Piperidine-Based Nocaine/Modafinil Hybrid Ligands as Highly Potent Monoamine Transporter Inhibitors: Efficient Drug Discovery by Rational Lead Hybridization

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Supporting Information

Supporting Information: Contains experimental details, spectra data and Table of ClogP data for all new compounds.

Experimental Section

NMR spectra were recorded on a Varian Unity Inova spectrometer at 300 MHz for proton and 75.46 MHz for carbon-13 spectra. $CDCl_3$ was used as solvent unless noted otherwise. Chemical shifts are reported in ppm relative to internal TMS. Thin-layer chromatography was performed using Merck silica gel 60F-254 plates. Column chromatography was performed using Merck silica gel (60-200 mesh). Mass spectra were measured in the EI mode at an ionization potential of 70 eV. Starting materials were obtained from Aldrich, Alfa Aesar or Acros. Solvents were obtained from Fisher Scientific or VWR and were used without further purification unless otherwise noted. DMF (DriSolv grade) was obtained from EM Science. The combustion analyses of some compounds that had to be recovered from their $CDCl_3$ solutions because of small sample size indicate the presence of fractional amounts of HCl which must be derived from the solvent.

(+)-(3*R*,4*S*)-4-(4-Chlorophenyl)-3-(hydroxymethyl)-1-methylpiperidine (4). To a solution of (3*R*,4*S*)-4-(4-chlorophenyl)-1-methylpiperidine-3-carboxylic acid methyl ester (2.0 g, 6.57 mmol) in anhydrous THF (40 mL) that was cooled to 0 °C was added $LiAlH_4$ (374 mg, 9.86 mmol). The resulting mixture was warmed to room temperature and stirred overnight, then quenched with a saturated solution of NH_4Cl (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4, concentrated and purified by column chromatography on silica gel with EtOAc/MeOH/Et_3N (8:1:1) as the eluent to yield the product as a white solid (1.45 g, 92%): $[\alpha]^{25}_D$ +27.1° (*c* 0.38, $CHCl_3$); ^{1}H NMR δ 1.69-1.82 (m, 2 H), 1.87 (dd, *J* = 10.5, 10.8 Hz, 1 H), 1.90-2.03 (m, 2 H), 2.24 (td, *J* = 6.3, 10.1 Hz, 1 H), 2.29 (s, 3 H), 2.84-2.94 (m, 1 H), 3.14 (dd, *J* = 7.2, 11.1 Hz, 2 H), 3.34 (dd, *J* = 2.7, 11.0 Hz, 1 H), 3.51 (br s, 1 H), 7.09 (d, *J* = 8.4 Hz, 2 H), 7.22 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR δ 34.3, 43.9, 44.1, 46.6, 56.2, 59.5, 63.3, 128.8, 128.9, 132.1, 142.9; MS *m/z* (%) 239 (M^+, 11), 208 (12), 183 (3), 125 (8), 115 (14), 100 (100).

(+)-(3*R*,4*S*)-4-(4-Chlorophenyl)-3-(iodomethyl)-1-methylpiperidine (5). To a solution of PPh_3 (2.41 g, 9.18 mmol) in anhydrous CH_2Cl_2 (60 mL) was added iodine (2.33 g, 9.18 mmol) under nitrogen at room temperature. After stirring at room temperature for 15 min, imidazole (0.71 g, 10.43 mmol) was added in one portion, followed by the addition of the alcohol (1.0 g, 4.17 mmol) dissolved in 20 mL of CH_2Cl_2 at room temperature. The resulting mixture was then heated to reflux for 2.5 h. After cooling to room temperature, the reaction mixture was washed with 5% aqueous sodium thiosulfate solution to remove the excess of iodine. The organic phase was dried over Na_2SO_4, concentrated and purified by column chromatography on silica gel first with EtOAc (to remove triphenylphosphine oxide) and then with EtOAc/Et_3N (98/2 to 95/5) as the eluent to provide the product as a colorless oil (1.25 g, 86%): $[\alpha]^{25}_D$ +56.4° (*c* 0.28, $CHCl_3$);

^{1}H NMR δ 1.66-1.82 (m, 2 H), 1.84-2.01 (m, 2 H), 2.08 (td, J = 3.0, 13.2 Hz, 1 H), 2.29 (td, J = 4.5, 11.3 Hz, 1 H), 2.38 (s, 3 H), 2.75 (dd, J = 6.9, 10.1 Hz, 1 H), 2.90-2.98 (m, 1 H), 3.04 (dd, J = 2.7, 12.9 Hz, 1 H), 3.08-3.17 (m, 1 H), 7.17 (d, J = 8.4 Hz, 2 H), 7.28 (d, J = 8.7 Hz, 2 H); ^{13}C NMR δ 10.7, 33.8, 41.4, 46.1, 46.6, 55.9, 61.9, 128.8 (2 overlapping signals), 132.2, 141.4; MS *m/z* (%) 349 (M^+, 14), 222 (100), 151 (8), 125 (16), 115 (44); Anal. Calcd for $C_{13}H_{17}ClIN \cdot 0.75H_2O$: C, 43.00; H, 5.13; N, 3.86. Found: C, 42.72; H, 4.75; N, 3.89.

(+)-2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]methylsulfanyl]acetic Acid Methyl Ester (6). To a solution of the above iodide (617 mg, 1.76 mmol) in anhydrous MeCN (20 mL) was added 316 μL of methyl thioglycolate (374 mg, 3.52 mmol) under nitrogen at room temperature, followed by cesium carbonate (1.43 g, 4.40 mmol). After stirring at room temperature overnight, the solvent was evaporated, and the residue was partitioned between CH_2Cl_2 and H_2O (20 mL each). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by column chromatography on silica gel using EtOAc/Et_3N (98/2 to 10/1) as the eluent to afford the product as a colorless oil (505 mg, 88%): R_f(EtOAc/Et_3N 10/1) 0.41; R_f(EtOAc/MeOH/Et_3N 8/1/1) 0.63; $[\alpha]^{25}_D$ +97.8° (*c* 0.27, $CHCl_3$); ^{1}H NMR δ 1.74-1.84 (m, 3 H), 1.96-2.28 (m, 4 H), 2.34 (s, 3 H), 2.50 (dd, J = 2.4, 7.5 Hz, 1 H), 2.92-2.97 (m, 1 H), 3.06 (q, J = 14.7, 18.0 Hz, 2 H), 3.22-3.28 (m, 1 H), 3.60 (s, 3 H), 7.12 (d, J = 8.4 Hz, 2 H), 7.27 (d, J = 8.7 Hz, 2 H); ^{13}C NMR δ 33.7, 34.5, 34.7, 41.0, 46.3, 46.9, 52.1, 56.0, 60.6, 128.6, 128.8, 132.0, 142.2, 170.4; MS) *m/z* (%) 327 (M^+, 14), 254 (100), 222 (42), 208 (33), 125 (19), 116 (40), 115 (37); Anal. Calcd for $C_{16}H_{22}ClNO_2S \cdot 0.1H_2O$: C, 58.29; H, 6.79; N, 4.25. Found: C, 58.19; H, 6.61; N, 4.23.

