 2.77 (t, $J = 7.1$ Hz, 2H), 3.01 (t, $J = 5.9$ Hz, 2H), 4.24 (t, $J = 5.9$ Hz, 2H), 5.39 (dd, $J = 8.1, 4.8$ Hz, 1H), 6.62 (d, $J = 7.3$ Hz, 1H), 6.98 (d, $J = 2.5$ Hz, 1H), 7.14 (dd, $J = 9.1, 2.5$ Hz, 2H), 7.26 – 7.19 (m, 2H), 7.35 – 7.28 (m, 2H), 7.43 – 7.36 (m, 2H), 8.12 (d, $J = 9.2$ Hz, 1H); MS (DCI/ NH_3) m/z 405 (M+H) $^+$) as well as a trace of compound C as a slower moving product.

1-(3-(methylamino)-1-phenylpropyl)-5-(2-(pyrrolidin-1-yl)ethoxy)naphthalen-2-ol (B). Compound B3 was treated with TFA (1 mL) at 60 °C for 5 min, concd and chromatographed on silica gel eluting with a gradient of 2 % to 10 % (9:1 MeOH:sat. aqu. NH_4OH sln) in CH_2Cl_2 to provide the title compound $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.86 – 1.76 (m, 4H), 2.44 – 2.29 (m, 1H), 2.45 (s, 3H), 2.62 – 2.51 (m, 1H), 2.75 – 2.63 (m, 5H), 2.87 – 2.77 (m, 1H), 3.02 (t, $J = 6.0$ Hz, 2H), 4.21 (t, $J = 6.0$ Hz, 2H), 5.17 (dd, $J = 12.6, 4.3$ Hz, 1H), 6.49 (dd, $J = 6.7, 1.7$ Hz, 1H), 6.98 – 6.87 (m, 2H), 7.14 – 7.06 (m, 1H), 7.26 – 7.16 (m, 5H), 8.16 (d, $J = 9.1$ Hz, 1H); MS (DCI/ NH_3) m/z 405 (M+H) $^+$.

Scheme 7. Synthesis of compounds **C** and **D**.^a



^a i. BnBr, NaH, DMF; ii. N-(2-chloroethyl)pyrrolidine-HCl, NaH, DMF, 70 °C; iii. Pd/C, H₂, MeOH; iv. α -[2-(methylamino)ethyl]benzyl alcohol, TFA

8-(benzyloxy)naphthalen-2-ol and 7-(benzyloxy)naphthalen-1-ol (C1). A sln of 1,7-dihydroxynaphthalene (10 g, 62 mmol) in DMF (100 mL) under N₂ was treated with NaH (60 % suspension in mineral oil, 2.50 g, 62 mmol), stirred for 30 min, treated all at once with benzyl bromide (7.4 mL, 62 mmol) (mixture became warm) and stirred overnight at room temp. The reaction was partitioned between water (250 mL) and Et₂O (250 mL). The layers were separated and the aqueous layer was extracted with Et₂O (250 mL). The combined Et₂O layers were washed with water (250 mL and 100 mL), washed with brine, dried (MgSO₄), filtered, concd and chromatographed on silica gel eluting with a gradient of 5:1 to 2:1 CH₂Cl₂:(9:1 CH₂Cl₂:EtOAc). (Chromatography may have worked better if eluted with a gradient of 5:1 to 1:1 hexane:(9:1 CH₂Cl₂:EtOAc).) The desired product was isolated as the major product but was contaminated with approximately 50 % of the isomer, 7-(benzyloxy)naphthalen-1-ol. ¹H NMR (300 MHz, CDCl₃) δ 4.97 (s, 0.3H), 5.17 (s, 0.7H), 5.20 (s, 1.6H), 5.22 (s, 0.6H), 6.79 (dd, *J* = 7.5, 0.5 Hz, 0.7H), 6.87 (d, *J* = 7.6 Hz, 0.3H), 7.11 (dd, *J* = 8.8, 2.6 Hz, 0.3H), 7.17 (dd, 0.7H), 7.24 (dd, *J* = 9.0, 2.4 Hz, 0.7H), 7.46 – 7.30 (m, 4H), 7.55–7.47 (m, 2H), 7.57 (d, *J* = 2.5 Hz, 0.7H), 7.62 (d, *J* = 2.6 Hz, 0.3H), 7.72 (d, *J* = 8.8 Hz, 0.3H), 7.73 (d, *J* = 9.0 Hz, 0.7H); M+H⁺ 251 (100%); MS (DCI/NH₃) *m/z* 251 (M+H)⁺, 268 (M+NH₄)⁺.

