SUPPORTING INFORMATION

Azepines and Piperidines with Dual Norepinephrine Dopamine Uptake Inhibition and Anti-Depressant Activity

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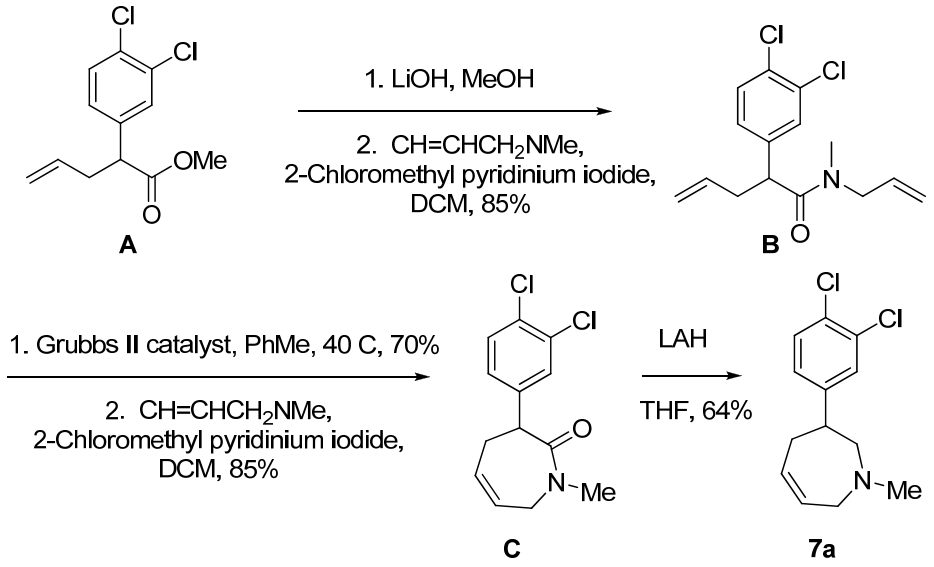
General. Optical rotations were determined at 20 ^{o}C utilizing a Perkin-Elmer 341 polarimeter in the solvents and concentrations specified. NMR spectra were obtained with either a Varian Unity 400 MHz or Bruker Avance DRX 400 or 300 operating at 300 MHz, 400 or 500 MHz. Chemical shifts are reported in parts-per-million (δ) from a tetramethylsilane internal standard. Chiral shift analysis was done utilizing enantiomerically pure TFAE (2,2,2-trifluoro-1-(9-anthryl)ethanol "-" or “+” isomer). LC-MS was taken with a Waters ZMD quadrupole mass spectrometer linked to a Waters 1525 LC system with Waters 996 diode array detector. Sample injection was done by a Waters 2700 autosampler. A typical column for the conditions was a Luna 3 micron C18(2) 30 x 4.6 mm or equivalent. The spectrometer had an electrospray source operating in positive and negative ion mode. A typical gradient employed a mobile phase A (H_2O, 0.1 % formic acid) and mobile phase B (CAN, 0.1 % formic acid) with a flow rate of 2 ml/min. The gradient ran from 95% A and 5%B to 95%B and 5%A over 6 minutes. Preperatory HPLC conditions utilized a Phenomenex Gemini C18 column (250 x 21.2 mm, 5 micron) as stationary phase and ACN in H_2O (+ 0.1% formic acid). X-ray quality crystals were submitted to Johns Hopkins University for data acquisition. The crystal structures were solved in-house using the Bruker ShellXTL software tools.

Scheme S-1. Representative Synthesis of N-Me azepines

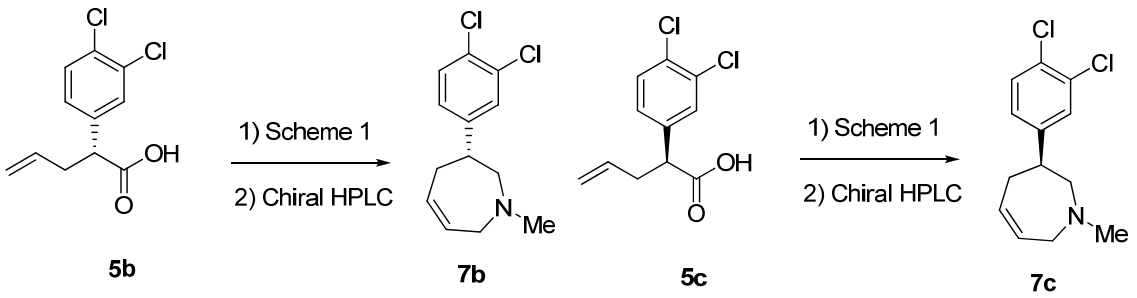


3-(3,4-Dichloro-phenyl)-1-methyl-1,3,4,7-tetrahydro-azepin-2-one (C). A solution of lithium hydroxide (5.76 g) in H_2O (185 ml) was added dropwise to a solution of ethyl 2-(3,4-dichlorophenyl)pent-4-enoate in MeOH (555 ml) (**A**, 50.5 g, 184.88 mmol). During the addition the reaction warmed to about 30ºC, then stirred at RT over night. The MeOH was removed under reduced pressure, acidified to pH 2-3 with 1N HCl (~112 mL) and then partitioned between H_2O and EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated to give 44.0 g clean acid (97 %) as an off white solid. ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ ppm 2.44-2.56 (m, 1 H) 2.72-2.87 (m, 1H) 3.56-3.65 (m, 1H) 4.98-5.13 (m, 2H) 5.59-5.76 (m, 1H) 7.15 (dd, 1H) 7.36-7.44 (m, 2H) 9.49 (br. s., 1H). A solution of anhydrous triethylamine (22 ml) in DCM (50 mL) was added drop-wise to a suspension of N-methylprop-2-en-1-amine (5.2 mL), **1c** (13.1 g) and 2-chloro-1-methylpyridinium iodide (27.4 g) in DCM (200 mL). The reaction was stirred at RT for 1.5 h. The reaction mixture was partitioned between H_2O and DCM. The organic layer was dried over $MgSO_4$, evaporated and the residue was purified by column chromatography on silica using increasing polar mixtures of EtOAc and hexanes to give 13.5g clean **B** (85%) as an amber oil. ^{1}H NMR (300 MHz, $CDCl_3$-*d*) d ppm 2.41 (dt, 1H) 2.74-2.86 (m, 1H) 2.90 (d, 3H) 3.61-3.80 (m, 2H) 3.89-4.02 (m, 1H) 4.93-5.25 (m, 4H) 5.57-5.79 (m, 2H) 7.15 (dt, 1H) 7.36 (d, 1

H) 7.40 (d, 1H) MS (M+H): *m/z* 298 and 300. [1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene] dichloro(phenylmethylene) (tricyclohexylphosphine)ruthenium (0.214 g), which is commercially available from Aldrich, was added to a deoxygenated solution of **B** (3 g, 10.06 mmol) in toluene (314 ml) under N_2. The solution was heated to 40^{o}C for 1.5 h and purified by column chromatography on silica using increasing polar mixtures of DCM and MeOH as eluent to give 1.9 g pure **C** (70%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.38-2.55 (m, 1H) 2.62-2.83 (m, 1H) 3.04 (s, 3 H) 3.43 (dd, 1H) 4.30 (dd, 1H) 4.37-4.56 (m, 1H) 5.83 (d, 2H) 7.14 (dd, 1H) 7.40 (dd, 2H). MS (M+H) : *m/z* 270 and 272.

3-(3,4-Dichloro-phenyl)-1-methyl-2,3,4,7-tetrahydro-1H-azepine (7a). A solution of **C** (2.0 g) in anhydrous THF (40 mL) was added drop-wise to an ice-cooled solution of LAH (3.80 mL, 2.4M in THF). The ice bath was removed and the reaction heated at reflux for 1 h. The mixture was cooled and quenched by careful addition of H_2O (0.3mL) followed by Rochelle's salt and then partitioned with EtOAc. The mixture was stirred for 20 min. and the aq. layer extracted with EtOAc. The organic layers were combined, washed with Rochelle's salt, brine, and then dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica using increasing polar mixtures of DCM and MeOH as eluent to give 1.4 g pure title compound (74%) as an oil. (Rochelle's salt can also be described as sat. sodium potassium tartrate). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.29 (dd, 1H) 2.40 (s, 3H) 2.55-2.69 (m, 1H) 2.69-2.81 (m, 1H) 2.86-3.06 (m, 2H) 3.12-3.28 (m, 2H) 5.70-5.81 (m, 1H) 5.83-5.93 (m, 1H) 7.04 (dd, 1H) 7.29 (d, 1H) 7.35 (d, 1H). MS (M+H): *m/z* 256 and 258.

Scheme S-2. Chiral separation of azepine stereoisomers.