(+)-2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]methanesulfinyl]acetic Acid Methyl Ester (7). To a solution of compound **6** (44.0 mg, 0.134 mmol) in acetic acid (2.0 mL) was added 35% H_2O_2 (14 μL) at room temperature. After stirring at room temperature for 2.5 h, the solvent was evaporated under vacuum. The crude product was purified by preparative TLC using EtOAc/Et_3N (10/1) as the developing solvent to afford the product as a white solid (37 mg, 80%): R_f(EtOAc/Et_3N 10/1) 0.21; $[\alpha]^{25}_D$ +67.8° (*c* 0.80, $CHCl_3$); ^{1}H NMR δ 1.80-1.94 (m, 2 H), 1.96-2.14 (m, 3 H), 2.26-2.41 (m, 1 H), 2.35 and 2.36 (each s, ratio 1:1, total 3 H), 2.46-2.66 (m, 2 H), 2.94-3.04 (m, 1 H), 3.26-3.36 (m, 1 H), 3.40-3.64 (m, 2 H), 3.67 and 3.68 (each s, ratio 1:1, total 3 H), 7.13 (dd, J = 1.2, 8.4 Hz, 2 H), 7.29 (dd, J = 1.5, 8.4 Hz, 2 H); ^{13}C NMR δ 34.2, 34.7 (1 C), 36.7, 39.1 (1 C), 46.1 (1 C), 47.1, 47.5 (1 C), 52.8 (1 C), 55.6, 55.7 (1 C), 55.8, 55.9 (1 C), 56.1, 56.4 (1 C), 60.4, 61.1 (1 C), 129.0 (1 C), 129.1 (1 C), 132.6, 132.7 (1 C), 141.3, 141.4 (1 C), 165.1, 165.3 (1 C); MS *m/z* (%) 326 (M^+ - 17, 48), 270 (9), 238 (11), 220 (100), 188 (19), 128 (14), 125 (20), 115 (48), 103 (12). HRMS-FAB calcd for $C_{16}H_{23}ClNO_3S$ ($M + H^+$) 344.1087; found 344.1093; Anal. Calcd for $C_{16}H_{22}ClNO_3S \cdot 0.5H_2O$: C, 54.46; H, 6.57; N, 3.97. Found: C, 54.42; H, 6.33; N, 3.95.

(+)-2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]methylsulfanyl]ethanol (8). To a solution of compound **6** (271 mg, 0.827 mmol) in anhydrous THF (10 mL) that was cooled to 0 °C was added $LiAlH_4$ (47.1 mg, 1.24 mmol). The resulting mixture was warmed to room temperature and stirred overnight, then quenched with a saturated solution of NH_4Cl (10 mL). The solution was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4, concentrated and purified by column chromatography on silica gel with EtOAc/Et_3N (10:1) to EtOAc/MeOH/Et_3N (8:1:1) as the eluent to yield the product as a colorless oil (203 mg, 82%): R_f(EtOAc/Et_3N 10/1) 0.27; $[\alpha]^{25}_D$ +81.6° (*c* 0.26, $CHCl_3$); ^{1}H NMR δ 1.64-

1.80 (m, 3 H), 1.90-2.04 (m, 3 H), 2.12-2.32 (m, 1 H), 2.25 (s, 3 H), 2.29-2.36 (m, 1 H), 2.46 (t, J = 5.4 Hz, 2 H), 2.82-2.87 (m, 1 H), 3.17-3.22 (m, 1 H), 3.14-3.52 (m, 2 H), 3.70 (br s, 1 H), 7.04 (d, J = 8.7 Hz, 2 H), 7.18 (d, J = 8.4 Hz, 2 H); ^{13}C NMR δ 33.9, 34.1, 35.5, 41.2, 46.1, 46.7, 55.9, 60.1, 60.4, 128.6, 128.7, 132.0, 142.2; MS *m/z* (%) 299 (M^+, 27), 254 (100), 222 (72), 208 (99), 188 (14), 174 (22), 125 (31), 115 (64), 111 (31); Anal. Calcd for $C_{15}H_{22}ClNOS \cdot 0.2H_2O$: C, 59.37; H, 7.44; N, 4.62. Found: C, 59.38; H, 7.38; N, 4.34.

(+)-2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)-1-methyl-piperidin-3-yl]methanesulfinyl]ethanol (9). To a solution of alcohol **8** (63 mg, 0.21 mmol) in acetic acid (2.0 mL) was added 35% H_2O_2 (20.8 μL) at room temperature. After stirring at room temperature for 2.5 h, the solvent was evaporated under vacuum. The crude product was purified by preparative TLC on silica gel using EtOAc/MeOH/Et_3N (8/1/1) as the developing solvent to afford the product as a colorless oil (46 mg, 69%): R_f(EtOAc/MeOH/Et_3N 8/1/1) 0.26; $[\alpha]^{25}_D$ +74.4° (*c* 0.31, $CHCl_3$); ^{1}H NMR δ 1.72-1.84 (m, 2 H), 1.89-2.09 (m, 2 H), 2.29 and 2.30 (each s, ratio 1:1, total 3 H), 2.19-2.35 (m, 2 H), 2.38-2.56 (m, 2 H), 2.58-2.67 (m, 1 H), 2.69-2.87 (m, 1 H), 2.88-2.96 (m, 1 H), 3.26-3.36 (m, 1 H), 3.84-4.01 (m, 2 H), 4.39 (br s, 1 H), 7.06 (dd, J = 2.1 and 8.7 Hz, 2 H), 7.22 (dd, J = 3.0, 8.4 Hz, 2 H); ^{13}C NMR δ 34.2, 34.6 (1 C), 36.7, 38.9 (1 C), 46.2, 46.3 (1 C), 47.2, 47.6 (1 C), 54.8 (1 C), 55.5, 55.7 (1 C), 55.8, 55.9 (1 C), 56.0, 56.1 (1 C), 60.6, 61.1 (1 C), 129.1, 129.2 (1 C), 129.3 (1 C), 132.8, 132.9 (1 C), 141.4, 141.5 (1 C); MS *m/z* (%) 298 (M^+ - 17, 100), 264 (12), 238 (38), 220 (70), 206 (18), 160 (55), 125 (28), 115 (52), 103 (10); Anal. Calcd for $C_{15}H_{22}ClNO_2S \cdot 3/4HCl$: C, 52.49; H, 6.68; N, 4.08. Found: C, 52.57; H, 6.85; N, 3.86.

