Supporting Information

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Experimental Section

Reagents and solvents were obtained from commercial suppliers and used as received unless otherwise indicated. Dry solvents were obtained according to the standard procedures. All reactions were performed under inert atmosphere (N_2) unless otherwise noted. Analytical silica gel-coated TLC plates (silica gel 60 F254) were purchased from EM Science and were visualized with UV light or by treatment with either phosphomolybdic acid (PMA) or ninhydrin. Imipramine, desipramine, fluoxetine, and reboxetine, and GBR 12909 dihydrochloride (1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]piperazine) were purchased from SIGMA-ALDRICH (St. Louis, MO). Flash chromatography was carried out on Baker Silica Gel 40 μM. ^{1}H NMR and ^{13}C spectra were routinely recorded with a Varian 400 spectrometer operating at 400 and 100 MHz, respectively. The NMR solvent used was either $CDCl_3$ or CD_3OD as indicated. TMS was used as an internal standard. NMR and rotation of free bases were recorded. Salts of free bases were used for biological characterization. Elemental analyses were performed by Atlantic Microlab Inc. and were within ± 0.4% of the theoretical value. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter.

Procedure A. (3S,6S)-6-Benzhydryl-N-(3,5-dimethoxybenzyl)tetrahydro-2H-pyran-3-amine (2a)

To a stirred solution of amine **1** (60 mg, 0.22 mmol) and 3,5-dimethoxybenzaldehyde (37 mg, 0.22 mmol) in 1,2-dichloroethane (6 mL) was added glacial acetic acid (13 µL, 0.22 mmol). After being stirred for 30 minutes, $NaCNBH_3$ (28 mg, 0.44 mmol) was added portion wise followed methanol (1 mL). The reaction mixture was stirred for overnight. The reaction mixture was quenched with saturated $NaHCO_3$ solution at 0^oC and extracted with dichloromethane (3 X 75 mL). The combined organic layer was washed with water, brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. Crude product was purified by column chromatography using 2% methanol in dichloromethane to give compound **2a** (50 mg, 53 %)) as thick syrup. $[\alpha]^{25}_D$ = (-) 69.2° (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.24-1.34 (m, 1H), 1.48-1.70 (m, 2H), 1.90-1.98 (m, 1H), 2.27 (br s, 1H), 2.67 (br s, 1H), 3.50-3.58 (m, 1H), 3.70-3.84 (m, 2H), 3.79 (s, 6H), 3.95-4.10 (m, 3H), 6.36 (br s, 1H), 6.53 (br s, 2H), 7.10-7.38 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 25.39, 27.63, 50.45, 50.95, 55.56, 57.47, 70.32, 79.52, 99.31, 106.16, 126.47, 126.67, 128.55, 128.71, 128.72, 128.75, 142.44, 142.62, 161.09. The product was converted into the corresponding hydrochloride salt; mp: 218-220°C. Anal. ($C_{27}H_{31}NO_3 \cdot HCl \cdot 0.4H_2O$) C, H, N.

N-(4-((((3S,6S)-6-Benzhydryltetrahydro-2H-pyran-3-yl)amino)methyl)phenyl) methanesulfonamide (2b).

Compound **1** (60 mg, 0.22 mmol) was reacted with N-(4-formylphenyl)methanesulfonamide (45 mg, 0.22 mmol), glacial acetic acid (13 µL, 0.22 mmol), and $NaCNBH_3$ (28 mg, 0.44 mmol) by following procedure A.

The crude product was purified by column chromatography using 3% methanol in dichloromethane to afford compound **2b** (55 mg, 54 %) as a thick syrup. $[\alpha]^{25}_{D}$ = (-) 57.2° (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.25-1.38 (m, 2H), 1.50-1.74 (m, 2H), 1.96-2.02 (m, 1H), 2.75 (br s, 1H), 2.95 (s, 3H), 3.50-3.58 (m, 1H), 3.80 (dd, *J* = 13.2, 16.0 Hz, 2H), 3.94-4.10 (m, 3H), 7.10-7.38 (m, 14H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 25.72, 27.15, 39.48, 50.11, 50.91, 57.35, 69.96, 79.52, 121.24, 126.49, 126.72, 128.54, 128.73, 128.78, 129.85, 136.18, 142.39, 142.51. The product was converted into the corresponding hydrochloride salt; mp: 208-210°C. Anal. ($C_{26}H_{30}N_2O_3S \cdot HCl \cdot 0.2H_2O$) C, H, N.

(3S,6S)-6-Benzhydryl-N-((2,3-dihydrobenzofuran-5-yl)methyl)tetrahydro-2H-pyran-3-amine (2c).

Compound **1** (50 mg, 0.19 mmol) was reacted with 2,3-dihydrobenzofuran-5-carbaldehyde (28 mg, 0.19 mmol), glacial acetic acid (11 µL, 0.19 mmol), and $NaCNBH_3$ (24 mg, 0.37 mmol) by following procedure A. The crude product was purified by column chromatography using 80% ethyl acetate in hexanes to afford compound **2c** (40 mg, 53 %) as a thick syrup. $[\alpha]^{25}_{D}$ = (-) 69.2° (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.28-1.34 (m, 1H), 1.44-1.58 (m, 1H), 1.64 (tt, *J* = 4.0, 13,2 Hz, 1H), 1.77 (br s, 1H), 1.86-1.96 (m, 1H), 2.65 (br s, 1H), 3.19 (t, *J* = 8.8 Hz, 2H), 3.55 (dd, *J* = 2.0, 12.0 Hz, 1H), 3.68 (dd, *J* = 12.8, 26.8 Hz, 2H), 3.92-410 (m, 3H), 4.56 (t, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 7.14-7.38 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 25.45, 27.83, 29.99, 50.47, 50.72, 57.42, 70.42, 71.48, 79.47, 109.13,

125.10, 126.47, 126.66, 127.32, 128.07, 128.54, 128.75, 128.81, 132.80, 142.47, 142.74, 159.32. The product was converted into the corresponding hydrochloride salt; mp: 242-244°C. Anal. ($C_{27}H_{29}NO_2$·HCl) C, H, N.

4-((((3S,6S)-6-Benzhydryltetrahydro-2H-pyran-3-yl)amino)methyl)benzene-1,2-diol (2d)

Compound **1** (60 mg, 0.22 mmol) was reacted with 3,4-dihydroxy-benzaldehyde (31 mg, 0.22 mmol), glacial acetic acid (13 µL, 0.22 mmol), and $NaCNBH_3$ (28 mg, 0.44 mmol) by following procedure A. The crude product was purified by column chromatography using 10% methanol in dichloromethane to afford compound **2d** (46 mg, 53%) as thick syrup. $[\alpha]^{25}_D$ = (-) 47.2° (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, MeOH-d_4): *δ* 1.24-1.38 (m, 1H), 1.46-1.58 (m, 1H), 1.76-1.86 (m, 1H), 1.96-2.20 (m 1H), 2.89 (br s, 1H), 3.63 (dd, *J* = 1.6, 12.4 Hz, 1H), 3.78-3.84 (m, 2H), 3.92-4.10 (m, 2H), 4.16-4.24 (m, 1H), 6.69 (dd, *J* = 1.2, 8.0 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 2.0 Hz, 1H), 7.10-7.36 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$ + MeOH-d_4): *δ* 24.76, 26.06, 49.49, 50.02, 57.12, 68.37, 79.48, 115.33, 115.91, 120.93, 126.42, 126.71, 128.42, 128.69, 141.95, 142.06, 144.98, 145.02. The product was converted into the corresponding hydrochloride salt; mp: 272-274°C. Anal. ($C_{25}H_{27}NO_3$·HCl·0.8H_2O) C, H, N.

(3S,6S)-6-Benzhydryl-N-(benzo[d][1,3]dioxol-5-ylmethyl)tetrahydro-2H-pyran-3-amine (2e)

Compound **1** (60 mg, 0.22 mmol) was reacted with 1,3-benzodioxole-5-carbaldehyde (34 mg, 0.22 mol), glacial acetic acid (13 µL, 0.22 mmol), and

$NaCNBH_3$ (28 mg, 0.22 mmol) by following procedure A. The crude product was purified by column chromatography using 50% ethyl acetate in hexanes to afford compound **2e** (65 mg, 72%) as a thick syrup. $[\alpha]^{25}_D$ = (-) 79.4° (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.27-1.34 (m, 1H), 1.45-1.55 (m, 1H), 1.58-1.68 (m, 1H), 1.88-1.94 (m, 1H), 2.63 (br s, 1H), 3.55 (dd, *J* = 1.6, 12.0 Hz, 1H), 3.72 (d, *J* = 12.8 Hz, 1H), 3.65 (d, *J* = 12.8 Hz, 1H), 3.84-4.10 (m, 3H), 5.94 (s, 2H), 6.75 (s, 2H), 6.86 (s, 1H), 7.14-7.38). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 25.43, 27.82, 50.31, 50.74, 57.46, 70.43, 79.47, 101.09, 108.26, 108.89, 121.30, 126.51, 126.67, 128.57, 128.73, 128.77, 134.75, 142.42, 142.68, 146.63, 147.90. The product was converted into the corresponding hydrochloride salt; mp: 233-235°C. Anal. ($C_{26}H_{27}NO_3 \cdot HCl$) C, H, N.