1-(2-(8-(benzyloxy)naphthalen-2-yloxy)ethyl)pyrrolidine and 1-(2-(7-(benzyloxy)naphthalen-1-yloxy)ethyl)pyrrolidine (C2). A 250 mL flask containing a sln of compound **C1** (1.42 g, 5.67 mmol) in DMF (15 mL) under N₂ was treated with 60 % NaH (1.4 g, 34 mmol), stirred at room temp for 30 min, treated with N-(2-chloroethyl)pyrrolidine hydrochloride (1.9 g, 11 mmol), stirred at 70 °C for 1.5 h, and at room temp overnight, treated with water (10 mL) and partitioned between water (50 mL)

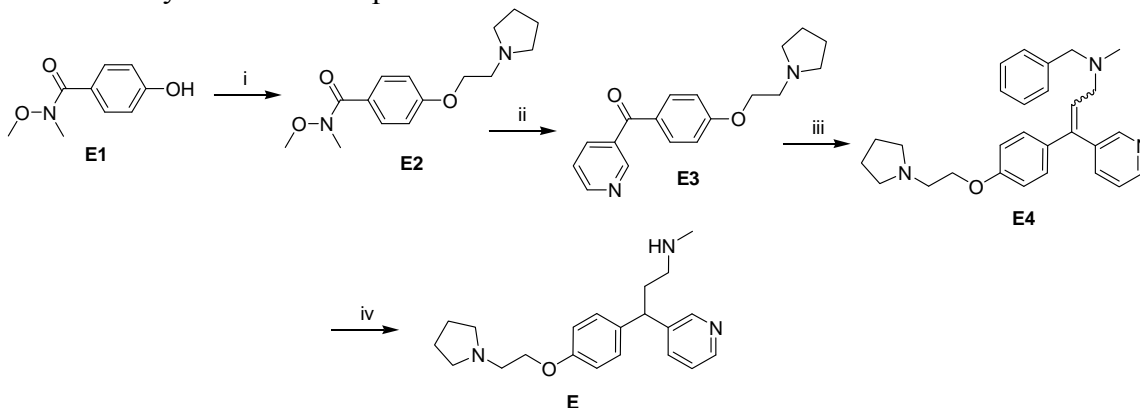
and Et₂O (100 mL). The layers were separated and the aqueous layer was extracted with Et₂O (50 mL). The combined Et₂O layers were washed with 0.1 M NaOH (60 mL), washed with brine, dried (MgSO₄), filtered, concd and chromatographed on silica gel eluting with a gradient of 2% to 10% (9:1 MeOH:NH₄OH sln) in CH₂Cl₂ to provide 1.12 g of a 7:2 mixture of the desired product **D2** and the isomer, 1-(2-(7-(benzyloxy)naphthalen-1-yloxy)ethyl)pyrrolidine. Further elution provided some of the major product, compound **D2**, from which the following NMR and mass spectrum was obtained. ¹H NMR (300 MHz, CDCl₃) δ 1.89 – 1.76 (m, 4H), 2.76 – 2.66 (m, 4H), 3.05 (t, *J* = 5.9 Hz, 2H), 4.30 (t, *J* = 5.9 Hz, 2H), 5.19 (s, 2H), 6.81 (d, *J* = 7.5 Hz, 1H), 7.27 – 7.19 (m, 2H), 7.44 – 7.29 (m, 4H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.67 (d, *J* = 2.3 Hz, 1H), 7.71 (d, *J* = 8.9 Hz, 1H); MS (DCI/NH₃) *m/z* 348 (M+H)⁺.