(+)-(3*R*,4*S*)-4-(4-Chlorophenyl)-3-[(2-methoxyethylsulfanyl)methyl]-1-methylpiperidine (10). To a solution of alcohol **8** (153 mg, 0.51 mmol) in anhydrous THF (6 mL) was added NaH (43 mg, 57-63% suspension in oil, 1.02 mmol) under nitrogen at 0 °C. After stirring for 10 min,

MeI (38 μL, 0.61 mmol) was added dropwise, followed by tetra-*n*-butylammonium iodide (19 mg, 0.051 mmol). After stirring at room temperature overnight, the reaction was quenched with aqueous NH_4Cl solution, and the mixture was extracted with EtOAc (3 × 25 mL). The combined extracts were washed with 5% aqueous sodium thiosulfate solution, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by column chromatography on silica gel using EtOAc/Et_3N (98/2 to 10/1) as the eluent to afford the product as a colorless oil (104 mg, 65%): R_f(EtOAc/Et_3N 10/1) 0.44; R_f(EtOAc/MeOH/Et_3N 8/1/1) 0.68; $[\alpha]^{25}_D$ +84.6° (*c* 0.46, $CHCl_3$); ^{1}H NMR δ 1.65-1.76 (m, 3 H), 1.88-2.05 (m, 3 H), 2.13-2.23 (m, 1 H), 2.27 (s, 3 H), 2.34 (dd, J = 1.8, 12.0 Hz, 1 H), 2.44 (t, J = 6.6 Hz, 2 H), 2.82-2.91 (m, 1 H), 3.19 (s, 3 H), 3.22-3.34 (m, 3 H), 7.05 (d, J = 8.7 Hz, 2 H), 7.20 (d, J = 8.7 Hz, 2 H); ^{13}C NMR δ 32.1, 34.7 (2 C overlapping), 41.8, 46.6, 47.1, 56.3, 58.8, 60.9, 71.9, 128.9, 129.1, 132.2, 142.8; MS (EI) *m/z* (%) 313 (M^+, 28), 254 (81), 222 (65), 208 (100), 125 (32), 116 (56), 111 (28); Anal. Calcd for $C_{16}H_{24}ClNOS \cdot 1/5HCl$: C, 59.83; H, 7.59; N, 4.36. Found: C, 59.87; H, 7.38; N, 4.08.

(+)-(3*R*,4*S*)-4-(4-Chlorophenyl)-3-[(2-methoxyethanesulfinyl)methyl]-1-methyl-piperidine (11). To a solution of the ether **10** (56.0 mg, 0.178 mmol) in acetic acid (2.0 mL) was added 35% H_2O_2 (17.6 μL) at room temperature. After stirring at room temperature for 2.5 h, the solvent was evaporated under vacuum. The crude product was purified by preparative TLC using EtOAc/Et_3N (10/1) as the developing solvent to afford the product as a colorless oil (36 mg, 61%): R_f(EtOAc/Et_3N 10/1) 0.28; $[\alpha]^{25}_D$ +80.8° (*c* 0.37, $CHCl_3$); ^{1}H NMR δ 1.72-1.82 (m, 2 H), 1.84-2.04 (m, 2 H), 2.27 (s, 3 H), 2.18-2.30 (m, 2 H), 2.38-2.78 (m, 4 H), 2.84-2.94 (m, 1 H), 3.20 and 3.22 (each s, ratio 1:1, total 3 H), 3.24-3.32 (m, 1 H), 3.52-3.68 (m, 2 H), 7.06 (dd, J = 1.8, 8.4 Hz, 2 H), 7.21 (dd, J = 1.8, 8.4 Hz, 2 H); ^{13}C NMR δ 34.5, 35.0 (1 C), 37.0, 39.6 (1 C),

46.4, 46.5 (1 C), 47.4, 47.7 (1 C), 53.2, 53.3 (1 C), 55.7, 56.0 (1 C), 56.0, 56.1 (1 C), 59.1 (1 C), 60.8, 61.4 (1 C), 64.7, 64.9 (1 C), 129.1, 129.2 (1 C), 129.2, 129.3 (1 C), 132.6, 132.7 (1 C), 141.8, 141.9 (1 C); MS *m/z* (%) 312 (M^+ - 17, 100), 278 (30), 238 (41), 220 (93), 206 (17), 186 (29), 174 (32), 125 (19), 115 (40); Anal. Calcd for $C_{16}H_{24}ClNO_2S \cdot 1/3HCl$: C, 56.18; H, 7.17; N, 4.10. Found: C, 56.30; H, 7.02; N, 3.89.

(+)-Acetic Acid 2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]methylsulfanyl] ethyl Ester (12). To a solution of the alcohol **8** (92.0 mg, 0.307 mmol) in pyridine (8 mL) was added 2.0 mL of Ac_2O under nitrogen at room temperature, followed by 1.0 mg of 4-(dimethylamino)pyridine (DMAP). After stirring at room temperature for 2 h, the solvent was evaporated, and the residue was diluted with ethyl acetate and washed with saturated $NaHCO_3$ aqueous solution (2 × 15 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by preparative TLC using EtOAc/Et_3N (10/1) as the developing solvent to afford the acetate as a colorless oil (74 mg, 70%): R_f(EtOAc/ Et_3N 10/1) 0.57; $[\alpha]^{25}_D$ +83.0° (*c* 0.54, $CHCl_3$); ^1H NMR δ 1.73-1.83 (m, 3 H), 1.96-2.10 (m, 3 H), 2.01 (s, 3 H), 2.18-2.30 (m, 1 H), 2.34 (s, 3 H), 2.42 (dd, J = 1.5, 10.2 Hz, 1 H), 2.56 (t, J = 6.9 Hz, 2 H), 2.90-2.96 (m, 1 H), 3.23-3.29 (m, 1 H), 3.96-4.08 (m, 2 H), 7.13 (d, J = 8.4 Hz, 2 H), 7.27 (d, J = 8.4 Hz, 2 H); ^{13}C NMR δ 21.0, 31.2, 34.8 (2 C overlapping), 41.8, 46.6, 47.2, 56.3, 60.9, 63.5, 129.0, 129.1, 132.4, 142.7, 170.9; MS *m/z* (%) 341 (M^+, 11), 282 (15), 254 (84), 222 (100), 208 (39), 188 (10), 151 (13), 125 (43), 115 (90), 111 (34), 103 (24); Anal. Calcd for $C_{17}H_{24}ClNO_2S \cdot 0.5HCl$: C, 56.70; H, 6.86; N, 3.89. Found: C, 57.02; H, 6.54; N, 3.80.

(+)-Acetic Acid 2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]methanesulfinyl] ethyl Ester (13). To a solution of the ester **12** (28.0 mg, 0.0819 mmol) in acetic acid (1.0 mL)