(3*S*,6*S*)-6-Benzhydryl-*N*-(3-methoxybenzyl)tetrahydro-2*H*-pyran-3-amine (2f)

Compound **1** (60 mg, 0.22 mmol) was reacted with 3-methoxy-benzaldehyde (31 mg, 0.22 mmol), glacial acetic acid (13 µL, 0.22 mmol), and $NaCNBH_3$ (18 mg, 0.29 mmol) by following procedure A. The crude product was purified by column chromatography using 5% methanol in dichloromethane to afford compound **2f** (78 mg, 90%) as a thick syrup. $[\alpha]^{25}_D$ = (-) 43.6 (*c* 1, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.20-1.36 (m, 1H), 1.41-1.68 (m, 2H), 1.91 (dt, *J* = 13.2 Hz, 2.8 Hz, 1H), 2.63 (s, 1H), 3.54 (dd, *J* = 11.6 Hz, 2 Hz, 1H), 3.65-3.84 (m, 4H), 3.89-4.10 (m, 3H), 6.79 (dd, *J* = 8 Hz, 2.4 Hz, 1H), 6.84-6.94 (m, 2H), 7.10-7.38 (m, 11 H). ^{13}C (100 MHz, $CDCl_3$,): *δ* 25.8, 28.2, 50.9, 51.3, 55.8, 57.9, 70.8, 79.9, 113.0, 114.1, 121.0, 126.9, 127.1, 129.0, 129.1, 130.0,

142.8, 142.83, 143.1, 160.3. The product was converted into the corresponding hydrochloride salt; mp: 191-196 ^{o}C. Anal. ($C_{26}H_{30}NO_2 \cdot HCl \cdot 0.5H_2O$) C, H, N.

4-((((3S,6S)-6-Benzhydryltetrahydro-2H-pyran-3-yl)amino)methyl) benzenesulfonamide (2g)

To an ice cooled stirred solution of compound **1** (60 mg, 0.22 mmol) in a mixture of DMF and THF (1:1, 4 mL) was added K_2CO_3 (28 mg, 0.20 mmol) followed by 4-(bromomethyl)benzenesulfonamide (45 mg, 0.18 mmol). The reaction mixture was allowed to warm to room temperature and stirred for overnight. The reaction mixture was extracted with ethyl acetate (3 X 75 mL) and water (25 mL). The combined organic layer was washed with water, brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using 35% ethyl acetate in hexanes to give compound **2g** (50 mg, 51 %). $[\alpha]^{25}_{D}$ = (-) 65.2° (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.32-1.38 (m, 1H), 1.48-1.59 (m, 1H), 1.60-1.72 (m, 1H), 1.88-1.98 (m, 1H), 2.63 (br s, 1H), 3.58 (d, *J* = 11.6 Hz, 1H), 3.85 (dd, *J* = 14.0, 23.6 Hz, 2H), 3.90-4.10 (m, 3H), 4.93 (br s, 2H), 7.14-7.36 (m, 10H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.84 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 25.36, 27.60, 50.36, 50.77, 57.52, 70.42, 79.61, 126.56, 126.66, 126.76, 128.60, 128.68, 128.75, 128.80, 140.86, 142.33, 142.46, 145.96. The product was converted into the corresponding hydrochloride salt; mp: 278-280°C. Anal. ($C_{25}H_{28}N_2O_3S \cdot HCl$) C, H, N.

N-((3S,6S)-6-Benzhydryltetrahydro-2H-pyran-3-yl)-4-methylbenzenesulfonamide (2h).

To ice cooled stirred solution of compound **1** (60 mg, 0.22 mmol) in dichloromethane (4 mL) was added triethylamine (94 µL, 0.67 mmol) followed by 4-methylbenzenesulfonyl chloride (45 mg, 0.22 mmol). The reaction mixture was allowed to warm to room temperature and stirred for overnight. The reaction mixture was extracted with dichloromethane (3 X 75 mL) and water (25 mL). The combined organic layer was washed with water, brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using 35% ethyl acetate in hexanes to give compound **2h** (70 mg, 74 %) as a white solid. Mp: 74-76°C. $[\alpha]^{25}_D$ = (-) 64.6° (*c* = 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.24-1.38 (m, 1H), 1.40-1.52 (m, 1H), 1.58-1.68 (m, 1H), 1.78-1.86 (m, 1H), 2.41 (s, 3H), 3.36-3.50 (m, 2H), 3.57 (d, *J* = 12.0 Hz, 1H), 3.89 (d, *J* = 8.8 Hz, 1H), 3.96-4.02 (m, 1H), 5.14 (d, *J* = 8.4 Hz, 1H), 7.14-7.32 (m, 12H), 7.72 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 21.69, 25.19, 29.07, 48.21, 57.71, 71.59, 79.56, 126.66, 126.86, 127.11, 128.60, 128.83, 129.93, 142.00, 143.50. Anal. ($C_{25}H_{27}NO_3S$) C, H, N.

(2*S*,4*R*,5*R*)-2-Benzhydryl-5-((benzo[d][1,3]dioxol-5-ylmethyl)amino)tetrahydro-2*H*-pyran-4-ol (4a):

Amine **3** (60 mg, 0.21 mmol) was reacted with 1,3-benzodioxole-5-carbaldehyde (32 mg, 0.21 mmol), glacial acetic acid (12 µL, 0.21 mmol), and $NaCNBH_3$ (20 mg, 0.32 mmol)) in 1,2-dichloroethane (6 mL) by following procedure A. The crude residue was purified by column chromatography using 60% ethylacetate in hexane to afford compound **4a** (74 mg, 84%).$[\alpha]^{25}_D$ = (-) 69.1 (*c* 1, CH_3OH). ^{1}H NMR (400 MHz, CD_3OD): *δ* 1.42 (dt, *J* = 14 Hz, 2.8 Hz,

1H), 1.61-1.74 (m, 1H), 2.43 (d, *J* = 2.4 Hz, 1H), 3.55-4.02 (m, 6H), 4.51 (t, *J* = 11.6 Hz, 1H), 5.90 (s, 2H), 6.70-6.79 (m, 2H), 6.84 (s, 1H), 7.08-7.39 (m, 10 H). ^{13}C NMR (100 MHz, CD_3OD): *δ* 32.9, 50.5, 56.0, 56.8, 64.2, 66.1, 73.9, 101.1, 107.8, 108.7, 121.6, 126.0, 126.3, 128.0, 128.3, 128.4, 128.6, 133.6, 142.6, 142.7, 147.0, 148.1. The product was converted into the corresponding hydrochloride salt; mp: 240-245 °C. Anal. ($C_{26}H_{27}NO_4 \cdot HCl \cdot 0.5H_2O$) C, H, N.

(2*S*,4*R*,5*R*)-2-Benzhydryl-5-((3-hydroxybenzyl)amino)tetrahydro-2*H*-pyran-4-ol (4b):

Amine **3** (60 mg, 0.21 mmol) was reacted with 3-hydroxy benzaldehyde (26 mg, 0.21 mmol), glacial acetic acid (12 µL, 0.21 mmol), and $NaCNBH_3$ (20 mg, 0.32 mmol)) in 1,2-dichloroethane (6 mL) by following procedure A. The crude residue was purified by column chromatography using 80% ethyl acetate in hexane to afford compound **4b** (63 mg, 76%). $[\alpha]^{25}_D$ = (-) 40.0 (*c* 1, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.28-1.42 (m, 1H), 1.44-1.59 (m, 1H), 2.35 (s, 1H), 3.46-3.96 (m, 6H), 4.43 (t, *J* = 9.6 Hz, 1H), 6.54-6.74 (m, 3H), 6.97-7.34 (m, 11 H). ^{13}C NMR (100 MHz, CD_3OD): δ 33.2, 51.0, 56.2, 56.8, 64.5, 66.4, 73.9, 114.4, 115.1, 119.7, 126.4, 126.6, 128.46, 128.48, 128.54, 128.7, 129.7, 140.9, 142.2, 157.1. The product was converted into the corresponding hydrochloride salt; mp: 137-142 ^{o}C. Anal. ($C_{25}H_{27}NO_3 \cdot HCl \cdot 0.9H_2O$) C, H, N.

4-((((3*R*,4*R*,6*S*)-6-Benzhydryl-4-hydroxytetrahydro-2*H*-pyran-3-yl)amino)methyl) benzene-1,2-diol (4c):

Amine **3** (60 mg, 0.21 mmol) was reacted with 3,4-dihydroxy-benzaldehyde (29 mg, 0.21 mmol), glacial acetic acid (12 µL, 0.21 mmol), and

$NaCNBH_3$ (20 mg, 0.32 mmol)) in 1,2-dichloroethane (6 mL) by following procedure A. The crude residue was purified by column chromatography using 10% methanol in dichloromethane to afford compound **4c** (60 mg, 70%). $[\alpha]^{25}_D$ = (-) 64.7 (*c* 1, CH_3OH). ^1H NMR (400 MHz, CD_3OD): *δ* 1.36-1.54 (m, 1H), 1.58-1.76 (m, 1H), 2.57 (s, 1H), 3.16-3.40 (m, 2H), 3.60-4.06 (m, 4H), 4.53 (t, *J* = 9.2 Hz, 1H), 6.58-6.88 (m, 4H), 7.00-7.51 (m, 9 H). ^{13}C NMR (100 MHz, CD_3OD): *δ* 34.2, 51.6, 57.3, 58.1, 64.9, 66.7, 75.3, 116.5, 117.2, 121.6, 127.3, 127.7, 129.4, 129.7, 129.73, 129.8, 143.7, 144.0, 146.3, 146.7. The product was converted into the corresponding hydrochloride salt; mp: 139-144 ^oC. Anal. ($C_{25}H_{27}NO_4 \cdot HCl \cdot 1.1H_2O$) C, H, N.