7-(2-(Pyrrolidin-1-yl)ethoxy)naphthalen-1-ol (C3). Compound **C2** (1.1 g, 3.2 mmol) was dissolved in MeOH (5 mL) and the atmosphere was exchanged with N₂, treated with 10% Pd/C, atmosphere was exchanged with N₂, atmosphere was exchanged with H₂, mixture was stirred over night, atmosphere was exchanged with N₂, mixture was diluted to 75 mL with MeOH, stirred for 15 min and filtered to remove the solids. The filtrate was concd and chromatographed on silica gel eluting with a gradient of 2% to 10% (9:1 MeOH:NH₄OH sln) in CH₂Cl₂ to provide the pure desired product. ¹H NMR (300 MHz, CDCl₃) δ 1.91 – 1.75 (m, 4H), 2.90 – 2.72 (m, 4H), 3.17 (t, *J* = 5.7 Hz, 2H), 4.35 (t, *J* = 5.7 Hz, 2H), 5.43 (s, 1H), 6.71 (d, *J* = 7.5 Hz, 1H), 7.07 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.13 (t, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.53 (d, *J* = 2.5 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 1H); MS (DCI/NH₃) *m/z* 258 (M+H)⁺.

N-methyl-3-phenyl-3-(7-(2-(pyrrolidin-1-yl)ethoxy)naphthalen-1-yloxy)propan-1-amine (C) and **4-(3-(methylamino)-1-phenylpropyl)-7-(2-(pyrrolidin-1-yl)ethoxy)naphthalen-1-ol (D)**. A vial containing compound **C3** (58 mg, 0.23 mmol) and α-[2-(methylamino)ethyl]benzyl alcohol (110 mg, 0.68 mmol) was treated with TFA (1 mL) and stirred over night. The mixture was concd and partitioned between 1 M NaOH (10 mL) and CH₂Cl₂ (25 mL). The aqueous layer was extracted with CH₂Cl₂ (25 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered, concd and chromatographed on silica gel eluting with a gradient of 2% to 10% (9:1 MeOH:NH₄OH sln) in CH₂Cl₂ to provide pure compound **C** (¹H NMR (300 MHz, CDCl₃) δ 1.87 – 1.79 (m, 4H), 2.15 – 2.02 (m, 1H), 2.34 – 2.19 (m, 1H), 2.45 (s, 3H), 2.71 – 2.62 (m, 4H), 2.80 (t, *J* = 6.9 Hz, 2H), 3.09 – 2.89 (m, 2H), 4.27 – 4.13 (m, 2H), 5.41 (dd, *J* = 8.2, 4.8 Hz, 1H), 6.72 (d, *J* = 7.5 Hz, 1H), 7.37 – 7.13 (m, 5H), 7.42 (d, *J* = 7.1 Hz, 2H), 7.48 (d, *J* = 2.5 Hz, 1H), 7.64 (d, *J* = 8.9 Hz, 1H); MS (DCI/NH₃) *m/z* 405 (M+H)⁺) and compound **D** which contained an impurity. Impure compound **D** was repurified by chromatographed on silica gel eluting with a gradient of 10:1:1 to 4:1:1 EtOAc:HCOOH:H₂O. The fractions containing the product were combined, concd and partitioned between 1 M NaOH (10 mL) and CH₂Cl₂ (25 mL). The aqueous layer was extracted with CH₂Cl₂ (25 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered and concd to provide pure compound **D**. ¹H NMR (300 MHz, CDCl₃) δ 1.88 – 1.75 (m, 4H), 2.38 – 2.24 (m, 2H), 2.40 (s, 3H), 2.78 – 2.59 (m, 6H), 3.06 (t, *J* = 5.8 Hz, 2H), 4.26 (t, *J* = 5.9 Hz, 2H), 4.66 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.89 (dd,

$J = 9.1, 2.7$ Hz, 1H), 7.12 (t, $J = 6.2$ Hz, 2H), 7.31 – 7.18 (m, 4H), 7.53 (d, $J = 2.7$ Hz, 1H), 7.83 (d, $J = 9.2$ Hz, 1H); MS (DCI/NH₃) m/z 405 (M+H)⁺.