was added 35% H_2O_2 (9 μL) at room temperature. After stirring at room temperature for 2.5 h, the solvent was evaporated under vacuum. The crude product was purified by preparative TLC using EtOAc/Et_3N (10/1) as the developing solvent to afford the product as a colorless oil (18.0 mg, 82%); in addition, 7.0 mg of starting material was recovered: R_f(EtOAc/Et_3N 10/1) 0.17; $[\alpha]^{25}_D$ +74.0° (*c* 0.27, $CHCl_3$); ^{1}H NMR δ 1.80-1.87 (m, 2 H), 1.89-2.12 (m, 3 H), 2.01 (s, 3 H), 2.20-2.38 (m, 1 H), 2.35 (s, 3 H), 2.43-2.64 (m, 2 H), 2.68-2.80 (m, 2 H), 2.94-2.99 (m, 1 H), 3.31-3.36 (m, 1 H), 4.28-4.48 (m, 2 H), 7.12 (d, J = 8.4 Hz, 2 H), 7.28 (dd, J = 2.7, 8.4 Hz, 2 H); ^{13}C NMR δ 20.9 (1 C), 34.5, 35.1 (1 C), 37.0, 39.4 (1 C), 46.4, 46.5 (1 C), 47.5, 47.9 (1 C), 51.9, 52.1 (1 C), 55.8, 56.0 (1 C), 56.1 (1 C), 57.1, 57.3 (1 C), 60.8, 61.5 (1 C), 129.1 (1 C), 129.2, 129.3 (1 C), 132.8, 132.9 (1 C), 141.7, 141.8 (1 C), 170.7 (1 C); MS *m/z* (%) 340 (M^+ - 17, 97), 238 (52), 220 (100), 202 (56), 151 (13), 125 (42), 115 (86), 103 (51); Anal. Calcd for $C_{17}H_{24}ClNO_3S \cdot 1/6H_2O$: C, 56.58; H, 6.80; N, 3.88. Found: C, 56.60; H, 6.60; N, 3.58.

(+)-Benzoic Acid 2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]methyl sulfanyl]ethyl Ester (14). To a solution of alcohol **8** (89.0 mg, 0.297 mmol) in anhydrous THF (8 mL) were added Et_3N (83 μL) and DMAP (1.0 mg) under nitrogen at 0 °C, followed by benzoyl chloride (52 μL, 63 mg, 0.45 mmol). After stirring at 0 °C to room temperature overnight, the solvent was evaporated, and the residue was diluted with ethyl acetate and washed with saturated aqueous $NaHCO_3$ solution (2 × 10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by preparative TLC using EtOAc/Et_3N (10/1) as the developing solvent to afford the benzoate as a colorless oil (81 mg, 68%):%): R_f(EtOAc/Et_3N 10/1) 0.51; $[\alpha]^{25}_D$ +63.7° (*c* 0.33, $CHCl_3$); ^{1}H NMR δ 1.68-1.81 (m, 3 H), 1.88-2.20 (m, 4 H), 2.27 (s, 3 H), 2.39 (dd, J = 2.1, 12.3 Hz, 1 H), 2.63 (t, J = 6.6 Hz, 2 H), 2.84-2.87 (m, 1 H), 3.17-3.22 (m, 1 H), 4.16-4.28 (m, 2 H),

7.05 (d, J = 8.7 Hz, 2 H), 7.18 (d, J = 8.1 Hz, 2 H), 7.34-7.39 (m, 2 H), 7.46-7.52 (m, 1 H), 7.91-7.96 (m, 2 H); ^{13}C NMR δ 31.5, 34.8, 34.9, 41.9, 46.6, 47.2, 56.4, 60.9, 63.9, 128.6, 129.0 (2 C overlapping), 129.8, 130.2, 132.4, 133.3, 142.7, 166.4; MS *m/z* (%) 403 (M^+, 2), 282 (14), 254 (74), 220 (100), 208 (33), 188 (40), 174 (15), 125 (20), 115 (45), 105 (92); Anal. Calcd for $C_{22}H_{26}ClNO_2S \cdot 2/3H_2O$: C, 63.52; H, 6.62; N, 3.37. Found: C, 63.59; H, 6.69; N, 3.29.

(+)-Benzoic Acid 2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]methane sulfinyl]ethyl Ester (15). To a solution of the ester **14** (56.0 mg, 0.139 mmol) in acetic acid (2.0 mL) was added 35% H_2O_2 (14 μL) at room temperature. After stirring at room temperature for 2.5 h, the solvent was evaporated under vacuum. The crude product was purified by preparative TLC using EtOAc/Et_3N (10/1) as the developing solvent to afford the product as a colorless oil (45 mg, 77%): R_f(EtOAc/Et_3N (10/1) 0.17; $[\alpha]^{25}_D$ +66.5° (*c* 0.43, $CHCl_3$); ^{1}H NMR δ 1.74-1.82 (m, 2 H), 1.87-2.02 (m, 2 H), 2.27 (s, 3 H), 2.21-2.34 (m, 2 H), 2.36-2.55 (m, 2 H), 2.71-2.92 (m, 3 H), 3.22-3.28 (m, 1 H), 4.46-4.68 (m, 2 H), 7.04 (dd, J = 2.7, 8.7 Hz, 2 H), 7.17 (dd, J = 5.4, 8.1 Hz, 2 H), 7.36-7.42 (m, 2 H), 7.48-7.58 (m, 1 H), 7.90-7.96 (m, 2 H); ^{13}C NMR δ 34.5, 35.0 (1 C), 37.0, 39.3 (1 C), 46.4 (1 C), 47.4, 47.8 (1 C), 52.3, 52.4 (1 C), 55.8, 55.9 (1 C), 56.0, 56.1 (1 C), 57.5, 57.8 (1 C), 60.8, 61.4 (1 C), 128.7 (1 C), 129.1 (1 C), 129.2, 129.3 (1 C), 129.6 (1 C), 129.9 (1 C), 132.8, 132.9 (1 C), 133.5, 133.6 (1 C), 141.6, 141.7 (1 C), 166.2 (1 C); MS *m/z* (%) 402 (M^+ - 17, 8), 238 (18), 220 (42), 206 (8), 149 (12), 125 (13), 115 (22), 105 (100); Anal. Calcd for $C_{22}H_{26}ClNO_3S \cdot 0.8H_2O$: C, 60.83; H, 6.40; N, 3.22. Found: C, 60.85; H, 6.45; N, 3.15.

(+)-2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]methylsulfanyl]acetamide (16a). To a solution of methyl ester **6** (176 mg, 0.54 mmol) in *t*-BuOH (3 mL), which was contained in a tube that was cooled with a dry ice-acetone bath, was introduced an excess of ammonia gas. Then the tube was capped, and the reaction mixture was stirred at room

temperature for 72 h (Caution! Use adequate shielding.). The tube was recooled and opened, and the solvent was evaporated under vacuum. The residue was purified by column chromatography on a silica gel using EtOAc/MeOH/Et_3N (8/1/1) as the eluent to give the amide as a white solid (160 mg, 95%): R_f(EtOAc/MeOH/Et_3N 8/1/1) 0.28; $[\alpha]^{25}_D$ +105° (*c* 0.11, $CHCl_3$); ^{1}H NMR δ 1.74-1.86 (m, 3 H), 1.96-2.28 (m, 4 H), 2.35 (s, 3 H), 2.42 (dd, J = 2.1, 12.0 Hz, 1 H), 2.90-2.98 (m, 1 H), 3.05 (dd, J = 14.4 and 14.7 Hz, 2 H), 3.21-3.26 (m, 1 H), 5.96 (br s, 1 H), 6.47 (br s, 1 H), 7.11 (d, J = 8.7 Hz, 2 H), 7.27 (d, J = 8.7 Hz, 2 H); ^{13}C NMR δ 34.6, 35.3, 36.3, 41.1, 46.3, 47.0, 56.0, 60.6, 128.8, 128.9, 132.3, 142.1, 171.3; MS *m/z* (%) 312 (M^+, 9), 254 (100), 222 (59), 208 (49), 151 (11), 128 (22), 125 (37), 116 (64), 115 (70), 103 (14); Anal. Calcd for $C_{15}H_{21}ClN_2OS$: C, 57.59; H, 6.77; N, 8.95. Found: C, 57.43; H, 6.63; N, 8.79.