(2S,4R,5R)-2-Benzhydryl-5-(((2,3-dihydrobenzofuran-5-yl)methyl)amino)tetrahydro-2H-pyran-4-ol (4d)

Compound **3** (60 mg, 0.21 mmol) was reacted with 2,3-dihydrobenzofuran-5-carbaldehyde (31 mg, 0.21 mmol), glacial acetic acid (12 µL, 0.21 mmol), and $NaCNBH_3$ (27 mg, 0.42 mmol) by following procedure A. The crude product was purified by column chromatography using 5% methanol in ethyl acetate to afford compound **4d** (55 mg, 63%) as a thick syrup. $[\alpha]^{25}_D$ = (-) 63.8° (*c* 0.5, MeOH). ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.38-1.46 (m, 1H), 1.60-1.68 (m, 1H), 1.70-1.78 (m, 1H), 2.45 (br s, 1H), 3.18 (t, *J* = 8.4 Hz, 2H), 3.64 (d, *J* = 12.8 Hz, 1H), 3.74-3.82 (m, 2H), 3.87-4.00 (m, 2H), 4.44-4.60 (m, 3H), 6.71 (d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 9.2 Hz, 1H), 7.10-7.38 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 29.94, 33.68, 51.37, 56.69, 56.79, 65.01, 67.70, 71.51, 73.82, 109.21, 125.17, 126.58, 126.78, 128.16, 128.65, 128.89, 132.44, 142.29, 142.38, 159.44.

The product was converted into the corresponding hydrochloride salt; mp: 211-213°C. Anal. ($C_{27}H_{29}NO_3 \cdot HCl \cdot 0.7H_2O$] C, H, N.

N-(4-((((3R,4R,6S)-6-Benzhydryl-4-hydroxytetrahydro-2H-pyran-3-yl)amino)methyl) phenyl) methanesulfonamide (4e)

Compound **3** (60 mg, 0.21 mmol) was reacted with N-(4-formylphenyl)methanesulfonamide (42 mg, 0.21 mmol), glacial acetic acid (12 µL, 0.21 mmol), and $NaCNBH_3$ (27 mg, 0.42 mmol) by following procedure A. The crude product was purified by column chromatography using 5% methanol in ethyl acetate afford compound **4e** (76 mg, 77%) as a thick syrup. $[\alpha]^{25}_D$ = (-) 66.2° (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.40-1.46 (m,1H), 1.52-1.64 (m, 2H), 1.68-1.78 (m, 1H), 2.43 (br s, 1H), 3.00 (s, 3H), 3.66-4.10 (m, 6H), 4.51 (dt, *J* = 2.4, 9.6 Hz, 1H), 7.12-7.36 (m, 14H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 33.62, 39.43, 50.79, 56.67, 56.88, 64.98, 67.44, 73.85, 121.28, 126.67, 126.82, 128.64, 128.91, 129.61, 135.87, 137.55, 142.23, 142.26. The product was converted into the corresponding hydrochloride salt; mp: 219-221°C. Anal. ($C_{26}H_{30}N_2O_4S \cdot HCl \cdot 0.8H_2O$] C, H, N.

4-((((3R,4R,6S)-6-Benzhydryl-4-hydroxytetrahydro-2H-pyran-3-yl)amino)methyl) benzenesulfonamide (4f)

To an ice cooled stirred solution of compound **3** (60 mg, 0.21 mmol) in mixture of DMF and THF (1:1, 4 mL) was added K_2CO_3 (26 mg, 0.19 mmol) followed by 4-(bromomethyl)benzenesulfonamide (42 mg, 0.17 mmol). The reaction mixture was allowed to warm to room temperature and stirred for overnight. The reaction mixture was extracted with ethyl acetate (3 X 75 mL) and

water (25 mL). The combined organic layer was washed with water, brine, dried over Na_2SO_4, and solvent was removed under reduced pressure. The crude product was purified by column chromatography using 10% methanol in dichloromethane to give compound **4f** (62 mg, 65%). $[\alpha]^{25}_D$ = (-) 57.2° (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.40-1.46 (m, 1H), 1.68-1.78 (m, 1H), 2.39 (br s, 1H), 3.76-3.82 (m, 2H), 3.88-4.00 (m, 1H), 5.00 (dt, *J* = 2.4, 12.0 Hz, 1H), 4.85 (br s, 2H), 7.14-7.35 (m, 10H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.40, 50.59, 56.40, 56.93, 64.86, 67.06, 73.92, 126.58, 126.87, 128.59, 128.70, 128.85, 128.94, 140.87, 142.12, 142.23, 145.53. The product was converted into the corresponding hydrochloride salt; mp: 225-227°C. Anal. ($C_{25}H_{28}N_2O_4S\cdot HCl\cdot H_2O$] C, H, N.

bis(4-Fluorophenyl)methanone (**6**)

To an oven-dried 2 L round bottom flask equipped with magnetic stir bar, compound **5** (19.4 g, 94.99 mmol) was added and dissolved in anhydrous acetonitrile (1.3 L) under a flow of nitrogen. After cooling the solution to 0 ^{o}C in an ice-bath, finely ground $KMNO_4$ (100 g, 632.78 mmol) was added in portion wise. The resulting solution slowly warmed to room temperature and stirred until all starting material was consumed. After completion, the reaction mixture was diluted with water (300 mL), the organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure to obtain a light pink solid. The crude product was purified by gradient silica gel column chromatography using a mixture of hexanes and ethyl acetate (30:1 to 10:1) to afford corresponding ketone **6** as white solid (20.45 g, 99%). ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.11-7.22

(m, 4 H), 7.76-7.87 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.8, 166.4, 164.3, 133.6, 132.5, 132.4, 115.6, 115.4.

4,4'-(2-Methoxyethene-1,1-diyl)bis(fluorobenzene) (**7**)

To a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (1.0 g, 2.92 mmol) in anhydrous THF (15 mL) at 0 ^oC under Nitrogen atmosphere, was added sodium amide (119 mg, 3.06 mmol) in portion wise. The solution was stirred for 10 minutes at room temperature and cooled to 0 ^oC. Then a solution of the ketone **6** (0.63 g, 2.89 mmol) in anhydrous THF (6 mL) was added slowly and the reaction mixture was allowed to reach room temperature. The progress of the reaction was monitored by TLC and stopped after **6** was completely consumed. The solvent was evaporated under reduced pressure and the residue was triturated with hot hexanes. The precipitated triphenylphosphine oxide was filtered off and the filtrate was concentrated under reduced pressure. The crude product **7** (1.1g, 97%) was sufficiently pure and used in the next step without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ 6.82-7.42 (m, 8H), 6.39 (s, 1H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 146.1, 134.2, 132.3, 129.8, 115.8, 115.4, 60.5.

2,2-bis(4-Fluoro-phenyl)-acetaldehyde (8)

Into a stirring solution of methoxy compound **7** (30.0 g, 121.82 mmol) in glacial acetic acid (280 mL), H_2SO_4 (32 mL) was added in a drop wise fashion under nitrogen atmosphere at room temperature. After stirring for 0.5 hour the reaction mixture was poured into crushed ice and extracted with diethyl ether (3 x 150 mL). The combined organic layer was washed with brine, dried over Na_2SO_4,

filtered and evaporated in vacuo to afford aldehyde **8** (20.65 g, 73%). ^{1}H (400 MHz, $CDCl_3$): δ 4.23 (s, 1H), 6.80-7.28 (m, 4H), 7.60-8.18 (m, 4H), 9.90 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.4, 115.4, 115.6, 115.9, 130.9, 130.99, 131.1, 131.2, 132.4, 132.5, 133.6, 164.1, 166.6.

2-[*Bis*-(4-fluoro-phenyl)-methyl]-oxirane (9)

Into a mixture of sulfoxonium iodide (24.64 g, 112 mmol) and NaH (4.2 g, 175 mmol, 63% dispersion in oil), DMSO (75 mL) was added. The reaction mixture was stirred at room temperature for 1 hour and then aldehyde **8** (20 g, 86.12 mmol) dissolved in DMSO (25 mL) was added into it. The reaction mixture was heated to 60 ^{o}C for 2 hours and then cooled down. The reaction mixture was extracted with diethyl ether (3 x 100 mL), washed with water, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel column chromatography (Hexane/EtOAc, 9.5:0.5) to give epoxide **9** (18.87 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15-7.25 (m, 4H), 6.95-7.06 (m, 4H), 3.86 (d, J = 6.5 Hz), 3.41-3.50 (m, 1H), 2.86 (dd, J = 4.7, 3.8 Hz, 1H), 2.48 (dd, J = 5.0, 2.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 160.6, 136.7, 136.6, 136.4, 136.3, 130.1, 130.0, 129.9, 129.8, 115.6, 115.4, 115.3, 115.2, 54.7, 51.6, 46.2.