Scheme 8. Synthesis of Compound **E**.^a



^a. i. N-(2-chloroethyl)pyrrolidine·HCl, NaH, DMF, 70 °C; ii. 3-bromopyridine, n-BuLi, Et₂O, -78 °C; iii. (2-(benzyl(methyl)amino)ethyl)triphenylphosphonium bromide, n-BuLi, THF, 0 °C; iv. 20% Pd(OH)₂-C, wet, MeOH, H₂.

4-Hydroxy-N-methoxy-N-methylbenzamide (E1). To a mixture of 4-hydroxybenzoic acid (5.0 g, 36 mmol), N,O-dimethylhydroxylamine hydrochloride (4.6 g, 47 mmol) and 1H-benzo[d][1,2,3]triazol-1-ol (4.9 g, 36 mmol) in CH₂Cl₂ (120 mL) was added Hunig'sBase (20 mL, 110 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (6.9 g, 36 mmol) at 0 °C. The mixture was stirred at room temp overnight. The mixture was washed with H₂O (2 x 100 mL), dried (MgSO₄), filtered and concd. TLC (1:1 CH₂Cl₂:EtOAc) indicated 2 or more products (R_f = 0.5). The residue was dissolved in CH₂Cl₂ (150 mL), washed with 1 M HCl (50 mL) and then washed with 1 M NaOH (100 mL) wherein a bad emulsion ensued. The flask was shaken for 5 min, then brought to pH 7 with concd HCl. The CH₂Cl₂ layer was isolated and the aqueous layer was extracted with CH₂Cl₂ (3 x 100 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered, concd and chromatographed on silica gel eluting with a gradient of 9:1 to 1:1 CH₂Cl₂:EtOAc to provide the desired product (1.5 g, 23 % yield). ¹H NMR (300 MHz, CDCl₃) δ 3.37 (s, 3H), 3.57 (s, 3H), 6.81 (d, $J = 8.7$ Hz, 2H), 6.84 (s, 1H), 7.64 (d, $J = 8.7$ Hz, 2H); MS (DCI/NH₃) m/z 182 (M+H)⁺, 199 (M+NH₄)⁺.

N-methoxy-N-methyl-4-(2-(pyrrolidin-1-yl)ethoxy)benzamide (E2). A sln of compound **E1** (0.37 g, 2.0 mmol) and N-(2-chloroethyl)pyrrolidine hydrochloride (0.35 g, 2.0 mmol) in DMF (6 mL) was treated with 60 % suspension of sodium hydride in mineral oil (0.18 g, 4.5 mmol), stirred at room temp for 10 min, heated to 70 °C for 30 min, cooled and partitioned between Et₂O (100 mL) and 0.1 M NaOH (25 mL). The layers were separated and the Et₂O layer was washed with 0.1 M NaOH (25 mL), washed

with brine, dried (MgSO₄), filtered, concd and chromatographed on silica gel eluting with a gradient of 2 % to 10 % (9:1 MeOH:NH₄OH sln) in CH₂Cl₂ to provide the desired product (260 mg, 46 % yield). ¹H NMR (300 MHz, CDCl₃) δ 1.84 – 1.79 (m, 4H), 2.67 – 2.60 (m, 4H), 2.92 (t, *J* = 6.0 Hz, 2H), 3.35 (s, 3H), 3.56 (s, 3H), 4.15 (t, *J* = 6.0 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.71 (d, *J* = 8.8 Hz, 2H); MS (DCI/NH₃) *m/z* 279 (M+H)⁺.