(+)-2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]methylsulfanyl]-*N*-hydroxy-acetamide (16b). A 766 mg (13.7 mmol) sample of KOH was dissolved in 5.0 mL of MeOH. To a solution of hydroxylamine hydrochloride (41.5 mg, 0.598 mmol) in 2.0 mL MeOH that was cooled to 5-10 °C was added 388 μL of the above KOH/methanol solution (59.4 mg, 1.06 mmol of KOH), followed by a solution of methyl ester **6** (98 mg, 0.299 mmol) in MeOH (2.0 mL). Then the reaction mixture was stirred at room temperature for 2 h. The precipitate was filtered off and rinsed with CH_2Cl_2, and the combined organic solutions were evaporated under vacuum. The crude product was purified by preparative TLC using EtOAc/MeOH/Et_3N (6/2/2) as the developing solvent followed by HPLC (conditions see below) to yield the hydroxamic acid as a colorless oil (75 mg, 76%): R_f(EtOAc/MeOH/Et_3N 6/2/2) 0.18; $[\alpha]^{25}_D$ +27.8° (*c* 0.37, CH_3OH); ^{1}H NMR (CD_3OD) δ 1.86-2.08 (m, 2 H), 2.26-2.44 (m, 2 H), 2.54-2.72 (m, 2 H), 2.88-3.01 (m, 2 H), 2.96 (s, 3 H), 3.03-3.24 (m, 2 H), 3.54-3.64 (m, 1 H), 3.86-3.93 (m, 1 H), 7.24 (d, J = 8.7 Hz, 2 H), 7.35 (d, J = 8.1 Hz, 2 H); ^{13}C NMR (CD_3OD) δ 33.0, 34.0, 34.9, 40.6, 44.4, 45.7, 55.8,

59.0, 130.4 (2 C overlapping), 134.3, 141.5, 169.4; MS *m/z* (%) 254 (100), 222 (49), 220 (27), 208 (44), 151 (11), 128 (20), 125 (24), 116 (51), 115 (67), 103 (25). HRMS-FAB calcd for $C_{15}H_{22}ClN_2O_2S$ (M + H^+) 329.1091; found 329.1111. HPLC conditions: Waters μBondapak C_{18} (300 × 7.8 mm); flow rate 2.8 mL/min; UV detection at 280 nm; linear gradient from 20% acetonitrile in water (0.05% CF_3COOH) to 80% acetonitrile in water (0.05% CF_3COOH) in 30 min; t_R = 10.8 min; purity (by peak area) 99%.

(+)-2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]methylsulfanyl]-*N*-methyl-acetamide (16c). Methyl ester **6** (124 mg, 0.378 mmol) was dissolved in a 2.0 M solution of methylamine in MeOH (5.0 mL). The resulting mixture was stirred at room temperature for 24 h. The solvent was then evaporated under vacuum. The residue was purified by preparative TLC using EtOAc/Et_3N (10/1) as the developing solvent to afford the product as a white solid (88.5 mg, 72%): R_f(EtOAc/Et_3N 10/1) 0.16; $[\alpha]^{25}_D$ +75.7° (*c* 0.66, $CHCl_3$); ^{1}H NMR δ 1.64-1.82 (m, 3 H), 1.88-2.10 (m, 3 H), 2.12-2.22 (m, 1 H), 2.24-2.36 (m, 1 H), 2.27 (s, 3 H), 2.62 (d, J = 5.1 Hz, 3 H), 2.82-2.90 (m, 1 H), 2.97 and 2.99 (ABq, J = 13.8 Hz, 2 H), 3.10-3.16 (m, 1 H), 6.47 (br, 1 H), 7.04 (d, J = 8.4 Hz, 2 H), 7.22 (d, J = 8.7 Hz, 2 H); ^{13}C NMR δ 26.5, 34.8, 35.4, 36.7, 41.4, 46.5, 47.0, 56.2, 60.8, 129.0 (2 C overlapping), 132.4, 142.3, 168.8; MS *m/z* (%) 326 (M^+, 14), 254 (100), 222 (44), 208 (64), 151 (8), 125 (22), 116 (46), 115 (45), 103 (9); Anal. Calcd for $C_{16}H_{23}ClN_2OS$: C, 58.79; H, 7.09; N, 8.57. Found: C, 58.62; H, 6.93; N, 8.49.

(+)-2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]methylsulfanyl]-*N*,*N*-dimethylacetamide (16d). Methyl ester **6** (92.0 mg, 0.281 mmol) was dissolved in a 2.0 M solution of dimethylamine in MeOH (4.0 mL). The resulting mixture was stirred at room temperature until TLC showed that the starting material had almost disappeared. The solvent was then evaporated under vacuum. The crude product was purified by preparative TLC using

EtOAc/Et_3N (10/1) as the developing solvent to afford the product as a colorless oil (87 mg, 91%); R_f(EtOAc/Et_3N 10/1) 0.28; $[\alpha]^{25}_D$ +75.3° (*c* 0.38, $CHCl_3$); ^1H NMR δ 1.75-1.87 (m, 3 H), 1.97-2.04 (m, 1 H), 2.04-2.16 (m, 1 H), 2.20-2.28 (m, 2 H), 2.34 (s, 3 H), 2.50 (dd, *J* = 2.7, 12.8 Hz, 1 H), 2.88 (s, 3 H), 2.89-2.97 (m, 1 H), 2.98 (s, 3 H), 3.12 and 3.18 (ABq, *J* = 13.8 Hz, 2 H), 3.20-3.28 (m, 1 H), 7.13 (d, *J* = 8.4 Hz, 2 H), 7.26 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR δ 34.5, 34.6, 34.7, 35.8, 37.9, 41.4, 46.5, 47.0, 56.2, 60.7, 128.8, 129.1, 132.2, 142.5, 168.9; MS *m/z* (%) 340 (M^+, 5), 254 (100), 220 (29), 206 (33), 125 (14), 116 (51), 115 (28); Anal. Calcd for $C_{17}H_{25}ClN_2OS \cdot 0.5H_2O$: C, 58.35; H, 7.49; N, 8.01. Found: C, 58.36; H, 7.26; N, 7.93.