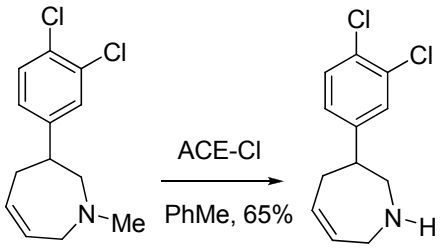


5b **7b** **5c** **7c**

(R,)-3-(3,4-dichlorophenyl)-1-methyl-2,3,4,7-tetrahydro-1H-azepine hydrochloride (7b). A procedure similar to that used to synthesize **7a** in Scheme 1 was used beginning with enantiomerically pure (*R*)-2-(3,4-dichlorophenyl)pent-4-enoic acid (**5b**, 7.0 g) to obtain 3.5g title compound (52%) as an amber oil contaminated with 10-20% of (*S*)-3-(3,4-dichlorophenyl)-1-methyl-2,3,4,7-tetrahydro-1H-azepine. The material was further purified to >98% ee by chiral chromatography using a Berger Multi-Gram II, a Diesel ADH column, 21.2 x 250 mm, 4.5 % 2-propanol with 0.5% N, N-dimethylethyl amine as an additive. The free base was converted to the hydrochloride salt to afford title compound as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.25-2.44 (m, 1H) 2.69-2.85 (m, 3H) 2.98 (d, 1H) 3.33-3.53 (m, 2H) 3.60 (t, 1H) 3.88-4.02 (m, 2H) 5.65-5.85 (m, 1H) 6.08-6.28 (m, 1H) 7.24-7.44 (m, 1H) 7.52-7.72 (m, 2H) 10.70-11.53 (m, 1H). MS (M+H): *m/z* 256 and 258 (Method MS-5). Optical rotation $[\alpha]^{D}_{20}$ = -48 (MeOH, c=1.02). Chiral purity was assessed with NMR chiral shift reagent and determined to be >98% ee.

(S)-3-(3,4-dichlorophenyl)-1-methyl-2,3,4,7-tetrahydro-1H-azepine hydrochloride (7c). The same procedure for making **7b** was used to make **7c**, beginning with (*S*)-2-(3,4-dichlorophenyl)pent-4-enoic acid (**5c**, 5.0 g). ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ ppm 2.29 (dd, 1H) 2.40 (s, 3H) 2.54-2.69 (m, 1H) 2.69-2.81 (m, 1H) 2.86-3.08 (m, 2H) 3.11-3.29 (m, 2H) 5.70-5.82 (m, 1H) 5.82-5.94 (m, 1H) 7.04 (dd, 1H) 7.29 (d, 1H) 7.35 (d, 1H). MS (M+H): *m/z* 256 and 258. Chiral purity was assessed with NMR chiral shift reagent and determined to be >98% ee.

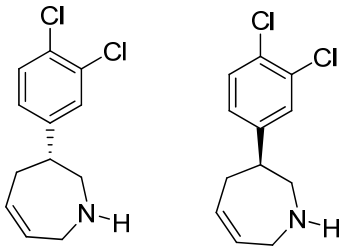
Scheme S-3. Representative Synthesis of N-H azepines



7a **8a**

3-(3,4-Dichloro-phenyl)-2,3,4,7-tetrahydro-1H-azepine (8a). 1-Chloroethlyl chloroformate (ACE-Cl, 4 mL) was added drop-wise to an ice cooled solution of **7a** (2.3 g) in anhydrous toluene (100 mL). The solution was then heated at reflux overnight. The solution was evaporated and the residue was diluted with MeOH (20 mL), stirred at 45^{o} C for 1 h. The solution was evaporated and the resultant solid was digested in refluxing EtOAc to afford 1.36 g of title compound as a tan solid (62 %). ^{1}H NMR (300 MHz, DMSO-d_6) δppm 2.36 (dd, 1H) 2.78 (t, 1H) 3.16-3.33 (m, 1H) 3.33-3.44 (m, 2H) 3.55-3.94 (m, 2H) 5.71-5.93 (m, 1H) 5.99-6.22 (m, 1H) 7.31 (dd, 1H) 7.55-7.77 (m, 2H) 9.10 (bs, 2H). MS (M+H): *m/z* 242 and 244.

Scheme S-4. Chiral separation of N-H azepines



8b **8c**

(*R*)-3-(3,4-Dichloro-phenyl)-1-methyl-2,3,4,7-tetrahydro-1H-azepine (8b). A procedure similar to that used to synthesize **8a** was used to obtain 197 mg of title compound **8b** (47 %) as a tan solid, wherein **7b** (368 mg) was substituted for **7a** in Scheme 3. . ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.19- 2.45 (m, 1H) 2.66-2.90 (m, 1H) 3.24 (d, 1H) 3.33-3.46 (m, 2H) 3.63-3.85 (m, 2H) 5.63-5.92 (m, 1H) 6.09 (t, 1H) 7.31 (dd, 1H) 7.49-7.75 (m, 2H) 9.12 (br. s., 2H). MS (M+H): *m/z* 242 and 244. Chiral purity was assessed with NMR chiral shift reagent and determined to be >98% ee. (See description of the chiral NMR procedure under the subheading of NMR conditions).

Figure S-1: Chiral shift assessment of 8b.

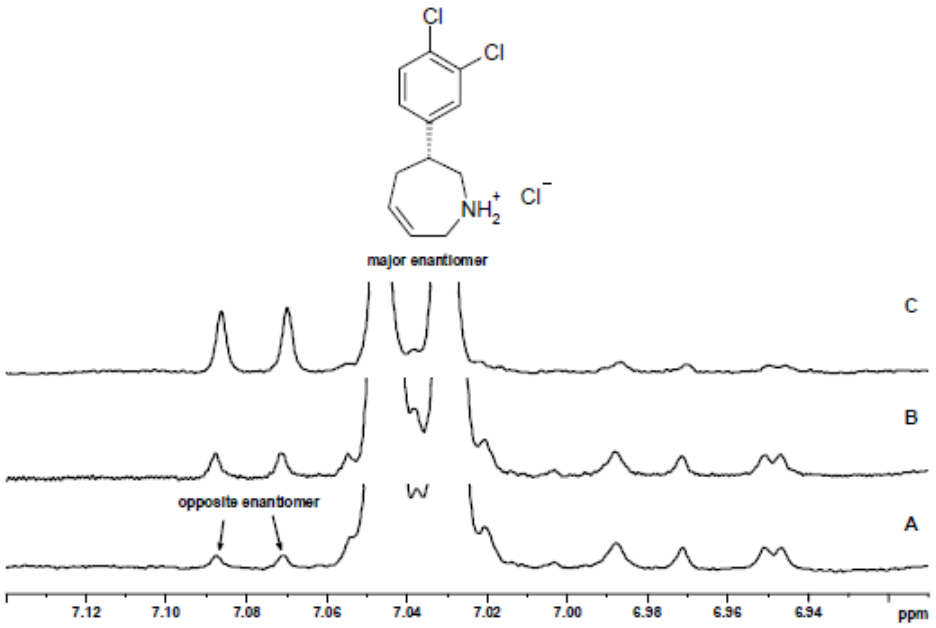
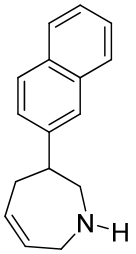


Figure 1. A) a portion of the 500 MHz proton NMR spectrum of EN00282-95-2 in $CDCl_3$ at 22°C after addition of TFAE; B) the same portion after addition of a small amount of EN00282-89-1; C) after addition of an additional amount of EN00282-89-1.

(*S*)-3-(3,4-dichlorophenyl)-2,3,4,7-tetrahydro-1H-azepine hydrochloride (8c). Using a procedure similar to that used in the synthesis of **8a** by substituting **7c** (81 mg) for **7a** to obtain 34mg title compound (44 %) as a tan solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.37 (dd, 1H) 2.71-2.90 (m, 1H) 3.17-3.27 (m, 1H) 3.34-3.44 (m, 2H) 3.60-3.90 (m, 2H) 5.70-5.95 (m, 1H) 5.95-6.23 (m, 1H) 7.31 (dd, 1H) 7.52-7.76 (m, 2H) 8.73-9.42 (bm, 2H). MS (M+H): *m/z* 242 and 244. Chiral purity was assessed with NMR chiral shift reagent and determined to be >98% ee.

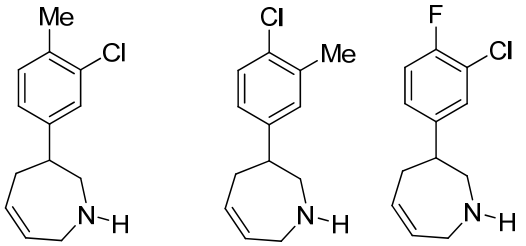
Scheme S-5. Napthtalene azepines.



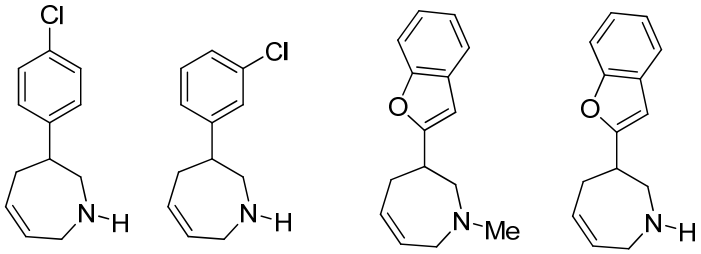
8b

3-Naphthalen-2-yl-2,3,4,7-tetrahydro-1H-azepine (8b). Title compound was prepared according to Scheme 1. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.46 (d, 1H) 2.83-3.02 (m, 1H) 3.32-3.43 (m, 1H) 3.43-3.53 (m, 2H) 3.67-3.95 (m, 2H) 5.77-5.90 (m, 1H) 6.09-6.22 (m, 1H) 7.43-7.57 (m, 3H) 7.80 (s, 1H) 7.85-7.96 (m, 3H) 9.01 (br. s., 1H) 9.35 (br. S, 1H). MS (M+H): *m/z* 224.