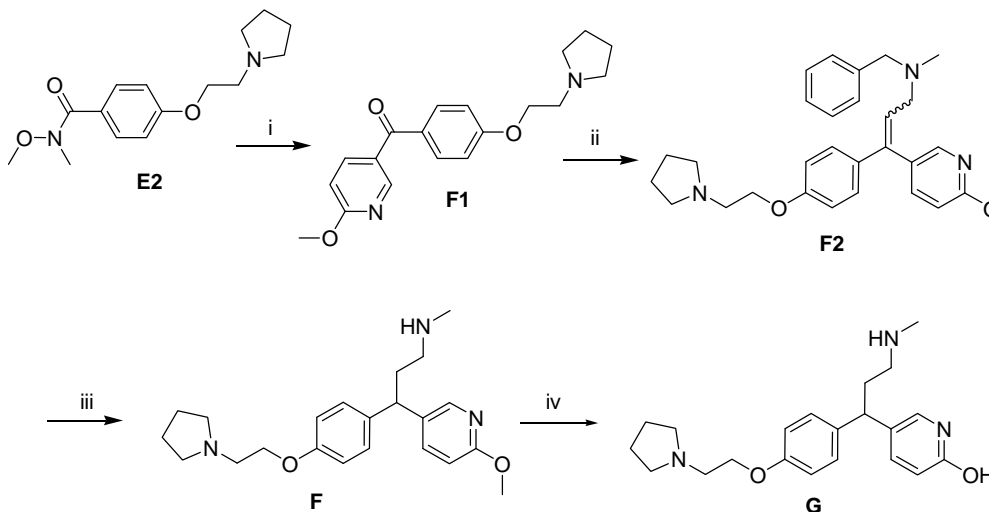
Pyridin-3-yl(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)methanone (E3). A sln of 3-bromopyridine (0.18 mL, 1.8 mmol) in Et₂O (2 mL) under N₂ was cooled to -78 °C, treated with 1.6 M *n*-butyllithium in hexanes (0.90 mL, 1.4 mmol) over 2 min, stirred at -78 °C for 10 min, treated with a sln of compound **E2** (250 mg, 0.90 mmol) in Et₂O (2 mL), stirred at room temp for 30 min, treated with 1 M HCl (5 mL), stirred for 10 min, basified with 1 M NaOH (10 mL) and extracted with CH₂Cl₂ (3 x 25 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered, concd and chromatographed on silica gel eluting with a gradient of 2 % to 10 % (9:1 MeOH:NH₄OH sln) in CH₂Cl₂ to provide the butyl ketone 1-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pentan-1-one as a faster moving product and the more polar desired product. ¹H NMR (300 MHz, CDCl₃) δ 1.86 – 1.78 (m, 4H), 2.69 – 2.60 (m, 4H), 2.95 (t, *J* = 5.9 Hz, 2H), 4.21 (t, *J* = 5.9 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.44 (dd, *J* = 7.8, 4.9 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 8.07 (dt, *J* = 7.8, 1.9 Hz, 1H), 8.79 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.96 (d, *J* = 2.0 Hz, 1H); MS (DCI/NH₃) *m/z* 297 (M+H)⁺.

N-benzyl-N-methyl-3-(pyridin-3-yl)-3-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)prop-2-en-1-amine (E4). A mixture of (2-(benzyl(methyl)amino)ethyl)triphenylphosphonium bromide (310 mg, 0.64 mmol) in THF (1.5 mL) under N₂ at 0 °C was treated with 1.6 M *n*BuLi in hexane (0.40 mL, 0.64 mmol), stirred at 0 °C for 1 h, treated with a sln of compound **E3** (110 mg, 0.36 mmol) in THF (2 mL), stirred at room temp over the weekend and partitioned between 1 M NaOH (10 mL) and CH₂Cl₂ (25 mL). The aqueous layer was extracted with CH₂Cl₂ (25 mL) and the combined CH₂Cl₂ layers were washed with brine, dried (MgSO₄), filtered, concd and chromatographed on silica gel eluting with a gradient of 2 % to 10 % (9:1 MeOH:NH₄OH sln) in CH₂Cl₂ to provide a product which was contaminated with a steaky lower R_f product (possibly the Wittig reagent). The fractions containing the product was concd and rechromatographed on silica gel eluting with a gradient of 3:1 to 0:1 EtOAc:[3:2:1 EtOAc:HCOOH:H₂O]. The fractions containing product were combined, concd to dryness, transferred to a separatory funnel with water, basified with 50% NaOH and extracted with CH₂Cl₂ (3 x 25 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered and concd to provide the desired product (86 mg, 55 % yield) as a 1:1 mixture of *cis* and *trans* isomers. MS (DCI/NH₃) *m/z* 428 (M+H)⁺.