(+)-2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]methylsulfanyl]-*N*-isopropyl acetamide (16e). Methyl ester **6** (116 mg, 0.354 mmol) was dissolved in a mixture of 1.0 mL of MeOH and 2.0 mL of isopropylamine. The resulting solution was stirred at room temperature until TLC indicated that the starting material had almost disappeared. The solvent was then evaporated under vacuum. The crude product was purified by preparative TLC using EtOAc/Et_3N (10/1) as the developing solvent to afford the product as a white solid (103 mg, 82%); R_f(EtOAc/ Et_3N 10/1) 0.40; $[\alpha]^{25}_D$ +72.7° (*c* 0.55, $CHCl_3$); ^1H NMR δ 0.93 (d, *J* = 6.6 Hz, 3 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 1.68-1.78 (m, 3 H), 1.88-2.08 (m, 3 H), 2.10-2.22 (m, 1 H), 2.24-2.30 (m, 1 H), 2.27 (s, 3 H), 2.82-2.88 (m, 1 H), 2.92 and 3.01 (ABq, *J* = 16.5 Hz, 2 H), 3.10-3.19 (m, 1 H), 3.80-3.92 (m, 1 H), 6.36 (d, *J* = 7.8 Hz, 1 H), 7.03 (d, *J* = 8.4 Hz, 2 H), 7.20 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR δ 22.6 (2 C overlapping), 34.8, 35.2, 36.7, 41.1, 41.6, 46.5, 47.2, 56.2, 60.9, 128.9, 129.0, 132.5, 142.3, 167.1; MS *m/z* (%) 354 (M^+, 11), 254 (100), 222 (32), 208 (53), 125 (14), 116 (36), 115 (24); Anal. Calcd for $C_{18}H_{27}ClN_2OS$: C, 60.91; H, 7.67; N, 7.89. Found: C, 60.75; H, 7.41; N, 7.72.

(+)-2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]methylsulfanyl]-1-(piperidin-1-yl)ethanone (16f). Methyl ester **6** (117 mg, 0.357 mmol) was dissolved in a mixture of 1.0 mL of MeOH and 2.0 mL of piperidine. The resulting solution was stirred at room temperature until TLC indicated that the starting material had almost disappeared. The solvent was then evaporated under vacuum. The crude product was purified by preparative TLC using EtOAc/Et_3N (10/1) as the developing solvent to afford the product as a pale yellow oil (125 mg, 92%); R_f(EtOAc/Et_3N 10/1) 0.38; $[\alpha]^{25}_D$ +72.4° (*c* 0.40, $CHCl_3$); ^{1}H NMR δ 1.38-1.48 (m, 2 H), 1.52-1.66 (m, 4 H), 1.72-1.86 (m, 3 H), 1.96-2.05 (m, 1 H), 2.06-2.16 (m, 1 H), 2.19-2.26 (m, 2 H), 2.34 (s, 3 H), 2.48 (dd, *J* = 2.7, 12.6 Hz, 1 H), 2.91-2.96 (m, 1 H), 3.14 and 3.19 (ABq, *J* = 13.8 Hz, 2 H), 3.21-3.25 (m, 1 H), 3.32 (dd, *J* = 5.4, 5.6 Hz, 2 H), 3.45 (dd, *J* = 4.8, 5.5 Hz, 2 H), 7.14 (d, *J* = 8.7 Hz, 2 H), 7.26 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR δ 24.3, 25.5, 26.3, 34.5, 34.6, 34.7, 41.1, 42.9, 46.4, 47.0, 47.4, 56.1, 60.7, 128.7, 129.0, 132.1, 142.4, 167.0; MS *m/z* (%) 380 (M^+, 2), 254 (100), 220 (23), 206 (24), 127 (20), 125 (12), 116 (53), 115 (22); Anal. Calcd for $C_{20}H_{29}ClN_2OS \cdot 0.5H_2O$: C, 61.60; H, 7.75; N, 7.18. Found: C, 61.46; H, 7.43; N, 7.08.

(+)-2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]methanesulfinyl]acetamide (17a). To a solution of compound **16a** (59.0 mg, 0.189 mmol) in acetic acid (2.0 mL) was added 35% H_2O_2 (19 μL) at room temperature. After stirring at room temperature for 2.5 h, the solvent was evaporated under vacuum. The crude product was purified by preparative TLC using EtOAc/MeOH/Et_3N (8/1/1) as the developing solvent to afford the product as a white solid (43 mg, 69%); R_f(EtOAc/MeOH/Et_3N 8/1/1) 0.14; $[\alpha]^{25}_D$ +72.2° (*c* 0.21, $CHCl_3$); ^{1}H NMR δ 1.80-1.96 (m, 2 H), 1.98-2.22 (m, 3 H), 2.26-2.41 (m, 1 H), 2.34 and 2.36 (each s, ratio 1:1, total 3 H), 2.42-2.53 (m, 1 H), 2.59-2.69 (m, 1 H), 2.98-3.05 (m, 1 H), 3.16 (dd, *J* = 14.1 and 14.4 Hz, 1 H), 3.27-3.40 (m, 1 H), 3.53 (dd, *J* = 9.9, 14.1 Hz, 1 H), 5.80 (d, *J* = 8.1 Hz, 1 H), 6.95 (d, *J* = 11.4

Hz, 1 H), 7.13 (dd, J = 1.5, 8.4 Hz, 2 H), 7.29 (dd, J = 1.5, 8.4 Hz, 2 H); ^{13}C NMR δ 33.8 and 34.0 (1 C), 36.3, 38.1 (1 C), 45.6 (1 C), 46.7, 47.3 (1 C), 53.6, 53.8 (1 C), 53.9, 54.2 (1 C), 55.3, 55.4 (1 C), 59.9, 60.5 (1 C), 128.9, 129.0 (1 C), 129.1, 129.2 (1 C), 132.7, 132.8 (1 C), 140.9, 141.0 (1 C), 165.8, 165.9 (1 C); MS *m/z* (%) 311 (M^+ - 17, 17), 270 (8), 220 (100), 186 (10), 129 (8), 115 (29). HRMS-FAB calcd for $C_{15}H_{22}ClN_2O_2S$ ($M + H^+$) 329.1091; found 329.1100. HPLC conditions: Waters μBondapak C_{18} (300 × 7.8 mm); flow rate 2.8 mL/min; UV detection at 280 nm; linear gradient from 20% acetonitrile in water (0.05% CF_3COOH) to 90% acetonitrile in water (0.05% CF_3COOH) in 30 min; t_R 8.7 min; purity (by peak area) 99%; Anal. Calcd for $C_{15}H_{21}ClN_2O_2S \cdot 0.7HCl$: C, 50.84; H, 6.17; N, 7.90. Found: C, 51.08; H, 6.24; N, 7.74.