Scheme S-6. 3-Substituted Azepines



8e **8f** **8g**



8h **8j** **7e** **8j**

3-(3-Chloro-4-methyl-phenyl)-2,3,4,7-tetrahydro-1H-azepine (8e). Title compound was prepared according to Scheme S-1. ^{1}H NMR (400MHz, $CDCl_3$) 2.33 (s, 3H), 2.37 (m, 1H), 2.63

(m, 1H), 2.90 (m, 2H), 3.26 – 3.51 (m, 3H), 5.85 (m, 2H), 6.97 (br dd, 1H), 7.14 (d, 1H), 7.17 (br d, 1H). MS (M+H): *m/z* 222.

3-(4-Chloro-3-methyl-phenyl)-2,3,4,7-tetrahydro-1H-azepine (8f). Title compound was prepared according to Scheme S-1. ^{1}H NMR (400MHz, $CDCl_3$) 2.35 (s + m, 4H), 2.63 (m, 1H), 2.89 (m, 2H), 3.25–3.51 (m, 3H), 5.86 (m, 2H), 6.95 (br dd, 1H), 7.04 (br d, 1H), 7.24 (d, 1H). MS (M+H): *m/z* 222.

3-(3-Chloro-4-fluoro-phenyl)-2,3,4,7-tetrahydro-1H-azepine (8g). Title compound was prepared according to Scheme S-1. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.36 (dd, 1H) 2.78 (t, 1H) 3.16-3.33 (m, 1H) 3.33-3.44 (m, 2H) 3.55-3.94 (m, 2 H) 5.71-5.93 (m, 1H) 5.99-6.22 (m, 1H) 7.31 (dd, 1H) 7.55-7.77 (m, 2H) 9.10 (bs, 2H). MS (M+H): *m/z* 226.

3-(4-Chloro-phenyl)-2,3,4,7-tetrahydro-1H-azepine monoformate (8h). Title compound was prepared according to Scheme S-1 and isolated as monoformate salt after HPLC. ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 2.48 (m, 1H), 2.72 (m, 1H), 3.15 (m, 2H), 3.47 (m, 1H), 3.58 (m, 1H), 3.73 (m, 1H), 5.83 (m, 1H), 6.07 (m, 1H), 7.13 (d, 2H), 7.28 (d, 2H), 8.48 (s, 1H). MS (M+H): *m/z* 208.

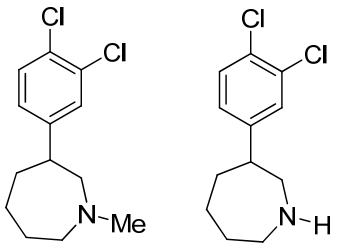
3-(3-Chloro-phenyl)-2,3,4,7-tetrahydro-1H-azepine (8j). Title compound was prepared according to Scheme S-1. ^{1}H NMR δ ppm (400MHz, $CDCl_3$) 2.37 (m, 1H), 2.65 (m, 1H), 2.92 (m, 2H), 3.28–3.52 (m, 3H), 5.86 (m, 2H), 7.07 (m, 1H), 7.20 (m, 3H). MS (M+H): *m/z* 208.

3-(Benzofuran-2-yl)-1-methyl-2,3,4,7-tetrahydro-1H-azepine (7e). Title compound was prepared according to Scheme S-1. ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ ppm 2.45 (s, 3 H) 2.52 - 2.74 (m, 2 H) 2.90 - 3.03 (m, 1 H) 3.14 - 3.38 (m, 4 H) 5.68 - 5.85 (m, 1 H), 5.92 (ddd, 1 H) 6.40 (s, 1 H) 7.11 - 7.25 (m, 1 H) 7.11 - 7.25 (m, 1 H) 7.41 (d, 1 H) 7.48 (dd, 1 H). MS (M+H): *m/z* 228.

3-(Benzofuran-2-yl)-2,3,4,7-tetrahydro-1H-azepine (8j). Title compound was prepared according to Scheme S-1. ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ ppm 2.85 (t, 2 H) 3.40 - 3.57 (m, 1

H) 3.63 - 3.83 (m, 2 H) 3.92 (d, 2 H) 5.88 (t, 1 H) 6.09 - 6.31 (m, 1H) 6.51 (s, 0 H) 7.15 - 7.31 (m, 2 H) 7.39 (d, 0 H) 7.49 (dd, 0 H) 10.11 (br. s., 2 H). MS (M+H): *m/z* 218.

Scheme S-7. Saturated azepanes



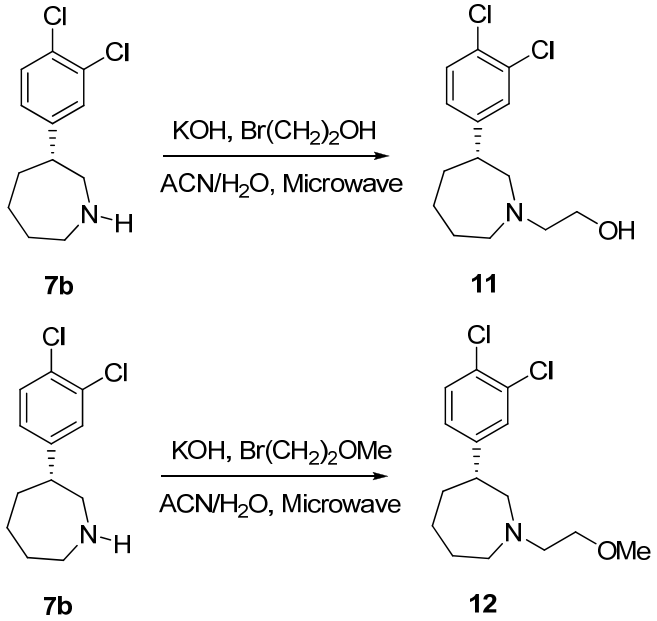
9 **10**

3-(3,4-Dichlorophenyl)-1-methylazepane (9). To a Parr bottle charged with a solution of (*Z*)-3-(3,4-dichlorophenyl)-1-methyl-2,3,4,7-tetrahydro-1H-azepine hydrochloride (230 mg, 0.79 mmol) in acetic acid (15 mL), was added 10% Pd/C (25 mg, 0.02 mmol). The reaction was placed under H_2 at 45 psi (purged 3x), and hydrogenated for 72 hours. The reaction was concentrated to dryness, solubilized in 2% EtOH/$CHCl_3$, filtered through Celite®, and then concentrated to oil (215 mg). The material was purified on a 12 g of SiO_2 (pre-equilibrated at 1%MeOH/$CHCl_3$/NH_3, gradient to 10%MeOH). The purest combined fractions were combined to give **9** as a clear oil after concentration (118 mg, 0.62 mmol, 79 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.70-1.93 (m, 6H), 2.37 (s, 3H), 2.55-2.60 (m, 2H), 2.66-2.76 (m, 2H), 2.87-2.91 (m, 1H), 7.04 (dd, 1H, J = 8.5 Hz, 2.1 Hz), 7.29-7.34 (m, 2H).. MS (M+H): *m/z* 258, 260.

3-(3,4-Dichlorophenyl)azepane (10). To a solution of (*Z*)-3-(3,4-dichlorophenyl)-2,3,4,7-tetrahydro-1H-azepine (40 mg, 0.17 mmol) in acetic acid (5 mL), was added platinum (IV) oxide (4 mg, 0.02 mmol). The flask was vacuum degassed (3x), and backfilled with H_2 (0.33 mg, 0.17 mmol) from a balloon. The reaction was stirred for 20 minutes, concentrated and then placed on 12 g of SiO_2 (pre-equilibrated with 2%MeOH/$CHCl_3$/NH_3, gradient to 10% MeOH). The purest fractions were combined

and concentrated to give **10** (30 mg, 0.12 mmol, 74.4 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.56-1.65 (m, 2H), 1.71-1.75 (m, 3H), 1.83-1.85 (m, 1H), 2.33-2.38 (br m, 1H), 2.71-2.81 (m, 4H), 2.92-3.00 (m, 1H), 7.21 (dd, 1H, J = 8.5HZ, 1.5 Hz), 7.43-7.45 (m, 2H). MS (M+H): *m/z* 244, 246.