N-methyl-3-(pyridin-3-yl)-3-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)propan-1-amine (E). Compound **E4** (85 mg, 0.20 mmol) and MeOH (10 ml) were added to 20% Pd(OH)₂-C, wet (17 mg) in a 50 ml pressure bottle and stirred at room temp for 16 h under H₂ at 30 psi. The mixture was filtered, concd and chromatographed on silica gel eluting with a gradient of 2 % to 10 % (9:1 MeOH:NH₄OH sln) in CH₂Cl₂ to provide the desired product (23 mg, 34 % yield). ¹H NMR (300 MHz, CDCl₃) δ 1.85 – 1.75 (m, 4H), 2.31 – 2.09 (m, 2H), 2.38 (s, 3H), 2.52 (t, *J* = 7.2 Hz, 2H), 2.66 – 2.56 (m, 4H), 2.88 (t, *J* = 6.0

Hz, 2H), 4.00 (t, $J = 7.7$ Hz, 1H), 4.07 (t, $J = 6.0$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H), 7.13 (d, $J = 8.6$ Hz, 2H), 7.19 (dd, $J = 7.8, 5.0$ Hz, 1H), 7.53 – 7.48 (m, 1H), 8.42 (dd, $J = 4.8, 1.5$ Hz, 1H), 8.52 (d, $J = 2.1$ Hz, 1H); MS (DCI/NH₃) m/z 340 (M+H)⁺. Anal. (C₂₁H₂₉N₃O•0.17 CH₂Cl₂) C, H, N).

Scheme 9. Synthesis of Compound **F** and **G**.^a



^a. i. 5-bromo-2-methoxypyridine, n-BuLi, Et₂O, -78 °C; ii. (2-(benzyl(methyl)amino)ethyl)triphenylphosphonium bromide, n-BuLi, THF, 0 °C; iii. 20% Pd(OH)₂-C, wet, MeOH, H₂; iv. 48 % HBr, 100 °C.

(6-Methoxypyridin-3-yl)(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)methanone (F1). A sln of 5-bromo-2-methoxypyridine (530 μ l, 4.1 mmol) in anhydrous Et₂O was cooled to -78 °C, treated dropwise with BuLi (1.3 mL, 2.0 mmol) over 5 min, stirred at -78 °C for 15 min, treated with a sln of compound **E2** (380 mg, 1.4 mmol) in Et₂O (4 mL), stirred at room temp over night, treated with 1 M HCl (20 mL) and stirred for 1 h (may need to only stir for 1 min). The mixture was washed with Et₂O (50 mL), basified with 50 % NaOH sln and extracted with CH₂Cl₂ (3 x 40 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered, concd and chromatographed on silica gel eluting with a gradient of 2 % to 10 % (9:1 MeOH:NH₄OH sln) in CH₂Cl₂ to provide the desired product (400 mg, 90 % yield). ¹H NMR (300 MHz, CDCl₃) δ 1.87 – 1.78 (m, 4H), 2.71 – 2.60 (m, 4H), 2.95 (t, $J = 5.9$ Hz, 2H), 4.02 (s, 3H), 4.20 (t, $J = 5.9$ Hz, 2H), 6.83 (d, $J = 8.7$ Hz, 1H), 6.99 (d, $J = 8.8$ Hz, 2H), 7.80 (d, $J = 8.7$ Hz, 2H), 8.05 (dd, $J = 8.6, 2.4$ Hz, 1H), 8.59 (d, $J = 2.4$ Hz, 1H); MS (DCI/NH₃) m/z 327 (M+H)⁺.