(*R*)-2-[*Bis*-(4-fluoro-phenyl)-methyl]-oxirane (10) and (*S*)-3,3-*bis*-(4-fluoro-phenyl)-propane-1,2-diol (11)

A mixture of (*R*,*R*)-(-)-*N*, *N*'-*bis*(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane diaminocobalt (II) (250 mg, 0.38 mmol), dichloromethane (15 mL), and acetic acid (45 μL, 0.78 mmol) was stirred for 1 h at room temperature. The solvent was removed under reduced pressure and the residue was dried. To this

residue, racemic epoxide **9** (18.8 g, 76.42 mmol) was added and the reaction mixture was cooled down in an ice bath. H_2O (1.0 mL, 53.49 mmol) was added next in a drop wise fashion and the reaction mixture was allowed to reach room temperature. After stirring for 12 days, the residue was purified by column chromatography to give compound **10** (9.02 g, 48%) and compound **11** (9.68 g, 48%). The enantiomeric excess of the epoxide **10** was determined to be 99% by chiral HPLC analysis. Data for compound **10**: $[\alpha]_D^{25}$ = (+) 12.6 (*c* 1.0, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$): δ 2.48 (dd, *J* = 4.8 Hz, 2.4 Hz, 1H), 2.86 (t, *J* = 4.8 Hz, 1H), 3.40-3.52 (m, 1H), 3.86 (d, *J* = 6.8 Hz, 1H), 6.80-7.30 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 160.6, 136.7, 136.6, 136.4, 136.3, 130.1, 130.0, 129.9, 129.8, 115.6, 115.4, 115.3, 115.2, 54.7, 51.6, 46.2. Data for compound **11**: Mp: 90-95 ^oC. $[\alpha]^{25}_D$ = (+) 45.6^o (*c* 1 MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ 3.36 (dd, *J* = 11.2 Hz, 6.4 Hz, 1H), 3.54 (d, *J* = 10.8 Hz, 1H), 3.98 (d, *J* = 9.2 Hz, 1H); 4.22-4.35 (m, 1H), 6.77-7.42 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.4, 64.5, 73.9, 115.5, 115.7, 129.4, 129.5, 130.0, 130.1, 136.6, 137.1, 160.4, 162.9.

(*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-1,1-*bis*-(4-fluoro-phenyl)propan-2-ol (12)

In to a stirring solution of alcohol **11** (10.0 g, 37.84 mmol) in dichloromethane (50 mL), *tert*-butyldimethyl silyl chloride (6.27 g, 41.62 mmol) and imidazole (5.15 g, 75.68 mmol) were added at 0 ^oC. Then the reaction mixture was stirred for 1 hour allowing the temperature to rise to room temperature. The product was extracted from the reaction mixture with CH_2Cl_2 (3 x 100 mL), washed with water, dried over Na_2SO_4, filtered, and concentrated.

The crude material was purified by column chromatography over silica gel (Hexane/EtOAc, 4:1) to give 13.18 g (92%) of **12**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.9 (s, 9H), 2.53 (d, *J* = 6.54 Hz, 1H), 3.41 (dd, *J* = 10 Hz, 6 Hz, 1H), 3.55 (dd, *J* = 11.2 Hz, 2.8 Hz, 1H), 4.02 (d, *J* = 8.2 Hz, 1H), 4.25-4.38 (m, 1H), 6.90-7.08 (m, 4H), 7.16-7.38 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ -5.49, -5.45, 25.8, 52.6, 65.1, 73.4, 115.2, 115.4, 115.6, 129.6, 129.7, 130.1, 130.2, 137.2, 137.8, 160.4, 162.8.

(*S*)-Methanesulfonic acid 1-(*tert*-butyl-dimethyl-silanyloxymethyl)-2,2-*bis*-(4-fluoro-phenyl)-ethyl ester (13)

In to a stirring solution of alcohol **12** (10.0 g, 26.42 mmol) in dichloromethane (50 mL), was added methanesulfonyl chloride (2.45 mL, 31.70 mmol) and Et_3N (7.3 mL, 52.84 mmol) at 0 ^{o}C. The reaction mixture was then stirred for 2 hours and the temperature was allowed to rise to room temperature. The reaction mixture was extracted with CH_2Cl_2 (3 x 100 mL), washed with water, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by column chromatography over silica gel (Hexane/EtOAc, 4:1) to give compound **13** (11.33 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.88 (s, 9H), 2.51 (s, 3H), 3.66 (dd, *J* = 12.2 Hz, 4.4 Hz, 1H), 3.81 (dd, *J* = 12.2 Hz, 4.4 Hz, 1H), 4.43 (d, *J* = 8.8 Hz, 1H), 5.2-5.29 (m, 1H), 6.94-7.08 (m, 4H), 7.20-7.38 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ -5.43, -5.39, 26.0, 38.4, 50.5, 63.5, 85.3, 115.7, 115.9, 116.1, 130.1, 130.2, 130.7, 130.8, 135.7, 136.0, 160.9, 163.3.

(*S*)-Methanesulfonic acid 2,2-*bis*-(4-fluoro-phenyl)-1-hydroxymethyl-ethyl ester (14)

In to a stirring solution of compound **13** (10.0 g, 21.9 mmol) in THF (100.0 mL), TBAF (24 mL, 1 M solution in THF, 24.09 mmol) was added slowly at 0 ^{o}C and the stirring was continued for 1 hour at the same temperature. THF was removed in vacuo and the crude product was extracted with dichloromethane (3 x 100 mL), washed with water, dried over Na_2SO_4, filtered, and concentrated to give compound **14** (6.75 g, 90%) which was used for the next reaction without further purification. Mp: 115-120 ^{o}C. $[\alpha]^{25}_{D}$ = (-) 32.9^{o} (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.35 (dd, *J* = 7.4, 5.3 Hz, 2H), 7.26 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.02 (dd, *J* = 15.5, 7.6 Hz, 4H), 5.21-5.29 (m, 1H), 4.42 (d, *J* = 8.8 Hz, 1H), 3.81-3.93 (m, 1H), 3.61-3.76 (m, 1H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 163.3, 160.9, 136.0, 135.7, 130.8, 130.7, 130.2, 130.1, 116.1, 115.9, 115.7, 85.4, 63.9, 50.5, 38.4.

(*R*)- 2-[*Bis*-(4-fluoro-phenyl)-methyl]-oxirane (10)

In to a stirring solution of alcohol **14** (6.0 g, 17.42 mmol) in anhydrous CH_3OH (30 mL), K_2CO_3 (2.88 g, 20.87 mmol) was added slowly at room temperature. The reaction mixture was stirred for 5 hours at the same temperature. CH_3OH was removed in vacuo and the crude product was purified by silica gel column chromatography (Hexane/EtOAc, 4:1) to give 3.84 g (89%) of **10** as colourless oil. $[\alpha]_D^{25}$ = (+) 12.6 (*c* 1.0, CH_3OH).

(*S*)-1,1-*Bis*-(4-fluoro-phenyl)-hex-5-en-2-ol (15)

To a stirred solution of epoxide **10** (9.0 g, 36.56 mmol) in anhydrous diethyl ether (90 mL) was added copper(I) iodide (700 mg, 3.65 mmol) and allylmagnesium chloride (22.78 mL, 2 M solution in tetrahydrofuran, 45.65 mmol) at -78 ^{o}C. After stirring overnight at room temperature under nitrogen atmosphere, the reaction mixture was quenched at 0 ^{o}C by addition of saturated NH_4Cl solution (50 mL) and extracted with ethyl acetate (3 x 75 mL). The combined organic layer was washed with water, brine and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography (ethyl acetate/hexanes, 1:9) to give compound **15** (9.27 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40-1.62 (m, 2H), 2.08-2.35 (m, 2H), 3.87 (d, *J* = 7.6 Hz, 1H), 4.20-4.35 (m, 1H), 4.89-5.08 (m, 2H), 5.68-5.86 (m, 1H), 6.92-7.08 (m, 4H), 7.21 (d, *J* = 5.6 Hz, 1H), 7.23 (d, *J* = 5.6 Hz, 1H), 7.31 (d, *J* = 5.6 Hz, 1H), 7.33 (d, *J* = 5.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.4, 34.5, 57.1, 73.5, 115.4, 115.7, 115.8, 115.9, 116.0, 129.8, 130.0, 130.5, 130.6, 137.2, 138.3, 138.4, 160.6, 163.2.

(*S*)-4,4'-(2-(Vinyloxy)hex-5-ene-1,1-diyl)*bis*(fluorobenzene) (16)

In to a stirred solution of alcohol **15** (9.0 g, 31.25 mmol) in excess of ethyl vinyl ether (100 mL) was added mercury (II) trifluoroacetate (2.66 g, 6.24 mmol) at room temperature, and stirring was continued for 12 hours under a nitrogen atmosphere. The solvent was removed under reduced pressure at room temperature. The crude product was dissolved in 5% ethyl acetate in hexanes and filtered through a basic alumina pad quickly, and the filtrate was concentrated under reduced pressure at room temperature to give product **16**

(7.26 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54-1.68 (m, 2H), 2.01-2.25 (m, 2H), 3.87 (dd, *J* = 8 Hz, 1.6 Hz, 1H), 4.08 (d, *J* = 7.2 Hz, 1H), 4.23 (dd, *J* = 14.0 Hz, 1.2 Hz, 1H), 4.30-4.39 (m, 1H), 4.91-5.08 (m, 2H), 5.64-5.82 (m, 1H), 6.10 (dd, *J* = 14.0 Hz, 6.4 Hz, 1H), 6.90-7.06 (m, 4H), 7.12-7.24 (m, 2H), 7.25-7.34 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7, 32.4, 54.4, 82.1, 88.5, 115.3, 115.5, 115.54, 115.59, 115.7, 130.1, 130.2, 130.7, 130.8, 136.9, 137.9, 152.0, 160.6, 163.1.