Scheme S-8. Synthesis of N-alkylated azepines



7b **11**

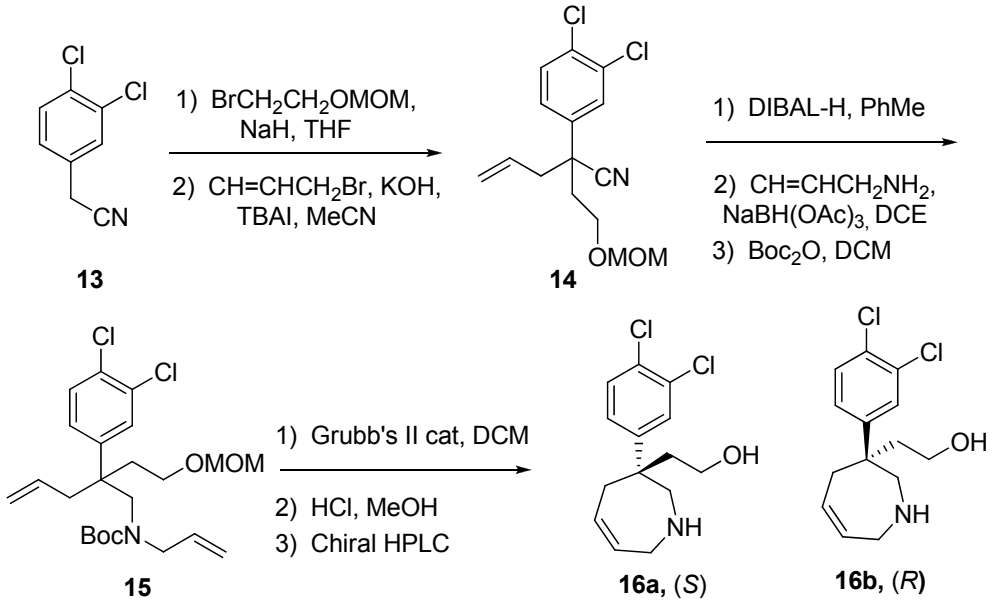
7b **12**

2-[(R)-3-(3,4-Dichloro-phenyl)-2,3,4,7-tetrahydro-azepin-1-yl]-ethanol (11). A mixture of **7b**, (1 equiv, 0.100 g), bromoethanol, (1.5 equiv) and KOH (3equiv) in ACN/H_2O (4:1) was microwaved at 150 ºC for 1 h. The reaction mixture was concentrated and the residue extracted with CH_2Cl_2. The extract was dried over Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography on silica gel eluted with MeOH/CH_2Cl_2 (0-5%) to give the title compound in 75% yield. ^{1}H NMR (500 MHz, $CDCl_3$) 2.36 (dd, 1H), 2.56- 2.66 (m, 1H), 2.66-2.80 (m, 2H), 2.85-2.94 (m, 1H), 2.99 (dt, 1H), 3.03-3.10 (m, 1H), 3.26-3.40 (m, 2H), 3.51-3.65 (m, 2H), 5.76 (dddd, *J*=10.9, 5.4, 5.2, 2.6 Hz, 1H), 5.85- 5.95 (m, 1H), 7.02 (dd, 1H), 7.28 (d, 1H), 7.36 (d, 1H). MS (M+H): *m/z* 286. $[\alpha]^{D}_{20}$ = -23 (*c* 0.17, methanol)

(R)-3-(3,4-dichlorophenyl)-1-(2-methoxyethyl)azepane (12). A procedure was employed identical to the synthesis of **11**, to yield the title compound **12** in 35% yield. ^{1}H NMR (400MHz,

$CDCl_3$) 2.33 (m, 1H), 2.60 (m, 1H), 2.81 (m, 2H),2.90 (dd, 1H), 2.99 (m, 1H), 3.14 (m, 1H), 3.35 (s, 3H), 3.39 (br d, 2H), 3.49 (m, 2H), 5.77 (m,1H), 5.91 (m, 1H), 7.02 (dd, 1H), 7.28 (br d, 1H), 7.35 (d, 1H). MS (M+H): *m/z* 300.

Scheme S-9. Synthesis of chiral quaternary substituted azepines.



2-(3,4-dichlorophenyl)-2-(2-(methoxymethoxy)ethyl)pent-4-enenitrile (13). Sodium hydride, 60% (0.387 g, 9.68 mmol) was added to a solution of 2-(3,4-dichlorophenyl)acetonitrile (1.50 g, 8.06 mmol) in THF (20 mL) under N_2. After 10 minutes, 1-bromo-2-(methoxymethoxy)ethane (0.950 mL, 8.06 mmol) was added. The mixture was stirred at rt for 2 hrs. The resulting suspension was concentrated and the residue was partitioned between EtOAc and water. The organic phase was separated, washed with brine, dried over $NaSO_4$, filtered and evaporated. The crude product was purified on 80 g of silica gel and eluted with EtOAc/hexanes (0 - 100%) to give 1.129 g of light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ ppm 2.05 - 2.26 (m, 2 H) 3.39 (s, 3 H) 3.57 (dt, *J* = 10.5, 5.2 Hz, 1 H) 3.72 (ddd, *J* = 6.3, 4.0, 3.8 Hz, 1 H) 4.05 (dd, *J* = 8.9, 6.7 Hz, 1 H) 4.64 (d, *J* = 1.3 Hz, 2 H) 7.21 (dd, *J* = 8.4,2.1 Hz, 1 H) 7.46 (d, *J* = 1.1 Hz, 1 H) 7.48 (d, *J* =4 .8 Hz, 1 H). MS (M+H): *m/z* 274. A mixture of 2-(3,4-dichlorophenyl)-4-(methoxymethoxy)butanenitrile (0.9

g, 3.28 mmol), 3-bromoprop-1-ene (0.343 mL, 3.94 mmol), KOH (0.4 g, 7.13 mmol), TBAI (0.061 g, 0.16 mmol), acetonitrile (10 mL) and water (0.5 mL) was stirred for 1 day. The completion of the reaction was confirmed by GC-MS. The organic phase was separated and and the aqueous phase was extracted with ether. The combined organic solutions were evaporated and the residue was extracted with hexanes. The extract was concentrated and the crude product was purified on 40 g silica gel eluted with CH_2Cl_2/hexanes (50 - 100%) to give 0.95 g of colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$-*d*) δ ppm 2.17 (ddd, *J* = 14.0, 7.9, 5.6 Hz, 1 H) 2.36 (dt, *J* = 14.3, 7.2 Hz,1 H) 2.61 - 2.68 (m, 1 H) 2.70 - 2.77 (m, 1 H) 3.30 (s, 3 H) 3.45 (ddd, *J* = 10.3, 7.7, 5.5 Hz, 1 H) 3.61 (dt,*J* = 10.1, 7.1 Hz, 1 H) 4.52 (s, 2 H) 5.11 - 5.21 (m, 2 H) 5.59 - 5.70 (m, *J* = 17.1, 10.0, 7.2, 7.2 Hz, 1 H) 7.27 (d,*J* = 2.1 Hz, 1 H) 7.47 (d, *J* = 8.5 Hz, 1 H) 7.52 (d, *J* = 2.1 Hz, 1 H).

2-(3,4-dichlorophenyl)-2-(2-(methoxymethoxy)ethyl)pent-4-enenitrile (15). To a dry ice cooled solution of 2-(3,4-dichlorophenyl)-2-(2-(methoxymethoxy)ethyl)pent-4-enenitrile (0.95 g, 3.02 mmol) in toluene (10 mL) was added DIBAL-H (4.54 mL, 4.54 mmol) dropwise under nitrogen. The mixture was stirred with dry ice bath for 30 minutes and allowed to warm to rt. Cold water (~0.5 ml) was carefully added, followed by citric acid, 15% (40 g, 31.23 mmol) and toluene (30 ml). The mixture was stirred vigorously for 6 hrs. The organic phase was separated, washed with brine, dried over Na_2SO_4, filtered and evaporated to give 0.728 g of product as light yellow oil. The crude product was used as is in the next step. To a stirring mixture of 2-(3,4-dichlorophenyl)-2-(2-(methoxymethoxy)ethyl)pent-4-enal (0.728 g, 2.30 mmol) and allylamine (0.206 mL, 2.75 mmol) in 1,2-dichloroethane (20 mL) was added sodium triacetoxyborohydride (0.730 g, 3.44 mmol). The stirring was continued overnight and the reaction was quenched with saturated $NaHCO_3$ (0.5 ml). The mixture was concentrated and the residue was extracted with hexanes. The extract was dried over Na_2SO_4, filtered and evaporated to give 0.76 g of product as colorless oil. The crude product was used as is in the next step. MS (M+H): *m/z* 358. To a solution of N-allyl-2-(3,4-dichlorophenyl)-2-(2-(methoxymethoxy)ethyl)pent-4-en-1-amine (0.75 g, 2.09 mmol) and