(+)-2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]methanesulfinyl]-*N*-hydroxy acetamide (17b). To a solution of compound **16b** (33 mg, 0.10 mmol) in acetic acid (1.0 mL) was added 35% H_2O_2 (10 μL) at room temperature. After stirring at room temperature for 2 h, the solvent was evaporated under vacuum. The crude product was purified by preparative TLC using EtOAc/MeOH/Et_3N/conc. aq. NH_3 (60/19/19/2) as the developing solvent followed by HPLC (conditions see below) to yield the product as a colorless oil (22 mg, 64%): R_f(EtOAc/MeOH/Et_3N/conc. aq. NH_3 60/19/19/2) 0.16; $[\alpha]^{25}_D$ +35.4° (*c* 0.31, CH_3OH); ^{1}H NMR (CD_3OD) δ 1.98-2.18 (m, 2 H), 2.62-2.90 (m, 4 H), 2.95 and 2.98 (each s, ratio 1:1, total 3 H), 3.04-3.22 (m, 2 H), 3.39 (dd, J = 11.1, 13.7 Hz, 1 H), 3.58 (dd, J = 10.2, 13.4 Hz, 1 H), 3.57-3.68 (m, 1 H), 3.80-3.94 (m, 1 H), 7.27 (dd, J = 3.6, 8.7 Hz, 2 H), 7.37 (dd, J = 2.7, 8.4 Hz, 2 H); ^{13}C NMR (CD_3OD) δ 32.8, 33.1 (1 C), 36.4, 38.1 (1 C), 44.4 (1 C), 45.3, 46.1 (1 C), 54.6, 54.7 (1 C), 55.5, 55.7 (1 C), 55.7, 56.0 (1 C), 58.4, 59.2 (1 C), 130.4, 130.5 (1 C), 130.6, 130.7 (1 C), 134.7, 134.8 (1 C), 140.8, 140.9 (1 C), 162.3, 163.0 (1 C); MS *m/z* (%) 327 (M^+ - 17, 3), 312 (8), 268 (43), 254 (50), 238 (16), 220 (99), 208 (26), 206 (21), 151 (13), 130 (54), 125 (41), 115

(100), 103 (25). HRMS-FAB calcd for $C_{15}H_{22}ClN_2O_3S$ $(M + H)^+$, 345.1040; found 345.1059. HPLC conditions: Waters μBondapak C_{18} (300 × 7.8 mm); flow rate 2.8 mL/min; UV detection at 280 nm; linear gradient from 20% acetonitrile in water (0.05% CF_3COOH) to 50% acetonitrile in water (0.05% CF_3COOH) in 30 min; t_R 10.2 min; purity (by peak area) 98.4%.

(+)-2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]methanesulfinyl]-*N*-methyl acetamide (17c). To a solution of compound **16c** (44 mg, 0.135 mmol) in acetic acid (1.5 mL) was added 35% H_2O_2 (14 μL) at room temperature. After stirring at room temperature for 2.5 h, the solvent was evaporated under vacuum. The crude product was purified by preparative TLC using a mixture of EtOAc/MeOH/Et_3N (8/1/1) as the developing solvent to provide the product as a colorless oil (37 mg, 80%). R_f(EtOAc/MeOH/Et_3N 8/1/1) 0.27; $[\alpha]^{25}_D$ +77.0° (*c* 0.34, $CHCl_3$); ^{1}H NMR δ 1.80-1.90 (m, 2 H), 1.92-2.14 (m, 2 H), 2.26-2.42 (m, 2 H), 2.34 and 2.36 (each s, ratio 1:1, total 3 H), 2.45-2.62 (m, 2 H), 2.65 and 2.73 (each d, ratio 1:1, J = 4.8 Hz, total 3 H), 2.94-3.04 (m, 1 H), 3.10 (dd, J = 14.4, 16.8 Hz, 1 H), 3.18-3.34 (m, 1 H), 3.48 (dd, J = 1.5, 14.3 Hz, 1 H), 6.84 (br, 1 H), 7.12 (dd, J = 2.4, 8.7 Hz, 2 H), 7.29 (dd, J = 2.7, 8.4 Hz, 2 H); ^{13}C NMR δ 26.3 and 26.4 (1 C), 34.4, 34.6 (1 C), 36.5,d 38.8 (1 C), 46.2 (1 C), 47.2, 47.7 (1 C), 53.8, 54.0 (1 C), 54.1, 54.3 (1 C), 55.8, 55.9 (1 C), 60.6, 61.1 (1 C), 129.2 (1 C), 129.3 (1 C), 132.8, 132.9 (1 C), 141.4 (1 C), 164.4, 164.6 (1 C); MS (EI) *m/z* (%) 325 (M^+ - 17, 7), 270 (9), 220 (100), 125 (8), 115 (17); Anal. Calcd for $C_{16}H_{23}ClN_2O_2S \cdot 0.8HCl$: C, 51.65; H, 6.45; N, 7.53. Found: C, 52.00; H, 6.55; N, 7.14.

(+)-2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]methanesulfinyl]-*N*,*N*-dimethylacetamide (17d). To a solution of compound **16d** (54 mg, 0.158 mmol) in acetic acid (1.5 mL) was added 35% H_2O_2 (15.7 μL) at room temperature. After stirring at room temperature for 2.5 h, the solvent was evaporated under vacuum. The crude product was purified

by preparative TLC using a mixture of EtOAc/MeOH/Et_3N (8/1/1) as the developing solvent to provide the product as a colorless oil (49 mg, 87%): R_f(EtOAc/MeOH/Et_3N 8/1/1) 0.34; $[\alpha]^{25}_D$ +93.1° (*c* 0.48, $CHCl_3$); ^{1}H NMR δ 1.78-1.94 (m, 2 H), 1.96-2.16 (m, 2 H), 2.28-2.42 (m, 1 H), 2.36 and 2.37 (each s, ratio 1:1, total 3 H), 2.52-2.64 (m, 2 H), 2.66-2.78 (m, 1 H), 2.90 and 2.91 (each s, ratio 1:1, total 3 H), 2.99 and 3.01 (each s, ratio 1:1, total 3 H), 2.96-3.04 (m, 1 H), 3.27-3.42 (m, 1 H), 3.58 (dd, *J* = 3.3, 14.0 Hz, 1 H), 3.72 (dd, *J* = 14.1 and 14.7 Hz, 1 H), 7.15 (dd, *J* = 5.7, 8.1 Hz, 2 H), 7.28 (d, *J* = 9.0 Hz, 2 H); ^{13}C NMR δ 34.1, 34.6 (1 C), 35.5, 35.7 (1 C), 36.4, 38.6 (1 C), 38.0, 38.2 (1 C), 46.0, 46.1 (1 C), 47.2, 47.5 (1 C), 55.6, 55.8 (1 C), 55.9, 56.0 (1 C), 56.2, 56.4 (1 C), 60.4, 61.0 (1 C), 129.0, 129.1 (1 C), 129.2, 129.4 (1 C), 132.6, 132.7 (1 C), 141.5, 141.7 (1 C), 164.1, 164.5 (1 C); MS (EI) *m/z* (%) 339 (M^+ - 17, 2), 270 (10), 220 (100), 125 (8), 119 (21), 116 (12), 115 (17); Anal. Calcd for $C_{17}H_{25}ClN_2O_2S \cdot 0.8H_2O$: C, 54.99; H, 7.22; N, 7.54. Found: C, 54.86; H, 6.92; N, 7.44.