(*S*)-2-(*Bis*(4-Fluorophenyl)methyl)-3,4-dihydro-2*H*-pyran (17)

Into a stirred solution of compound **16** (7.0 g, 22.26 mmol) in anhydrous benzene (100 mL) was added Grubb's (first generation) catalyst (900 mg, 1.09 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was slowly heated to reflux, and the refluxing was continued for 2 hours. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure. The crude residue was purified by column chromatography (ethyl acetate/hexanes, 0.5:9.5) to give compound **17** (4.78 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50-1.62 (m, 1H), 1.68-1.82 (m, 1H), 1.84-2.14 (m, 2H), 4.02 (d, *J* = 8 Hz, 1H), 4.45 (t, *J* = 9.2 Hz, 1H), 4.64-4.76 (m, 1H), 6.34 (d, *J* = 6 Hz, 1H), 6.89-7.06 (m, 4H), 7.12-7.24 (m, 2H), 7.24-7.34 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.0, 26.4, 54.8, 76.6, 100.9, 101.0, 115.3, 115.5, 115.6, 115.8, 130.0, 130.1, 130.3, 130.4, 137.5, 138.0, 143.8, 143.9, 160.2, 163.0.

6-[*Bis*-(4-Fluoro-phenyl)-methyl]-tetrahydro-pyran-3-ol (Mixture of 18a and 18b)

To a stirred solution of compound **17** (4.70 g, 16.43 mmol) in anhydrous THF (20 mL) was added 9-BBN (81.5 mL, 0.5 M solution in tetrahydrofuran, 31.1 mmol) under a nitrogen atmosphere. After being stirred overnight at room temperature, the reaction mixture was cooled to 0 ^{o}C, quenched by the addition of ethanol (15 mL), and stirred for 10 minutes. Next, aqueous 10% NaOH solution (15 mL) and 30% H_2O_2 (10 mL) were added, and the resulting solution was heated to 50 ^{o}C for 1 hour. After cooling to room temperature, the reaction mixture was treated with water (40 mL) and extracted with ethyl acetate (3 x 75 mL). The combined organic layers were washed with water, brine and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography using ethyl acetate/hexanes (1:3) to give compounds **18a** and **18b** (4.65 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10-1.88 (m, 3H), 2.04-2.14 (m, 1H), 3.13 (t, J = 10.8 Hz, 1H), 3.62-3.74 (m, 1H), 3.82-3.95 (m, 2H), 3.96-4.04 (m, 1H), 6.90-7.03 (m, 4H), 7.12-7.20 (m, 2H), 7.20-7.28 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 24.8, 28.5, 29.4, 30.0, 33.1, 36.5, 55.6, 56.0, 64.6, 66.4, 73.1, 78.9, 79.6, 115.3, 115.5, 115.6, 115.8, 129.9, 130.0, 130.1, 130.2, 137.8, 138.4, 160.5, 162.9.

(3*R*,6*S*)-6-(*Bis*(4-Fluorophenyl)methyl)tetrahydro-2*H*-pyran-3-yl methanesulfonate (19a)

To an ice-cooled stirred mixture of compounds **18a** and **18b** (4.6 g, 15.08 mmol) and triethylamine (4.1 mL, 30.2 mmol) in anhydrous dichloromethane (60 mL) was added methanesulfonyl chloride (1.73 mL, 22.52 mmol) under a nitrogen atmosphere. After being stirred for 2 hours at room temperature, the

reaction mixture was extracted with ethyl acetate (3 x 75 mL). The combined organic layers were washed with water, brine and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by column chromatography using ethyl acetate/hexanes (1:3) to elute the trans compound **19a** (4.45 g, 77%) first followed by cis compound **19b** (692 mg, 12%). Spectral data for **19a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36-1.80 (m, 3H), 2.20-2.32 (m, 1H), 3.00 (s, 3H), 3.26-3.42 (m, 1H), 3.82-3.96 (m, 2H), 4.15 (dd, *J* = 11.0 Hz, 2.4 Hz, 1H), 4.60 (septet, *J* = 4.8 Hz, 1H), 6.92-7.02 (m, 4H), 7.12-7.25 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.4, 30.5, 38.7, 55.3, 69.9, 74.9, 79.0, 115.4, 115.6, 115.7, 115.9, 129.9, 130.0, 130.1, 130.2, 137.8, 138.4, 161.0, 163.2. Spectral data for **19b**: **(3*S*,6*S*)-6-(*bis*(4-Fluorophenyl)methyl)tetrahydro-2*H*-pyran-3-yl methanesulfonate:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22-1.86 (m, 3H), 2.14-2.24 (m, 1H), 3.02 (s, 3H), 3.64 (d, *J* = 12.8 Hz, 1H), 3.90-4.06 (m, 2H), 4.17 (d, *J* = 14.0 Hz, 1H), 4.72-4.82 (m, 1H), 6.90-7.04 (m, 4H), 7.10-7.21 (m, 2H), 7.22-7.30 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.7, 28.7, 39.2, 55.8, 70.1, 74.6, 79.2, 115.3, 115.5, 115.6, 115.9, 130.0, 130.06, 130.08, 130.1, 137.8, 138.0, 161.1, 163.4.

(2*S*,5*S*)-5-Azido-2-[*bis*-(4-fluoro-phenyl)-methyl]-tetrahydro-pyran (20).

Into a stirring solution of compound **19a** (4.40 g, 11.51 mmol) in DMF (60 mL) was added sodium azide (3.75 g, 57.76 mmol). After being stirred overnight at 80 ^{o}C, the reaction mixture was cooled to room temperature, treated with water, and extracted with diethyl ether (3 x 75 mL). The combined organic layer was washed with water, brine (40 mL) and dried over Na_2SO_4, and the solvent

was removed under reduced pressure. The crude residue was purified by column chromatography ethyl acetate/hexanes (0.5:9.5) to give compound **20** (3.22 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20-1.44 (m, 1H), 1.46-1.83 (m, 2H), 1.83-2.14 (m, 1H), 3.52-3.68 (m, 2H), 3.70-4.18 (m, 3H), 6.86-7.06 (m, 4H), 7.12-7.23 (m, 2H), 7.24-7.34 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3, 27.6, 55.4, 55.8, 69.8, 79.5, 115.3, 115.5, 115.6, 115.8, 130.0, 130.1, 130.2, 137.8, 140.0, 160.6, 163.0.

(3*S*,6*S*)-6-[*bis*-(4-Fluoro-phenyl)-methyl]-tetrahydro-pyran-3-ylamine (21)

Azide **20** (3.12 g, 9.47 mmol) in methanol (40 mL) was hydrogenated (50 psi) in the presence of 10% Pd-C (312 mg, 10 wt %) for 2 hours. The reaction mixture was filtered through a short bed of Celite, and the solvent was removed under reduced pressure to afford amine **21** (2.87 g) in quantitative yield. The product was pure enough for continuation to the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01-1.88 (m, 4H), 2.90 (s, 1H), 3.62 (d, J = 11.2 Hz, 1H), 3.77 (d, J = 11.6 Hz, 1H), 3.84-4.04 (m, 2H), 6.82-7.06 (m, 4H), 7.08-7.22 (m, 2 H), 7.22-7.36 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.2, 31.4, 45.8, 56.3, 74.3, 80.0, 115.7, 115.9, 116.1, 130.4, 130.5, 130.6, 130.7, 138.0, 138.5, 160.8, 163.2.

(3*S*,6*S*)-6-(*Bis*(4-Fluorophenyl)methyl)-*N*-(4-nitrobenzyl)tetrahydro-2*H*-pyran-3-amine (22)

Amine **21** (60 mg, 0.20 mmol) was reacted with 4-nitro-benzaldehyde (30 mg, 0.20 mmol), glacial acetic acid (12 µL, 0.20 mmol), and $NaCNBH_3$ (19 mg, 0.30 mmol)) in 1,2-dichloroethane (6 mL) by following procedure A. The crude residue was purified by column chromatography using 20% ethyl acetate in

hexane to afford compound **22** (68 mg, 78%). $[\alpha]_D^{25}$ = (-) 63.0 (*c* 1, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.16-1.38 (m, 1H), 1.40-1.60 (m, 1H), 1.60-1.72 (m, 1H), 1.84-2.10 (m, 2H), 2.62 (s, 1H), 3.58 (d, *J* = 12 Hz, 1H), 3.76-4.06 (m, 4H), 6.82-7.06 (m, 4H), 7.12-7.38 (m, 4H), 7.50 (d, *J* = 8.4 Hz, 2 H), 8.16 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 25.7, 28.1, 50.8, 51.1, 56.3, 71.0, 80.0, 115.7, 115.8, 115.9, 116.1, 129.2, 130.4, 130.5, 130.6, 130.7, 138.0, 138.4, 149.5, 160.8, 163.8.