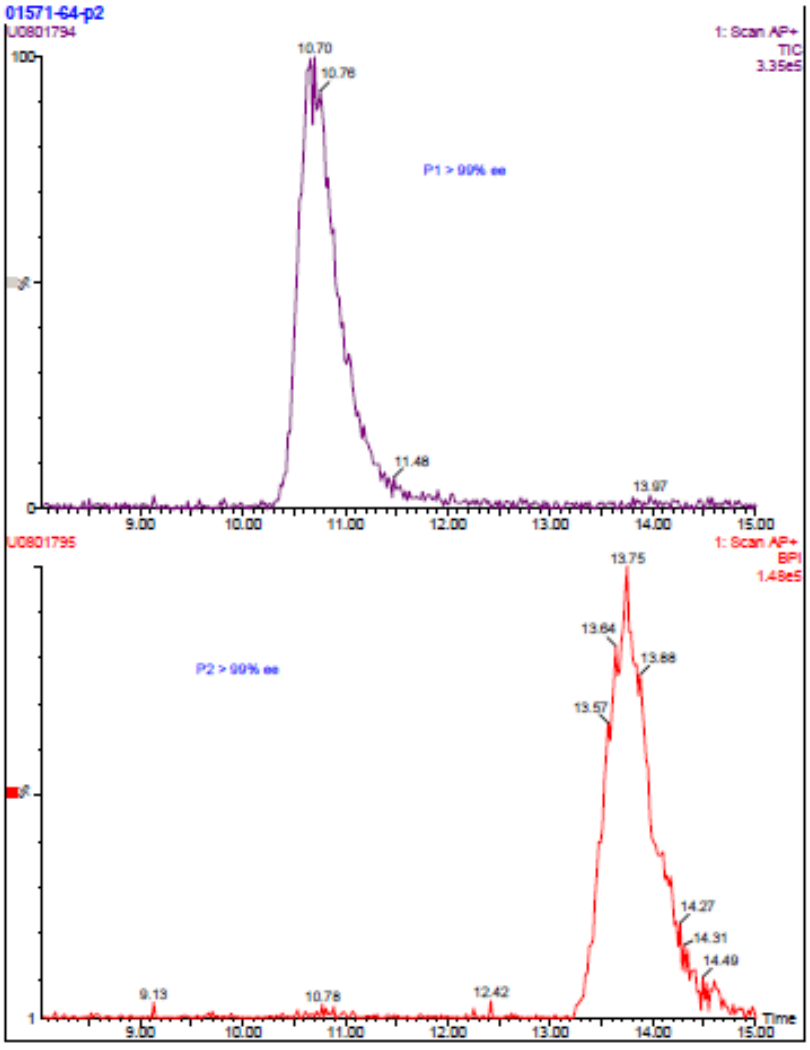
BOC-anhydride (0.535 mL, 2.30 mmol) in CH_2Cl_2 (20 mL) was added triethylamine (0.438 mL, 3.14 mmol) dropwise. The resulting solution was stirred for 3 days and evaporated. The residue was extracted with ether and the extract was evaporated. The residue was purified on 40 g silica gel eluted with ether/hexanes (0 - 100%) to give 0.5 g of product as colorless oil used as is without further purification (52%).

(*S*)-2-(3-(3,4-Dichlorophenyl)-2,3,4,7-tetrahydro-1H-azepin-3-yl)ethanol (16a). A mixture of **15**, (17.3 g, 40.20 mmol), MeOH (200 mL) and HCl (60 mL, 1974.72 mmol) was stirred for 1.5 days. The reaction was almost complete by LCMS. The mixture was refluxed for 3 hrs and evaporated. To the residue was added CH_2Cl_2 (200 ml) and water (150 mL). The pH was adjusted to 12 with NaOH. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (200 ml). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to give 11.87 g of tan viacous oil. RACEMIC ^{1}H NMR (500 MHz, CDCl3-*d*) δ ppm 1.91 - 2.04 (m, 2 H) 2.56 - 2.72 (m, 2 H) 3.23 - 3.34 (m, 2 H) 3.37 - 3.43 (m, 1 H) 3.46 (ddd, *J* = 11.1, 6.7, 6.6 Hz, 1 H) 3.49 - 3.55 (m, 1 H) 3.59 (dt, *J* = 11.0, 6.9 Hz, 1 H) 5.72 - 5.78 (m, 1 H) 5.78 - 5.86 (m, 1 H) 7.15 (dd, *J* = 8.5, 2.4 Hz, 1 H) 7.38 (s, 1 H) 7.39 (d, *J* = 6.1 Hz, 1 H). MS (M+H): *m/z* 286.

The racemic material (11.87 g) was purified by chiral HPLC as described above. The fractions were isolated as two batches. The first batch gave 1.19 g of P1 (Peak 1) as a light yellow solid with 99% ee and 1.5 g of P2 (Peak 2) as light yellow solid with 92% ee. The second batch gave 3.01 g of P1 as light yellow solid wit 99% ee and 3.25 g of P2 as light yellow solid with 91% ee. Single crystals of P1 were obtained and submitted for x-ray structure determination. Single crystal x-ray diffraction analysis of P1 clearly indicated the compound to be present in the *S* configuration. By exclusion sample P2 is therefore, accordingly assigned to the *R* configuration. Infrared vibrational circular dichroism (VCD) analysis produced identical results (see below). ^{1}H NMR (500 MHz, $CDCl_3$-*d*) δ ppm 1.87 - 1.95 (m, 1 H) 1.95 - 2.02 (m, 1 H) 2.55 - 2.62 (m, 1 H) 2.65 - 2.73 (m, 1 H) 3.15 (d, *J* = 14.0 Hz, 1 H) 3.30 (d, *J* = 14.0 Hz, 1 H) 3.34 - 3.41 (m, 1 H) 3.42 - 3.50 (m, 2H) 3.57 (dt, *J* = 11.0,

7.0 Hz, 1 H) 5.70 - 5.82 (m, 2 H) 7.15 (dd, *J* = 8.5, 2.4 Hz, 1 H) 7.38 (d, *J* = 2.4 Hz, 1 H) 7.39 (d, *J*=4.0 Hz, 1 H). MS (M+H): *m/z* 286. Chiral t_R = 9.30, 99% ee. $[\alpha]_D$ -23 (*c* 0.17, methanol).

Figure S-2. Chiral HPLC of **16a** and **16b**.

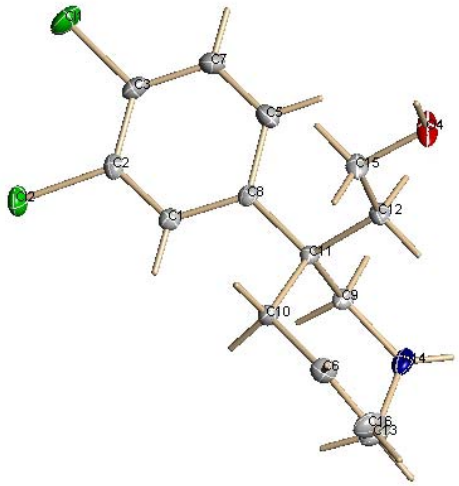


Computational Spectral Simulations: Monte Carlo molecular mechanics search of the low energy *R* conformers were conducted using *MacroModel* within the *Maestro* graphical interface (Schrödinger Inc.). The 41 lowest energy conformers identified were used as starting points and minimized using density functional theory (DFT) within *Gaussian03*. Optimized structures, harmonic vibrational frequencies/intensities, VCD rotational strengths, and free energies at STP (including zero-point energies) were determined for each

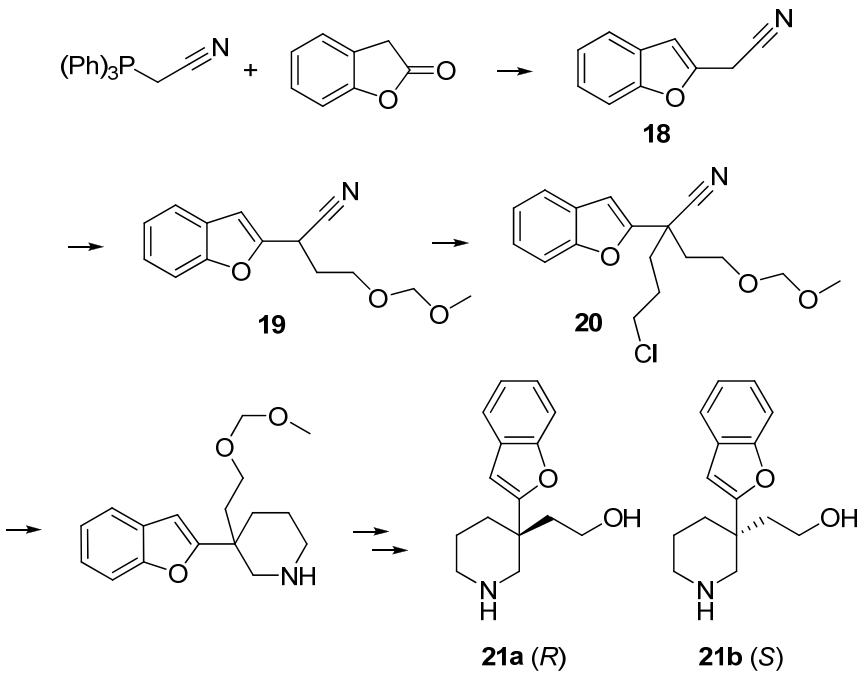
conformer. In these calculations, the B3LYP generalized gradient approximation (GGA) exchange-correlation density functional was used.[1] The 6-311++G** basis set was used for the computations shown in this report.[2] Simulations of infrared and VCD spectra for each conformation were generated using an in-house written program to fit Lorentzian line shapes (16 cm^{-1} line width) to the computed spectra to allow direct comparisons between simulated and experimental spectra. The calculated *R* conformer bands at 1460 cm^{-1} and 1340 cm^{-1}, more closely parallel the experimental bands of P2. Therefore, P1 has been assigned to the *S* enantiomer and P2 has been assigned to the *R* enantiomer, accordingly, consistent with the single crystal experiment.