N-Benzyl-3-(6-methoxypyridin-3-yl)-N-methyl-3-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)prop-2-en-1-amine (F2). A suspension of (2-(benzyl(methylamino)ethyl)triphenylphosphonium bromide³⁸ (1.1 g, 2.3 mmol) in THF (5 mL) was cooled to 0 °C under N₂, treated dropwise with 1.6 M BuLi in hexanes (1.4 mL, 2.3 mmol), stirred at 0 °C for 1 h, treated with a sln of compound **F1** (400 mg, 1.3 mmol) in THF (5 mL), stirred over night at room temp, treated with 20 mL 1 M HCl, washed with Et₂O (2 x 50 mL), basified with 50 % NaOH sln and extracted with CH₂Cl₂ (4 x 30 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered, concd and chromatographed on silica gel eluting with a gradient of 2 % to 10 % (9:1 MeOH:NH₄OH sln) in CH₂Cl₂ to provide the desired product (350 mg, 63 % yield). ¹H NMR (300 MHz, CDCl₃) δ 1.90 – 1.75 (m, 4H), 2.19 (s, 3H), 2.71 – 2.58 (m, 4H), 2.93 (t, *J* = 6.0 Hz, 2H), 3.13 (d, *J* = 6.8 Hz, 2H), 3.46 (s, 2H), 3.92 (s, 3H), 4.13 (t, *J* = 6.0 Hz, 2H), 6.11 (t, *J* = 6.7 Hz, 1H), 6.64 (dd, *J* = 8.5, 0.6 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 8.7 Hz, 2H), 7.34 – 7.19 (m, 5H), 7.43 (dd, *J* = 8.6, 2.5 Hz, 1H), 8.04 (dd, *J* = 2.6, 0.5 Hz, 1H); MS (DCI/NH₃) *m/z* 458 (M+H)⁺.

3-(6-Methoxypyridin-3-yl)-N-methyl-3-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)propan-1-amine (F). A sln of compound **F2** (200 mg, 0.44 mmol) in MeOH (20 ml) was added to 20% Pd(OH)₂-C, wet (40 mg) in a 50 ml pressure bottle and stirred under a H₂ atm at room temp for 15 h at 30 psi. The mixture was filtered, concd and chromatographed on silica gel eluting with a gradient of 4 % to 20 % (9:1 MeOH:NH₄OH sln) in CH₂Cl₂ to provide desired product (36 mg, 22 % yield). ¹H NMR (300 MHz, CDCl₃) δ 1.83 – 1.76 (m, 4H), 2.22 – 2.09 (m, 2H), 2.38 (s, 3H), 2.51 (t, *J* = 7.2 Hz, 2H), 2.60 (tdd, *J* = 5.1, 3.1, 1.9 Hz, 4H), 2.87 (t, *J* = 6.0 Hz, 2H), 3.90 (s, 3H), 3.95 – 3.88 (m, 1H), 4.07 (t, *J* = 6.1 Hz, 2H), 6.65 (d, *J* = 8.9 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 7.39 (dd, *J* = 8.6, 2.5 Hz, 1H), 8.04 (d, *J* = 2.6 Hz, 1H); MS (DCI/NH₃) *m/z* 370 (M+H)⁺. Anal. (C₂₂H₃₁N₃O₂) Theo: C, 71.51; H, 8.46; N, 11.37; Found: C, 69.91; H, 7.20; N, 10.59.