(3*S*,6*S*)-*N*-(4-Aminobenzyl)-6-(*bis*(4-fluorophenyl)methyl)tetrahydro-2*H*-pyran-3-amine (23a)

Compound **22** (60 mg, 2.28 mmol) in methanol (10 mL) was hydrogenated (50 psi) in the presence of 10% Pd/C (6 mg, 10 wt %) for 1 h. The reaction mixture was filtered through a short bed of Celite, and the solvent was removed under reduced pressure. The product was purified by column chromatography using 10% methanol in dichloromethane to afford compound **23** (55 mg, 99%). $[\alpha]_D^{25}$ = (-) 11.9 (*c*, CH_3OH). ^1H ($CDCl_3$, 400 MHz): *δ* 1.10-1.32 (m, 1H), 1.34-1.80 (m, 3H), 1.80-2.04 (m, 1H), 2.64 (s, 1H), 3.30-3.80 (m, 4H), 3.82-4.22 (m, 2H), 6.64 (d, *J* = 8.4, 1H), 6.82-7.02 (m, 4H), 7.07 (d, *J* = 8 Hz, 2 H), 7.10-7.20 (m, 2H), 7.22-7.38 (m, 2H). ^{13}C ($CDCl_3$, 100 MHz): *δ* 25.3, 27.7, 50.2, 50.5, 55.7, 70.5, 76.0, 79.4, 110.0, 115.2, 115.3, 115.5, 115.7, 129.4, 130.0, 130.1, 130.2, 130.3, 130.7, 137.9, 138.4, 145.5, 160.5. The product was converted into the corresponding hydrochloride salt; mp: 180-185 ^oC. Anal. ($C_{25}H_{26}F_2N_2O \cdot 2HCl \cdot 1.3H_2O$) C, H, N.

4-((((3*S*,6*S*)-6-(*Bis*(4-Fluorophenyl)methyl)tetrahydro-2*H*-pyran-3-yl)amino)methyl)phenol (23b)

Amine **21** (60 mg, 0.20 mmol) was reacted with 4-hydroxy-benzaldehyde (24 mg, 0.20 mmol),, glacial acetic acid (12 µL, 0.20 mmol), and $NaCNBH_3$ (19 mg, 0.30 mmol)) in 1,2-dichloroethane (6 mL) by following procedure A. Crude product was purified by column chromatography (methanol/dichloromethane, 0.5:9.5) to give compound **23b** (58 mg, 69%). $[\alpha]_D^{25}$ = (-) 27.8 (*c* 1, CH_3OH). ^1H ($CDCl_3$, 400 MHz): *δ* 1.28-1.40 (m, 1H), 1.40-1.56 (m, 1H), 1.60-1.78 (m, 1H), 1.94-2.14 (m, 1H), 2.73 (s, 1H), 3.48-3.72 (m, 3H), 3-88-4.14 (m, 3H), 4.60 (bs, 1H), 6.49 (d, *J* = 8.0 Hz, 2H), 6.78-7.08 (m, 5H), 7.10-7.40 (m, 5H). ^{13}C ($CDCl_3$, 100 MHz): *δ* 25.2, 27.1, 50.4, 50.6, 55.5, 70.0, 79.4, 115.3, 115.5, 115.7, 116.1, 129.8, 130.0, 130.1, 130.4, 130.5, 137.8, 140.0, 156.0, 161.2, 162.8. Free base was converted into hydrochloride salt. M.p. 118-185 ^oC. Anal. ($C_{25}H_{25}F_2NO_2$ ·HCl) C, H, N.

(3*S*,6*S*)-*N*-((1*H*-Indol-5-yl)methyl)-6-(*bis*(4-fluorophenyl)methyl)tetrahydro-2*H*-pyran-3-amine (23c)

Amine **21** (60 mg, 0.20 mmol) was reacted with 1*H*-indole-5-carbaldehyde (29 mg, 0.20 mmol), glacial acetic acid (12 µL, 0.20 mmol), and $NaCNBH_3$ (19 mg, 0.30 mmol)) in 1,2-dichloroethane (6 mL) by following procedure A. The crude residue was purified by column chromatography using 5% methanol in ethyl acetate to afford compound **23c** (59 mg, 69%). $[\alpha]_D^{25}$ = (-) 35.3 (*c* 1, CH_3OH). ^1H ($CDCl_3$, 400 MHz): *δ* 1.20-1.36 (m, 1H), 1.45-1.75 (m, 2H), 1.80-2.10 (m, 2H), 2.72 (s, 1H), 3.55 (d, *J* = 12 Hz, 1H), 3.78-4.10 (m, 4H), 6.52 (s, 1H),

6.82-7.05 (m, 4H), 7.06-7.42 (m, 6H), 7.56 (s, 2H), 8.37 (bs, 1H). ^{13}C ($CDCl_3$, 100 MHz): δ 25.3, 27.7, 50.2, 51.4, 55.7, 70.5, 79.5, 102.6, 111.3, 115.5, 115.7, 120.3, 122.9, 124.8, 128.2, 130.05, 130.1, 130.2, 130.3, 131.8, 135.2, 138.0, 138.4, 160.1, 162.5. Free base was converted into hydrochloride salt. M.p. 197-201 ^{o}C. Anal. ($C_{27}H_{26}F_2N_2O \cdot 2HCl \cdot 0.09H_2O$) C, H, N.

{6-[Bis-(4-fluoro-phenyl)-methyl]-tetrahydro-pyran-3-yl}-(2,3-dihydro-benzofuran-5-ylmethyl)-amine (23d).

Amine **21** (50 mg, 0.17 mmol) was reacted with 2,3-dihydrobenzofuran-5-carboxaldehyde (25 mg, 0.17 mmol), glacial acetic acid (11 µL, 0.17 mmol), and $NaCNBH_3$ (16 mg, 0.25 mmol)) in 1,2-dichloroethane (6 mL) by following procedure A. The crude residue was purified by column chromatography using 2% methanol in ethyl acetate to afford compound **23d** (55 mg, 76%). $[\alpha]_D^{25}$ = (-) 32.0 (*c* 1, CH_3OH). ^1H ($CDCl_3$, 400 MHz): δ 1.20-1.36 (m, 1H), 1.40-1.75 (m, 2H), 1.80-2.10 (m, 2H), 2.65 (s, 1H), 3.18 (t, *J* = 8.8 Hz, 2H), 3.53 (dd, *J* = 12.4 Hz, 1.6 Hz, 1H), 3.68 (q, *J* = 12.0 Hz, 2H), 3.90-4.08 (m, 3H), 4.56 (t, *J* = 8.0 Hz, 2H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.88-7.05 (m, 5H), 7.10-7.20 (m, 3H), 7.23-7.30 (m, 3H). ^{13}C ($CDCl_3$, 100 MHz): δ 25.6, 27.9, 50.3, 50.5, 55.7, 70.5, 76.0, 79.4, 111.0, 115.2, 115.3, 116.5, 115.7, 129.4, 130.0, 130.1, 130.2, 130.3, 130.7, 137.9, 138.4, 145.5, 160.5. Free base was converted into mesylate salt. Mp 86-89 ^{o}C. Anal. ($C_{27}H_{28}F_2NO_2S \cdot CH_3SO_3H \cdot 0.7CH_2Cl_2$) C, H, N.

(*S*)-1,1-bis(4-Fluorophenyl)pent-4-en-2-ol (**24**)

To a round bottom flask containing epoxide **10** (7.71 g, 31.32 mmol), anhydrous CuI (0.60 g, 3.14 mmol) was added under nitrogen atmosphere. The

mixture was then dissolved in anhydrous THF (80 mL) and cooled to -78 ^{o}C. Next, vinyl magnesium bromide (78.3 mL, 1 M solution in THF, 78.3 mmol) was added drop wise and the resulting reaction mixture was allowed to reach room temperature slowly and stirred for 24 h. The reaction was quenched by the addition of saturated NH_4Cl (40 mL) and water (16 mL) at 0 ^{o}C. The mixture was then extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with water (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The syrupy residue was purified by gradient silica gel column chromatography using a mixture of hexanes and ethyl acetate (10:1 to 3:1) to afford corresponding allylic alcohol **24** as a colorless syrup (7.99 g, 93%). $[\alpha]^{25}_{D}$ = (-) 19.2^{o} (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.15-7.40 (m, 4H), 6.90-7.07 (m, 4H), 5.76-5.95 (m, 1H), 4.95-5.20 (m, 2H), 4.21-4.42 (m, 1H), 3.90 (d, *J* = 7.9 Hz, 1H), 2.21-2.38 (m, 1H), 2.01-2.17 (m, 1H), 1.74 (d, *J* = 3.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 162.9, 162.8, 160.5, 160.3, 137.9, 137.8, 136.7, 130.3, 130.2, 129.7, 129.6, 118.4, 115.6, 115.4, 72.7, 55.9, 39.7.

(*S*)-4,4'-(2-(Allyloxy)pent-4-ene-1,1-diyl)bis(fluorobenzene) (**25**)

To an oven-dried round bottom flask equipped with magnetic stir bar, the allylic alcohol **24** (4.0 g, 14.58 mmol) was added and dissolved in anhydrous DMF (65 mL) under nitrogen atmosphere. The solution was then cooled to 0 ^{o}C in an ice-bath and NaH (1.28 g, 60% in mineral oil, 32.0 mmol) was added in portions. The reaction mixture was then stirred for 30 minutes until evolution of H_2 gas stopped. Next, allyl bromide (3.7 mL, 43.74 mmol) was added dropwise

and after 5 minutes the resulting reaction mixture was stirred at room temperature for 1.5 h after which TLC showed complete consumption of starting material. After cooling at 0 ^{o}C, the reaction was quenched by the addition of MeOH (5 mL) followed by water (5 mL). The reaction was diluted with water (300 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude syrup was purified by gradient silica gel column chromatography using a mixture of hexanes and ethyl acetate (20:1 to 5:1) to afford corresponding ether **25** as a colorless syrup (4.34 g, 95%). $[\alpha]^{25}_{D}$ = (+) 13.5^{o} (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.16-7.41 (m, 4H), 6.88-7.03 (m, 4H), 5.77-5.93 (m, 1H), 5.64-5.75 (m, 1H), 4.91-5.15 (m, 4H), 4.01 (d, *J* = 7.3 Hz, 1H), 3.91-3.99 (m, 2H), 3.64-3.75 (m, 1H), 2.13-2.38 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 163.0, 162.9, 160.6, 160.5, 138.6, 138.5, 137.6, 137.5, 134.9, 134.5, 134.4, 130.9, 130.8, 130.2, 130.1, 117.9, 116.9, 115.6, 115.4, 115.3, 115.1, 81.7, 71.6, 54.2, 37.0.