VCD Experimental: ~20 mgs of P1 and P2 were dissolved in ~0.25 ml of $CDCl_3$, respectively. Analysis was conducted at 4 cm^{-1} resolution using the dual source, VCD scan protocol. All analyses were conducted using the BioTools ChiralIR instrument. The instrument incorporated a dual photo-elastic modulator set for polarization modulation at 37.024 kHz with $\lambda/4$ retardation (optimized for acquisition of the spectral region centered around 1400 cm^{-1}). Lock-in amplification with a 30μs time constant, and a 20 kHz high pass and a 4 kHz low pass filter was used.

Figure S-3. Compound **16a** X-ray structure of P1.



Scheme S-10. Synthesis of quaternary substituted 2-benzofuran-3-piperidines.



2-(Benzofuran-2-yl)acetonitrile (18). To a stirred suspension of (triphenylphosphoranylidene)acetonitrile (23.6 g, 78.32 mmol) in xylenes (150 mL) was added benzofuran-2(3H)-one (10.3 g, 76.79 mmol) and heated to reflux for 12 hours. The reaction mixture was poured onto 100 g silica gel and filtered through with CH_2Cl_2. The material was chromatographed (2x) on 120 gm silica gel cartridge eluting with 0 to 25% EtOAc in hexanes to obtain **18** (9.8 g, 81%), which was used in the next reaction without further purification.

2-(Benzofuran-2-yl)-4-(methoxymethoxy)butanenitrile (19). To a suspension of sodium hydride (1.67 g, 41.75 mmol) in dry THF (25mL) was added a solution of 2-(benzofuran-2-yl)acetonitrile (**29**, 6 g, 38.18 mmol) in dry THF (25.00 mL). After 40 minutes to this was added a solution of 2-bromoethylmethoxymethyl ether (6.45 g, 38.18 mmol) in dry THF (5

mL). The reaction was allowed to stir for 2 hours, quenched with water, and then adjusted to pH = 5 with a small amount of 1 M HCl. The material was extracted (3x) with EtOAc and dried over $MgSO_4$. The material was evaporated and chromatographed on 120 g SiO_2 (0 to 20 % EtOAc in hexane) to give the title compound **19** (3.40 g, 36.3%)

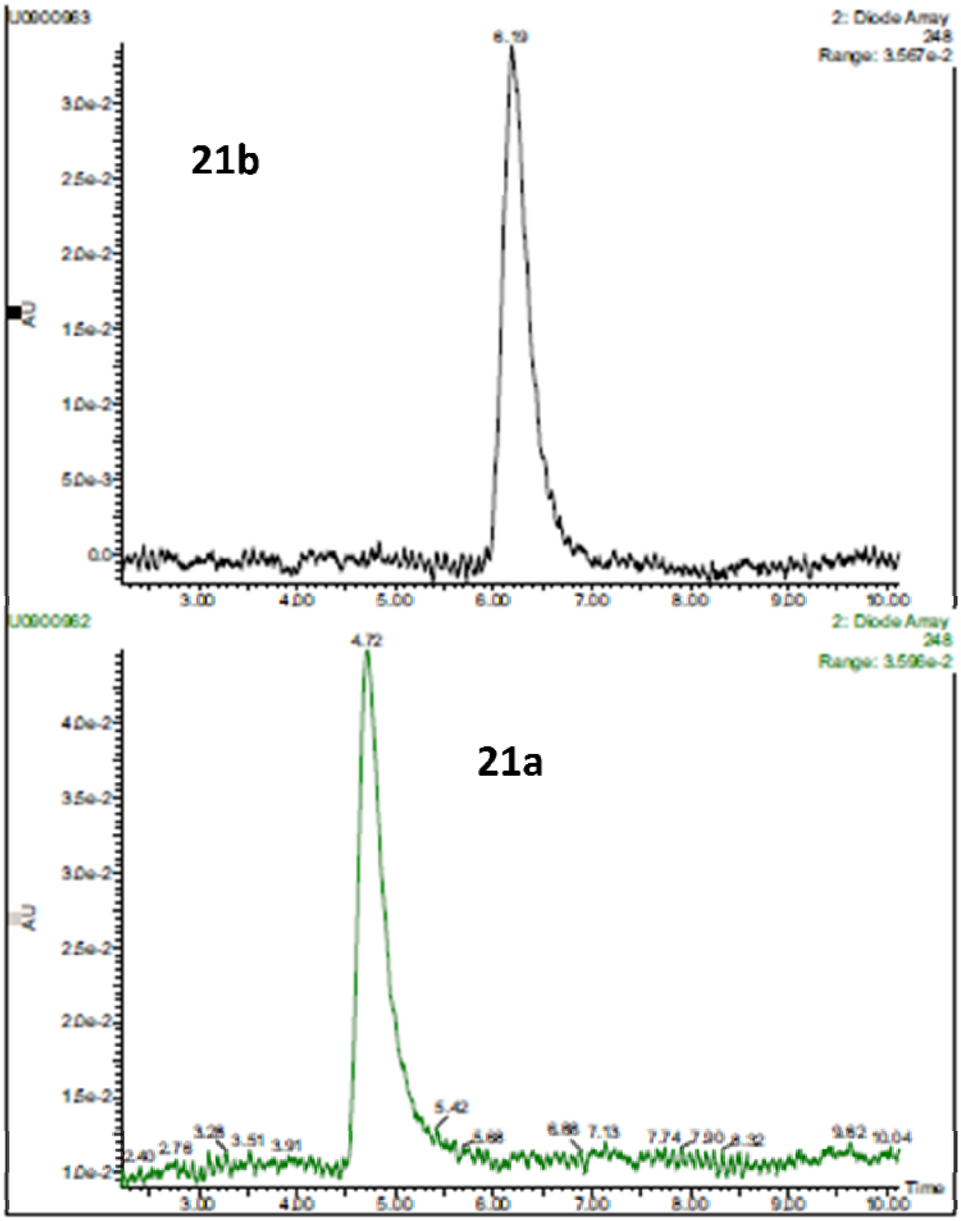
2-(Benzofuran-2-yl)-5-chloro-2-(2-(methoxymethoxy)ethyl)pentanenitrile (20). To a suspension of sodium hydride (0.665 g, 16.63 mmol) in dry THF (20 mL) was added a solution of 2-(benzofuran-2-yl)-4-(methoxymethoxy)butanenitrile (**19**, 3.4 g, 13.86 mmol) in dry THF (20 mL). The reaction was stirred for 30 minutes, and to this was added a solution of 1-bromo-3-chloropropane (2.62 g, 16.63 mmol) in dry THF (20 mL). This mixture was stirred for 48h, quenched with water, and then adjusted to pH=5 by the addition of aqueous HCl. The solution was extracted into EtOAc, dried over NaCl (sat.), and then dried over $MgSO_4$. The organic layer was concentrated and then chromatographed on 120 g silica gel (gradient of 0 to 20 % EtOAc in hexane) to obtain 3.7 gm (brown oil). 1H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 7.66 (1 H, d, *J*=7.0 Hz), 7.60 (1 H, d, *J*=8.2 Hz), 7.31 - 7.39 (1 H, m), 7.25 - 7.31 (1 H, m), 7.00 (1 H, s), 4.47 (2 H, s), 3.61 - 3.71 (2 H, m), 3.45 - 3.59 (2 H, m), 3.19 (3 H, s), 2.32 - 2.45 (2 H, m), 2.14 - 2.30 (2 H, m), 1.79 - 1.93 (1 H, m), 1.54 - 1.69 (1 H, m).

3-(Benzofuran-2-yl)-3-(2-(methoxymethoxy)ethyl)piperidine. 2-(Benzofuran-2-yl)-5-chloro-2-(2-(methoxymethoxy)ethyl)pentanenitrile (**20**, 0.3 g, 0.93 mmol) was dissolved in methanol (10 mL), and to this was added Raney nickel® (1.3 g, 22.15 mmol) and ammonium hydroxide (2 mL, 51.36 mmol). The reaction was subjected to hydrogenation for 1 hour at 55psi at 50°C. The catalyst was filtered off, the solution concentrated and chromatographed (12 g silica gel eluting with a gradient of 0 to 10% MeOH + 1%NH_4OH in CH_2Cl_2.). The title compound was obtained product as colorless oil (220 mg, 82%). 1H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 1.49-1.75 (m, 2H), 1.77-1.89 (m, 1H), 1.91-2.04 (m, 2H), 2.24-2.41 (m, 1H), 2.70-3.00 (m ,3H), 3.24 (s, 3H), 3.35 (s, 4H), 4.45 (s, 2H), 6.67 (s, 1H), 7.11-7.28 (m, 2H), 7.38-7.49 (m, 1H), 7.50-7.60 (m, 1H).