5-(3-(methylamino)-1-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)propyl)pyridin-2-ol (G). A mixture of compound **F** (62 mg, 0.17 mmol) and 48 % HBr in water (1.3 mL, 12 mmol) was heated to 80 °C for 20 min, heated at 100 °C 7 h and then stirred at room temp over the weekend. The HBr sln was evaporated using a stream of N₂ and a warm water bath. The residue was dissolved in MeOH/CH₂Cl₂ and directly chromatographed on silica gel eluting with a gradient of 8 % to 40 % (9:1 MeOH:NH₄OH sln) in CH₂Cl₂ to provide the desired product (22 mg, 36 % yield). ¹H NMR (300 MHz, CDCl₃) δ 1.86 – 1.77 (m, 4H), 2.15 (dd, *J* = 14.6, 7.6 Hz, 2H), 2.45 (s, 3H), 2.62 (dt, *J* = 12.3, 7.4 Hz, 6H), 2.90 (t, *J* = 5.9 Hz, 2H), 3.78 (t, *J* = 7.7 Hz, 1H), 4.09 (t, *J* = 5.9 Hz, 2H), 6.48 (d, *J* = 9.4 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 2.4 Hz, 1H), 7.32 (dd, *J* = 9.4, 2.6 Hz, 1H); MS (DCI/NH₃) *m/z* 356 (M+H)⁺. Anal. (C₂₁H₂₉N₃O₂•0.55 CH₂Cl₂) C, H, N).

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Rat NET Competition Binding

Frozen rat cortices (Pel-Freez, Rogers, AZ) were thawed, homogenized in buffer containing 50 mM Tris (pH7.4), 120 mM NaCl, and 5 mM KCl, and centrifuged for 10 minutes at 40,000 *g*. The pellet was resuspended, homogenized, and centrifuged, as above, and repeated one additional time. The final pellet was resuspended in buffer containing 50 mM Tris (pH7.4), 300 mM NaCl, and 5 mM KCl, using 6.25 ml buffer per gram pellet weight. Aliquots were frozen and stored at -80°C until use.

Frozen cell membranes were thawed and re-homogenized with 50 mM Tris-HCl, 300 mM NaCl, and 5 mM KCl, pH 7.4. Diluted membrane (~ 40 ug) preparations were incubated with 1.0 nM [³H]-Nisoxetine (Perkin Elmer, Boston, MA) in the presence or absence of various concentrations of compound for competition binding. The binding reactions were carried out in a total volume of 0.5 ml for 4 hours at 4°C, and were harvested using 0.3% PEI pre-soaked glass fiber FB MultiScreen plates (Millipore,), followed by three washes with ice-cold 50 mM Tris-HCl, 300 mM NaCl pH 7.4. Nonspecific binding was defined with 1 μ M desipramine (Sigma, St. Louis, MO).

Combustion analysis

Cmpd #	Formula	Results
4	$C_{26}H_{32}N_2O_2 \cdot 0.1 H_2O$	Theo: C, 76.85; H, 7.99; N, 6.89 Found: C, 76.60; H, 8.05; N, 6.84
5	$C_{26}H_{32}N_2O_2 \cdot H_3PO_4 \cdot 1.5 H_2O$	Theo: C, 58.97; H, 7.23; N, 5.29 Found: C, 59.06; H, 7.06; N, 5.47
6	$C_{21}H_{29}N_3O \cdot 0.3 H_2O$	Theo: C, 73.13; H, 8.65; N, 12.18 Found: C, 73.29; H, 8.61; N, 12.22
7	$C_{22}H_{31}N_3O \cdot 0.3 H_2O$	Theo: C, 73.62; H, 8.87; N, 11.71 Found: C, 73.57; H, 9.01; N, 11.43
8	$C_{22}H_{30}N_2O \cdot 2 C_4H_4O_4$	Theo: C, 63.14; H, 6.71; N, 4.91 Found: C, 63.22; H, 6.75; N, 4.88
9	$C_{23}H_{32}N_2O \cdot 2 C_4H_4O_4$	Theo: C, 63.68; H, 6.90; N, 4.79 Found: C, 63.71; H, 6.82; N, 4.70
E	$C_{21}H_{29}N_3O \cdot 0.17 CH_2Cl_2$	Theo: C, 71.84; H, 8.36; N, 11.87 Found: C, 71.93; H, 8.09; N, 11.61
F	$C_{22}H_{31}N_3O_2$	Theo: C, 71.51; H, 8.46; N, 11.37 Found: C, 69.91; H, 7.20; N, 10.59
G	$C_{21}H_{29}N_3O_2 \cdot 0.55 CH_2Cl_2$	Theo: C, 64.36; H, 7.54; N, 10.45 Found: C, 64.06; H, 7.51; N, 10.40