(*S*)-2-(Bis(4-Fluorophenyl)methyl)-3,6-dihydro-2H-pyran (**26**)

To an oven-dried round bottom flask equipped with magnetic stir bar under a flow of nitrogen, the ether **25** (4.31 g, 13.71 mmol) was added along with Grubbs catalyst (0.23 g, 0.27 mmol). Anhydrous benzene (143 mL) was then added to the flask and slowly refluxed for 2-3 h until TLC showed complete consumption of starting material. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. The black residue was purified by gradient silica gel column chromatography using a mixture of hexanes

and ethyl acetate (20:1 to 5:1) to afford corresponding olefin **26** as a white solid (3.77 g, 96%). Mp: 80-85 ^{o}C. $[\alpha]^{25}_{D}$ = (-) 52.3^{o} (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12-7.34 (m, 4H), 6.89-7.04 (m, 4H), 5.66-5.80 (m, 2H), 4.12-4.25 (m, 3H), 3.93 (d, *J* = 8.8 Hz, 1H), 1.96-2.11 (m, 1H), 1.67-1.81 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7, 162.6, 160.3, 160.2, 137.9, 137.8, 137.7, 137.6, 129.9, 129.8, 129.8, 129.7, 115.5, 115.3, 115.0, 75.2, 66.1, 55.4, 29.7.

(2*S*,4*R*,5*R*)-2-(Bis(4-Fluorophenyl)methyl)-5-bromotetrahydro-2H-pyran-4-ol (**27**)

Compound **26** (4.0 g, 13.97 mmol) was dissolved in dioxane (40 mL) and then water (40 mL) was added. The solution was then cooled to 0 ^{o}C in an ice-bath and *N*-bromoacetamide (2.89 g, 20.96 mmol) was added in portions. The resulting reaction mixture was stirred at room temperature for 4 h and then diluted with diethyl ether (100 mL). The organic layer was separated and washed with saturated $NaHCO_3$ (100 mL). The organic layer was separated and the aqueous layer was extracted with additional ditheyl ether (2 × 50 mL). The combined organic layer was washed with water (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The syrupy residue was purified by gradient silica gel column chromatography using a mixture of hexanes and ethyl acetate (10:1 to 1:1) to afford corresponding halohydrin **27** as a white solid (4.38 g, 82%). Mp: 60-65 ^{o}C. $[\alpha]^{25}_{D}$ = (-) 85.7^{o} (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (dd, *J* = 8.5, 5.6 Hz, 2H), 7.17 (dd, *J* = 8.5, 5.6 Hz, 2H), 6.89-7.05 (m, 4H), 4.44 (dt, *J* = 8.8, 1.8 Hz, 1H), 4.20 (dd, *J* = 13.5, 2.6 Hz, 1H), 3.99 (d, *J* = 9.1 Hz, 1H), 3.84-3.91 (m, 2H), 2.70 (s, 1H), 2.05-2.16 (dq, *J* = 10.6,

2.9 Hz, 1H), 1.35-1.67 (d, *J* = 14.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 162.7, 162.6, 160.3, 162.2, 137.5, 137.4, 137.2, 137.1, 129.9, 129.8, 129.7, 129.7, 115.5, 115.3, 115.2, 115.0, 73.8, 68.1, 67.0, 54.6, 49.9, 31.9.

(1*S*,4*S*,6*S*)-4-(Bis(4-Fluorophenyl)methyl)-3,7-dioxabicyclo[4.1.0]heptane (**28**)

The halohydrin **27** (4.38 g, 11.43 mmol) was taken into a round bottom flask equipped with magnetic stir bar and dissolved in dioxane (35 mL). After cooling the solution to 0 ^{o}C, 20% NaOH solution (35 mL) was added. The resulting reaction mixture was stirred for 30 minutes at room temperature and TLC showed complete consumption of starting material. The reaction mixture was then diluted with water (100 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with water (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The solid residue was purified by gradient silica gel column chromatography using a mixture of hexanes and ethyl acetate (10:1 to 1:1) to afford corresponding *trans*-epoxide **28** as a white solid (3.11 g, 90%). Mp: 110-115 ^{o}C. $[\alpha]^{25}_{D}$ = (-) 44.7^{o} (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.20 (dd, *J* = 8.5, 5.6 Hz, 2H), 7.11 (dd, *J* = 8.5, 5.6 Hz, 2H), 6.87-7.02 (m, 4H), 4.19 (dd, *J* = 13.8, 4.1 Hz, 1H), 4.02 (dq, *J* = 8.8, 2.4 Hz, 1H), 3.91 (d, *J* = 13.5 Hz, 1H), 3.78 (d, *J* = 8.5 Hz, 1H), 3.32 (s, 1H), 3.24 (t, *J* = 4.1 Hz, 1H), 1.86 (d, *J* = 14.7 Hz, 1H), 1.66 (dd, *J* = 14.4, 11.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 162.8, 162.7, 160.3, 160.2, 137.4, 137.3, 137.3, 137.2, 129.9, 129.8, 129.7, 129.6, 115.5, 115.3, 115.2, 115.0, 71.6, 65.9, 55.2, 51.0, 30.1.

(2*S*,4*R*,5*R*)-5-Azido-2-(bis(4-fluorophenyl)methyl)tetrahydro-2H-pyran-4-ol (**29**)

The *trans*-epoxide **28** (2.65 g, 8.77 mmol) was taken in a round bottom flask equipped with magnetic stir bar and dissolved in a 8:1 mixture of methanol/water (95 mL). Sodium azide (2.85 g, 43.83 mmol) and ammonium chloride (0.94 g, 17.54 mmol) were added to the solution. The resulting reaction mixture was refluxed at 80 ^{o}C for 24 h and then cooled to room temperature. The reaction was then diluted with water (100 mL) and extracted with ethyl acetate (3 ×40 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by gradient silica gel column chromatography using a mixture of hexanes and ethyl acetate (8:1 to 1:3) to afford corresponding azido compound **29** as white syrup (2.91 g, 96%). $[\alpha]^{25}_{D}$ = (-) 87.3^{o} (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.27 (dd, *J* = 7.9, 5.3 Hz, 2H), 7.15 (dd, *J* = 7.9, 5.3 Hz, 2H), 6.95 (dd, *J* = 16.4, 7.9 Hz, 4H), 4.38 (t, *J* = 9.9 Hz, 1H), 3.79-4.04 (m, 4H), 3.26 (s, 1H), 1.99 (s, 1H), 1.75 (dq, *J* = 11.1, 2.6 Hz, 1H), 1.42 (d, *J* = 14.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 162.8, 162.7, 160.3, 160.2, 137.4, 137.3, 137.2, 137.1, 129.9, 129.8, 129.7, 129.6, 115.6, 115.4, 115.3, 115.0, 73.3, 65.9, 64.5, 59.1, 55.0, 33.1.

(2*S*,4*R*,5*R*)-5-Amino-2-(bis(4-fluorophenyl)methyl)tetrahydro-2H-pyran-4-ol (**30**)

The azido compound **29** (2.54 g, 7.36 mmol) was dissolved in methanol (50 mL) and hydrogenated on a Parr apparatus in the presence of 10% Pd/C

(0.25 g) at 30 psi. The reaction mixture was then filtered through a short bed of celite and the filtrate was concentrated under reduced pressure to obtain the amine **30** (2.51 g, 98%) as off-white solid. $[\alpha]^{25}_{D}$ = (-) 45.6^{o} (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.27 (dd, *J* = 9.1, 5.6 Hz, 2H), 7.16 (dd, *J* = 8.5, 5.6 Hz, 2H), 6.85-7.03 (m, 4H), 4.38 (dt, *J* = 8.5, 1.8 Hz, 1H), 3.98(dd, *J* = 11.7, 1.5 Hz, 1H), 3.88 (d, *J* = 8.8 Hz, 1H), 3.81 (d, *J* = 2.6 Hz, 1H), 3.59 (d, *J* = 11.4 Hz, 1H), 2.63 (s, 1H), 1.69 (dq, *J* = 10.9, 2.6 Hz, 1H), 1.39 (d, *J* = 14.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 163.0, 162.9, 160.6, 160.5, 140.0, 137.9, 137.7, 137.6, 130.2, 130.1, 130.0, 129.9, 115.8, 115.6, 115.5, 115.4, 74.0, 69.2, 68.5, 55.3, 51.3, 32.9.