(±)-2-(3-(Benzofuran-2-yl)piperidin-3-yl)ethanol. To a dissolved solution of 3-(benzofuran-2-yl)-3-(2-(methoxymethoxy)ethyl)piperidine (0.23 g, 0.79 mmol) in methanol (5 mL), was added 12M HCl (1 mL, 12.00 mmol) and the reaction stirred for 30 minutes. The reaction was quenched by adding 10M NaOH (completed when strongly basic to pH paper). The material was extracted with EtOAc (2x), washed with brine and dried over Na_2SO_4. The material was chromatographed (4 g SiO_2 eluting with a gradient of 0 to 10% MeOH + 1% NH_4OH in CH_2Cl_2) to give the title compound. (0.13 g, 66.7%). 1H NMR (500 MHz, MeOD) δ ppm 7.53 (1 H, d), 7.42 (1 H, d), 7.14 - 7.28 (2 H, m), 6.65 (1 H, s), 3.33 - 3.52 (4 H, m), 2.81 - 2.99 (2 H, m), 2.72 - 2.83 (1 H, m), 2.30 (1 H, br. s.), 1.87 - 1.98 (2 H, m), 1.74 - 1.86 (1 H, m), 1.51 - 1.73 (2 H, m).

(*R*)-2-(3-(benzofuran-2-yl)piperidin-3-yl)ethanol (21a). A total of 1.5 grams of racemic (±)-2-(3-(benzofuran-2-yl)piperidin-3-yl)ethanol was subjected to chiral HPLC chromatography (described in general experimental) yielding two peaks in clean separation P1 (Peak 1) and P2 (Peak 2) (assigned based on order of the t_R). The pure enantiomers upon separation were dissolved in MeOH and evaporated to colorless oil then crystallized by addition of Et_2O. The material was collected solid by vacuum filtration and dried *in vacuo* at 95°C overnight. Peak 1. 1H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 7.52 - 7.58 (1 H, m), 7.49 (1 H, d), 7.12 - 7.26 (2 H, m), 6.64 (1 H, s), 4.11 - 4.43 (1 H, m), 3.07 - 3.27 (3 H, m), 2.76 (1 H, d), 2.59 - 2.70 (2 H, m), 1.92 - 2.21 (2 H, m), 1.75 - 1.94 (2 H, m), 1.70 (1 H, ddd), 1.45 - 1.55 (1 H, m), 1.33 - 1.44 (1 H, m).

Figure S-4. Chiral HPLC of **21a** and **21b**.



VCD Analysis of absolute configuration: Figure S-5 contains the experimental VCD spectra for **21a** and **21b**. Since the two compounds are enantiomers, digital subtraction of the two spectra serves to remove any static artifacts in the spectra. Furthermore the difference spectrum corresponds to an enhanced quality spectrum of the minuend species of the subtraction. Accordingly, inversion of the minuend spectrum yields the enhanced

subtrahend spectrum. Finally, the system software "auto-smooth" function was applied to each of the experimentally acquired spectra.

Figure 3 contains the experimental VCD spectrum of **21b** in duplicate (blue). The first **21b** spectrum has been overlaid with the ab-initio calculated VCD spectrum of the *S* enantiomer (green). The second spectrum of **21b** has been overlaid with the calculated VCD spectrum of the *R* enantiomer (red). In the region from 1300-1000 cm^{-1}, it is particularly clear that simulated the *S* enantiomer spectrum provides a closer phase match with the experimental spectrum.

Computational Spectral Simulations: A Monte Carlo molecular mechanics search of low energy conformations for each of the possible isomers was conducted using *MacroModel* within the *Maestro* graphical interface (Schrödinger Inc.). Low energy conformations were then used as starting points for density functional theory (DFT) minimizations within *Gaussian03*.

Optimized structures, harmonic vibrational frequencies/intensities, VCD rotational strengths, and free energies at STP (including zero-point energies) were determined for each conformer. In these calculations, the B3LYP and B3PW91 generalized gradient approximation (GGA) exchange-correlation density functionals were both tested. The 6-31G* basis set was used. Simulations for each conformation were generated using an in-house authored program to fit Lorentzian line shapes (16 cm^{-1} line width) to the Boltzmann-weighted computed spectra thereby allowing direct comparisons between simulated and experimental spectra.

VCD Experimental: ~15 mgs of ELN **21b** and **21a** were respectively dissolved in ~0.2 ml of $CDCl_3$. Analyses were conducted at 4 cm^{-1} resolution using the dual source, dual PEM, VCD scan protocol. All analyses were conducted using the BioTools ChiralIR instrument.

The instrument incorporated a dual photo-elastic modulator set for polarization modulation at 37.024 kHz with λ/4 retardation (optimized for acquisition of the spectral region centered around 1300 cm^{-1}). Lock-in amplification with a 30μs time constant, and a 20 kHz high pass and a 4 kHz low pass filter was used.

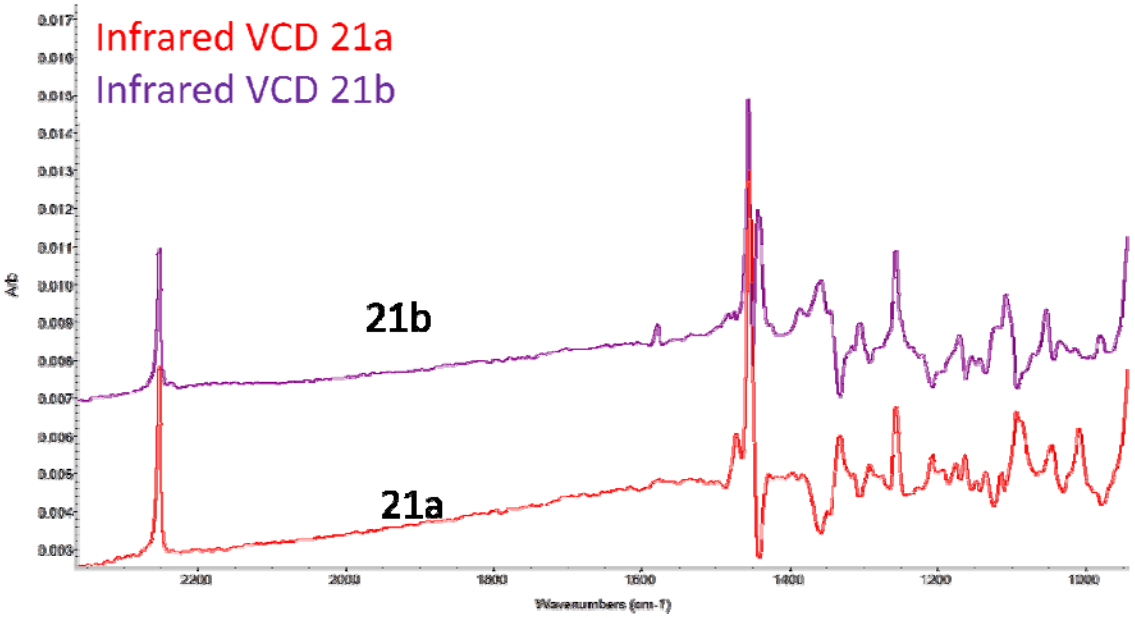


Figure 2: The VCD Spectra. The experimental VCD spectrum of **21b** (violet) presented in an overlay with the experimental VCD spectrum of **21a** (red).

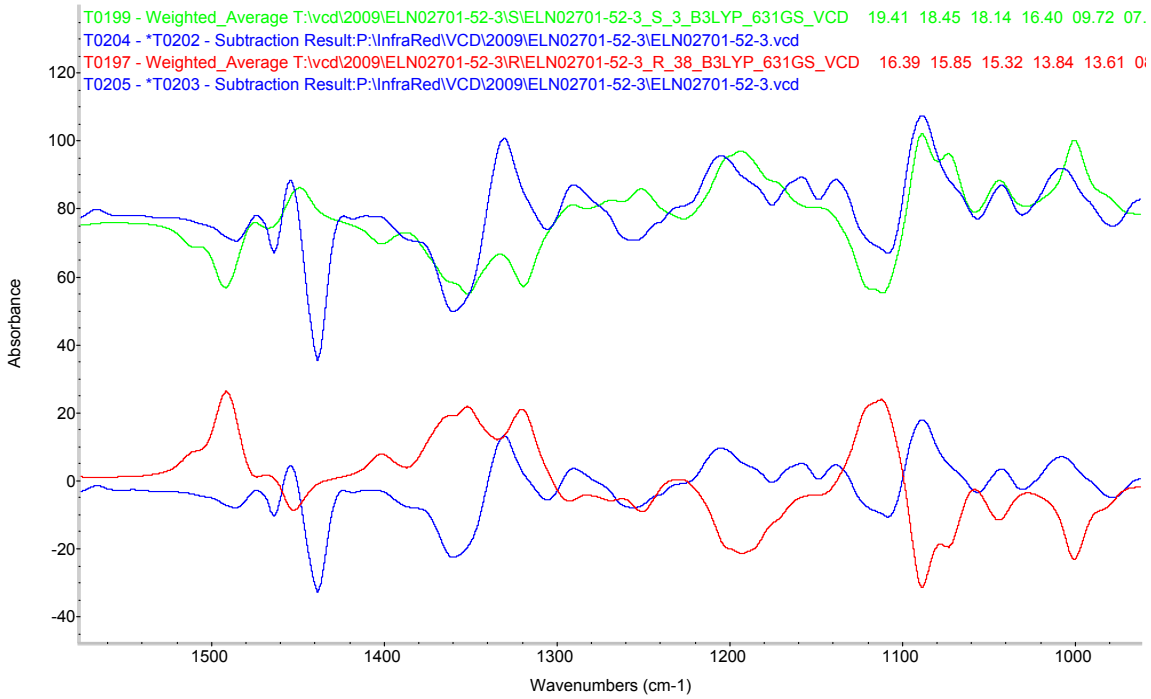


Figure 3: The experimental VCD spectrum of **21b** (blue) obtained by the smoothed subtraction of **21a** from **21b**. The calculated VCD spectrum for the *S* configuration is illustrated in green. The calculated VCD spectrum for the *R* configuration is illustrated in red.