(2*S*,4*R*,5*R*)-2-(bis(4-Fluorophenyl)methyl)-5-((4-hydroxybenzyl)amino)tetrahydro-2H-pyran-4-ol (**31a**)

Amine **30** (60 mg, 0.19 mmol) was reacted with 4-hydroxy-benzaldehyde (24 mg, 0.20 mmol), glacial acetic acid (13 µL, 0.22 mmol), and $NaCNBH_3$ (18 mg, 0.29 mmol) in 1,2-dichloroethane (6 mL) by following procedure A. The residue was purified by gradient silica gel column chromatography using a mixture of dichloromethane and methanol (20:1 to 6:1) to afford corresponding compound **31a** as colorless syrup (60 mg, 75%). $[\alpha]^{25}_{D}$ = (-) 46.5^{o} (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.21 (dd, *J* = 8.2, 5.6 Hz, 2H), 7.08 (dd, *J* = 8.2, 5.3 Hz, 2H), 7.01 (d, *J* = 7.9 Hz, 2H), 6.91 (dt, *J* = 19.6, 8.5 Hz, 4H), 6.54 (d, *J* = 7.9 Hz, 2H), 4.89 (br s, 1H), 4.40 (t, *J* = 8.8 Hz, 1H), 4.03 (s, 1H), 3.66-3.98 (m, 4H), 3.61 (d, *J* = 12.6 Hz, 1H), 2.54 (s, 1H), 1.61-179 (m, 1H), 1.42 (d, *J* = 12.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 162.7, 162.6, 160.3, 160.2, 155.9, 137.5,

137.4, 137.3, 137.2, 130.0, 129.9, 129.8, 129.7, 129.6, 128.4, 115.8, 115.6, 115.4, 115.3, 115.1, 73.8, 65.8, 63.5, 56.1, 54.6, 50.2, 32.9. The free base was converted into the corresponding hydrochloride salt; mp: 210-225 ^{o}C. Anal. ($C_{25}H_{25}F_2NO_3 \cdot 1.17HCl \cdot H_2O$) C, H, N.

(2*S*,4*R*,5*R*)-5-(((1H-Indol-5-yl)methyl)amino)-2-(bis(4-fluorophenyl)methyl)tetrahydro-2H-pyran-4-ol (**31b**)

Amine **30** (60 mg, 0.19 mmol) was reacted with Indole-5-carbaldehyde (29 mg, 0.20 mmol), glacial acetic acid (13 µL, 0.22 mmol), and $NaCNBH_3$ (18 mg, 0.29 mmol) in 1,2-dichloroethane (6 mL) by following procedure A. The residue was purified by gradient silica gel column chromatography using a mixture of dichloromethane and methanol (20:1 to 6:1) to afford corresponding compound **31b** as colorless syrup (73 mg, 87%). $[\alpha]^{25}_{D}$ = (-) 46.0^{o} (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.57 (s, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.06-7.34 (m, 6H), 6.94 (dd, *J* = 17.6, 8.8 Hz, 4H), 6.50 (d, *J* = 2.9 Hz, 1H), 4.43 (t, *J* = 10.0 Hz, 1H), 3.89-4.12 (m, 4H), 3.80 (d, *J* = 12.9 Hz, 1H), 3.05 (br s, 1H), 2.84 (s, 1H), 1.61-179 (m, 1H), 1.42 (d, *J* = 14.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 162.7, 162.6, 160.3, 160.2, 137.4, 137.3, 137.1, 137.0, 135.9, 129.8, 129.7, 129.6, 129.5, 128.0, 125.7, 125.6, 122.8, 122.6, 121.9, 115.5, 115.3, 115.2, 115.0, 112.0, 102.1, 74.1, 63.5, 62.3, 55.5, 54.5, 50.7, 32.5. The free base was converted into the corresponding hydrochloride salt. Mp: 200-215 ^{o}C. Anal. ($C_{27}H_{26}F_2N_2O_2 \cdot 2HCl \cdot 0.6H_2O$) C, H, N.

In vitro experiments:

Monoamine transport inhibition

The ability of test compounds to inhibit substrate uptake by rat monoamine transporters was monitored as described by us previously[23, 24] with minor modifications. A detailed description of our protocols can be found in ref. 24, and the following modifications were introduced in the present work: [^{3}H]dopamine was used instead of [^{3}H]norepinephrine for monitoring uptake by rat NET in cerebral cortex; incubation times (all in linear phase of uptake) were 5 min for DAT, 10 min for SERT, and 7 min for NET; and drug stocks contained an additional 0.01% (w/v) bovine serum albumin in order to reduce absorption of drug to the walls of the assay plates. Otherwise the details were as in ref. 24. At least five triplicate concentrations of each test compound were studied, spaced evenly around the IC_{50} value. The latter was estimated by nonlinear computer curve-fitting procedures and converted to K_i with the Cheng-Prusoff equation as we described previously.[33] With observed K_m values and [^{3}H]ligand concentrations used, the conversion factors (multipliers applied to IC_{50} for calculating K_i) were $\geq$ 0.84. The use of [^{3}H]DA instead of [^{3}H]norepinephrine for rat NET greatly reduced nonspecific uptake; it is well established that DA is an excellent substrate for NET, both in cells with cloned transporters [34-36] and in rat tissue[37-39]; and control experiments with a number of test compounds did not detect significant differences between K_i values obtained with [^{3}H]dopamine and [^{3}H]norepinephrine.

In vivo experiments:

Animals

Male Sprague-Dawley rats (200-225 g) were purchased from Harlan. Animals were housed in a temperature and humidity controlled room with 12 h light /dark cycle. Food and water were accessible to animals freely through out the duration of study. All testing occurred during the light component. All animal procedures were reviewed and approved by Wayne State University animal investigation committee consistent with AALAC guidelines.

Effect of compound 2g in the rat forced swimming test as a measure of its antidepressant property

The subjects were male Swiss Sprague Dawley rats (Harlam Sprague Dawley Inc., Indianapolis, IN, USA) weighing 200-225 g housed in cages for at least 1 week prior to testing. Animals were maintained in a temperature-controlled environment under a 12 h light-dark cycle. All subjects were naive and used only once.

Rats were transported to the testing room at least for 1 h prior to testing for acclimatization and adaptation purposes. Experimental sessions were conducted between 9 AM to 2 PM daily. Animals were assigned randomly and were placed individually in a glass cylinder (24.5 cm X 35.5 cm) filled with water at room temperature to a depth of 22 cm. All the test sessions were recorded by a video camera. The water was changed in the beginning of each session and the temperature was maintained constant at 24-25 ^{o}C. Rats were judged to be immobile if making minimum movement to barely keep afloat.

The procedure consisted of a pretest and a test session separated by 24 h. [29] During the pretest period, rats were placed in the swim chamber for 15 min.

Followed by the initial swim exposure; rats were patted dry and were transferred to the individual cages. Drugs or vehicle were then administered (i.p.) 15 min after the initial swim exposure and were then transported to their home cages. On the following day the rats were brought back to the testing room at least 1 h before the beginning of test session. Rats were administered either drugs or vehicle 1 h before the swim test. Each rat underwent a 5 min swim session, which was videotaped and scored later. In the case of imipramine, pretreatment time was 30 min.

All drugs were prepared freshly on the test days. Compound **2g** and imipramine were dissolved in **5** % β-hydroxypropyl cyclodextrin solution. All drugs and vehicles were administered i.p. **2g** was administered at a dose of 10 mg/kg and the volume of injections was maintained at 2 mL/ kg. Imipramine was administered at 15 mg/kg. All drugs and vehicles were administered 1 h prior to testing for FST. Imipramine was administered 30 min prior testing. An individual, blinded to the treatment, scored the videotapes for immobility. Immobility scores were analyzed by one way ANOVA test.

Effect of compound 2g on Locomotor Activity

Sprague Dawley Rats were tested at 10 mg/kg doses of **2g** to evaluate changes of any locomotor activity in acrylic Versamax monitor chambers (AccuScan Instrument, Inc; Columbus, Ohio). The purpose behind this study was to evaluate locomotor activity of the doses of drug, which was used in forced swim and tail suspension tests. Rats were acclimated in the test chambers for 2 h prior to administration of drugs. Locomotor activity of the drugs were measured

for one and a half an hour post administration of drug which corresponded to the time of measurement in the forced swimming experiment.

Table 1. Elemental Analysis of target compounds

Compound	Elemental Analysis					
	Calculated			Found		
	C	H	N	C	H	N
D-405 (2a)	70.31	7.17	3.04	70.18	7.09	3.09
D-406 (2b)	63.64	6.45	5.71	63.63	6.39	5.64
D-422 (2c)	74.38	6.94	3.21	74.08	7.02	3.19
D-453 (2d)	68.19	6.78	3.18	68.21	6.78	3.21
D-454 (2e)	71.30	6.44	3.20	71.03	6.23	3.28
D-445 (2f)	72.12	7.22	3.23	72.44	7.15	3.24
D-408 (2g)	63.48	6.18	5.92	63.51	6.14	5.97
D-407 (2h)	71.23	6.46	3.32	71.01	6.54	3.26
D-446 (4a)	67.45	6.31	3.03	67.54	6.39	3.01
D-447 (4b)	67.91	6.79	3.17	67.80	6.89	3.23
D-448 (4c)	65.03	6.59	3.03	65.04	6.80	2.91
D-455 (4d)	69.80	6.81	3.01	69.83	6.88	3.02
D-456 (4e)	60.35	6.35	5.41	60.44	6.45	5.18
D-457 (4f)	59.22	6.16	5.52	59.19	6.40	5.32

D-451 (23a)	59.48	6.11	5.55	59.37	6.04	5.54
D-449 (23b)	67.34	5.88	3.14	67.14	5.93	3.10
D-450 (23c)	63.96	5.60	5.52	63.66	6.01	5.39
D-478 (23d)	58.32	5.53	2.37	58.25	5.94	2.37
D-471 (31a)	61.77	5.84	2.88	61.06	5.65	2.95
D-472 (31b)	60.93	5.53	5.26	60.76	5.72	5.22