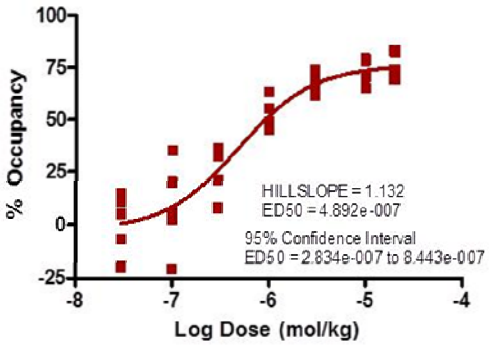
Forced Swim Assay (FST): Male, Sprague-Dawley rats (Charles River) were utilized in the experiment at a weight of 190-230g. A total of 60 rats (n~10/group, 6 groups) were placed in cylinders of water for 15 min (pre-test session on day 1) and 5 min 24 hr later (test session on day 2). The amount of behaviours (swimming, climbing and immobility) was quantified with 5 min test session. Desipramine (15 mg/kg in water, i.p.) and a test compound (10, 3, 1 mg/kg in water s.c.) were administered 23.5 hr, 5 hr and 1 hr prior to test session. Water (both i.p. and s.c.) was used as vehicle controls for desipramine and nomifensine respectively.

Spontaneous Locomotive activity (LMA): Male, Sprague-Dawley rats (Charles River) were tested one week after arrival. Rats were ordered at a weight of 130-150g, and a total of 121 rats (n=23-37/ group) and 40 (n=8/group) were used for FST and LMA, respectively. LMA chambers (MED Associates Inc., St. Albans, VT) measuring 17" x 17" were contained

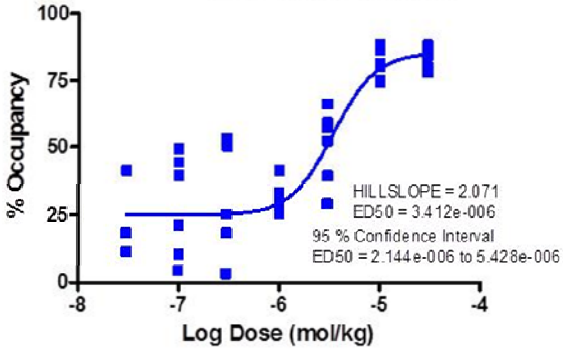
within sound attenuated boxes (San Diego Instruments) and illuminated with a 15W bulb. Activity was tracked by infrared photobeams using IR sources and sensors juxtaposed around the periphery of the chamber. The number of beam breaks was quantified for each recording period. The same dosing protocol for FST was used in the LMA study; however, behavioral testing only occurred on day 2. Prior to the last dose on day 2, rats were habituated to the LMA chambers for 1 hour. Activity data was collected for 75 minutes after the last injection, with the last 15 minutes representing the time FST data would be collected. Locomotor activity was quantified as distance traveled (cm). Stereotypic behavior was operationally defined as consecutive breaks of the same photobeam. Data are presented as group means in 5-min blocks ± SEM and as an average of the last 15-min block, the time when FST would be assessed. Only the last 15-min block was analyzed statistically using a one-way, between groups ANOVA. Group differences were further analyzed using a Bonferroni post-hoc test only after a main effect was determined in the ANOVA. Data are presented as group means ± SEM.

Receptor Occupancy: For NET occupancy, Long Evans rats were first administered (*s.c.*) the test compound at various doses. Thirty minutes later animals were dosed *i.v.* (*via* surgically implanted jugular vein cannulas) with [^{3}H]-MeNER. Ninety minutes after administration of [^{3}H]-MeNER animals were sacrificed and tissue samples from thalamus were collected for NET occupancy analysis. For DAT occupancy, animals were first administered (sc) the test compound. 30 minutes later animals were dosed *i.v.* (*via* surgically implanted jugular vein cannulas) with [^{3}H]-WIN 35,428 or [^{3}H]-PE2I (s prepared in-house). One hour after administration of the radiolabeled compound tissue samples from striatum were collected for DAT occupancy analysis.

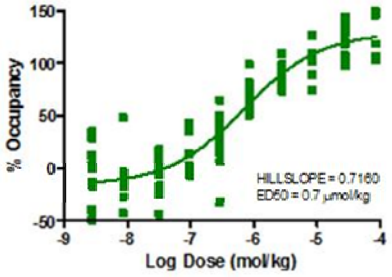
21a: : NET RO in Thalamus



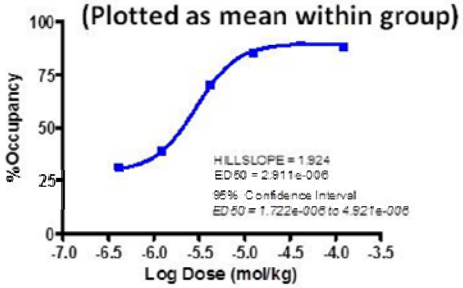
21a: : DAT RO in Striatum



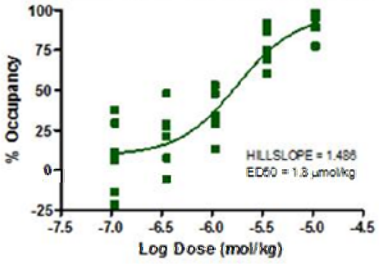
3: NET RO in Thalamus



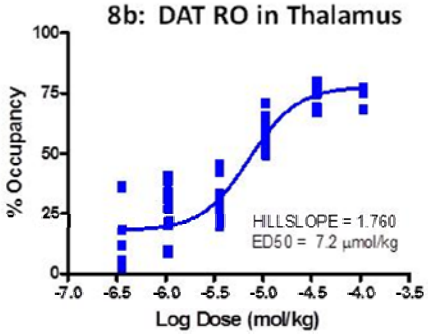
3: DAT RO in Striatum (Plotted as mean within group)



8b: NET RO in Thalamus



8b: DAT RO in Thalamus



PK/PD of 8b in RO and FST Assays

Table SI1. Dose vs. Occupancy and Free concentration for Receptor Occupancy Experiments for **8b**

Dose (mg/kg)[a]	%Occupancy NET	%Occupancy DAT	Free Concentration in NET experiment[b]	Free Concentration in DAT experiment[b]
0.03	8	nm	2.079	nm
0.1	21	1	6.083	10
0.3	35	20	28.028	30
1	76	23	90.07	144
3	91	53	287.133	306
10	nm	73	nm	2118

[a] Dose given 30 minutes prior to adminstration of radioligand. Data collected 90 minutes post adminstration of radioligand.

[b]See plots on page 25 for magnitude of error within the assay. Free concentration is the amount free based on rat plasma protein binding

Table SI2. Dose vs. Free Concentration in FST assay for **8b**

Dose (mg/kg)[a]	Free concentration FST	SEM	%RO NET[b]	%RO DAT[b]
1 (tid)	507	507 ± 154 (N=11)	>90%	50-70%
3 (tid)	1487	1487 ± 305 (N=11)	>90%	50-70%
10 (tid)	6579	6579 ± 1043 (N=11)	>90%	>70%

[a] Dosed 23.5, 5, and 1 hour prior to test.

[b]In the absence of efflux and uptake, it is anticipated that unbound plasma will rapidly equilibrate with unbound brain concentrations. The %RO NET and DAT are estimated given the free concentration in the FST assay and the free concentration in the RO assay from Table SI1.

Animal husbandry practices

In general, all animals were maintained in rooms with constant temperature (approximately 22 °C) and a 12 h light/dark cycle, with free access to food and water. All facilities were approved by the American Association for Accreditation of Laboratory Animal Care (AAALAC) and all testing procedures were performed using protocols approved by the Institutional Animal Care and Use Committee at

AstraZeneca R&D Wilmington, in accordance with *The Guide for the Care and Use of Laboratory Animals*.

References

1. B3LYP method: a) Becke, A. D., *J. Chem. Phys.*, **1993**, *98*, 5648-5652, b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785-789.
2. Reference for 6-311++G** basis set: R. Krishnan, J. S. Binkley, R. Seeger, J. A. Pople, *J. Chem. Phys.*, **1980**, *72*, 650-654.