(+)-2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]methanesulfinyl]-*N*-isopropylacetamide (17e). To a solution of compound **16e** (58 mg, 0.163 mmol) in acetic acid (2.0 mL) was added 35% H_2O_2 (16.2 μL) at room temperature. After stirring at room temperature for 2.5 h, the solvent was evaporated under vacuum. The crude product was purified by preparative TLC using a mixture of EtOAc/MeOH/Et_3N (8/1/1) as the developing solvent to provide the product as a colorless oil (52 mg, 86%): R_f(EtOAc/MeOH/Et_3N 8/1/1) 0.57; $[\alpha]^{25}_D$ +76.8° (*c* 0.50, $CHCl_3$); ^{1}H NMR δ 0.82 and 0.94 (each d, *J* = 6.6 Hz, 3 H), 1.01 and 1.04 (each d, *J* = 6.6 Hz, 3 H), 1.72-1.84 (m, 2 H), 1.84-2.05 (m, 2 H), 2.18-2.36 (m, 2 H), 2.27 and 2.29 (each s, ratio 1:1, total 3 H), 2.38-2.58 (m, 2 H), 2.84-2.94 (m, 1 H), 2.96 (dd, *J* = 2.1, 11.0 Hz, 1 H), 3.14-3.28 (m, 1 H), 3.41 (dd, *J* = 7.2, 14.3 Hz, 1 H), 3.78-3.98 (m, 1 H), 6.68 (br d, *J* = 7.5 Hz, 1 H), 7.06 (dd, *J* = 3.3, 8.4 Hz, 2 H), 7.22 (dd, *J* = 3.6, 8.4 Hz, 2 H); ^{13}C NMR δ 22.4, 22.5

(1 C), 22.6 (2 C, overlapping), 34.3, 34.6 (1 C), 36.5, 38.6 (1 C), 41.9, 42.0 (1 C), 46.1, 46.2 (1 C), 47.3, 47.7 (1 C), 53.9, 54.1 (1 C), 55.7, 55.8 (1 C), 60.5, 61.1 (1 C), 129.1 (1 C), 129.2, 129.3 (1 C), 132.8, 132.9 (1 C), 141.3 (1 C), 162.8, 162.9 (1 C); MS (EI) *m/z* (%) 353 (M^+ - 17, 3), 270 (9), 220 (100), 186 (12), 133 (13), 125 (8), 116 (12), 115 (17); Anal. Calcd for $C_{18}H_{27}ClN_2O_2S \cdot 0.9HCl$: C, 53.55; H, 6.97; N, 6.94. Found: C, 53.60; H, 6.86; N, 6.70.

(+)-2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]methanesulfinyl]-1-(piperidin-1-yl)ethanone (17f). To a solution of compound **16f** (56 mg, 0.147 mmol) in acetic acid (2.0 mL) was added 35% H_2O_2 (14.5 μL) at room temperature. After stirring at room temperature for 2.5 h, the solvent was evaporated under vacuum. The crude product was purified by preparative TLC using a mixture of EtOAc/MeOH/Et_3N (84/8/8) as the developing solvent to provide the product a colorless oil (44 mg, 75%): R_f(EtOAc/MeOH/Et_3N 8/1/1) 0.46; $[\alpha]^{25}_D$ +79.0° (*c* 0.39, $CHCl_3$); ^1H NMR δ 1.42-1.54 (m, 4 H), 1.54-1.68 (m, 2 H), 1.74-1.92 (m, 2 H), 1.94-2.16 (m, 2 H), 2.35 and 2.36 (each s, ratio 1:1, total 3 H), 2.26-2.44 (m, 1 H), 2.46-2.76 (m, 3 H), 2.96-3.04 (m, 1 H), 3.26-3.40 (m, 3 H), 3.42-3.53 (m, 2 H), 3.60 (dd, J = 1.5, 12.9 Hz, 1 H), 3.69 (dd, J = 13.8 and 14.1 Hz, 1 H), 7.14 (dd, J = 5.4, 8.4 Hz, 2 H), 7.28 (dd, J = 2.7, 8.4 Hz, 2 H); ^{13}C NMR δ 24.3 (1 C), 25.5 (1 C), 26.6, 26.7 (1 C), 34.3, 34.8 (1 C), 36.4, 38.6 (1 C), 43.1, 43.2 (1 C), 46.1, 46.2 (1 C), 47.2, 47.5 (1 C), 47.7, 47.9 (1 C), 55.7, 55.8 (1 C), 55.9, 56.1 (1 C), 56.2, 56.9 (1 C), 60.4, 61.2 (1 C), 129.1, 129.2 (1 C), 129.3, 129.5 (1 C), 132.6, 132.7 (1 C), 141.6, 141.8 (1 C), 162.2, 162.6 (1 C); MS (EI) *m/z* (%) 379 (M^+ - 17, 1), 270 (12), 220 (100), 186 (6), 159 (13), 126 (12), 116 (10), 115 (14); Anal. Calcd for $C_{20}H_{29}ClN_2O_2S \cdot 0.6HCl$: C, 57.35; H, 7.12; N, 6.69. Found: C, 57.60; H, 6.76; N, 6.52.

(+)-(3*R*,4*S*)-[[4-(4-Chlorophenyl)-1-methyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)methyl sulfanyl]methyl]piperidine (18). To a solution of acetamide oxime (67.8 mg, 0.915 mmol) in

anhydrous THF (8.0 mL) was added NaH (38.5 mg, 57-63% suspension in oil, 0.915 mmol) at room temperature. The resulting mixture was stirred at reflux for 2.5 h and then cooled to room temperature. To the reaction mixture was added 4 Å molecular sieves (700 mg), followed by the solution of compound **6** (150 mg, 0.458 mmol) in THF (2.0 mL). The resulting mixture was stirred at reflux for 16 h, then cooled to room temperature and filtered, and the residue was washed with THF. The solvent was then evaporated under vacuum. The crude product was purified by column chromatography on silica gel with EtOAc/Et_3N (98:2) as the eluent to yield the product as a colorless oil (127 mg, 79%): R_f(EtOAc/ Et_3N 10/1) 0.54; $[\alpha]^{25}_D$ +106.0° (*c* 0.52, $CHCl_3$); ^{1}H NMR δ 1.65-1.80 (m, 3 H), 1.87-2.04 (m, 2 H), 2.07-2.22 (m, 2 H), 2.24 (s, 3 H), 2.25 (s, 3 H), 2.46 (dd, J = 2.7, 12.6 Hz, 1 H), 2.83-2.89 (m, 1 H), 3.09-3.16 (m, 1 H), 3.53 and 3.61 (ABq, J = 15.3 Hz, 2 H), 7.01 (d, J = 8.7 Hz, 2 H), 7.17 (d, J = 8.1 Hz, 2 H); ^{13}C NMR δ 11.6, 26.0, 34.5 (2 C), 41.0, 46.4, 46.9, 56.1, 60.7, 128.8, 128.9, 132.2, 142.1, 167.3, 176.3; MS (EI) *m/z* (%) 351 (M^+, 9), 254 (100), 220 (69), 206 (29), 151 (10), 127 (18), 125 (31), 116 (64), 115 (60), 103 (14); Anal. Calcd for $C_{17}H_{22}ClN_3OS \cdot 0.2H_2O$: C, 57.44; H, 6.35; N, 11.82. Found: C, 57.45; H, 6.18; N, 11.86.

(+)-(3*R*,4*S*)-[[4-(4-Chlorophenyl)-1-methyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)methane sulfinyl]methyl]piperidine (19). To a solution of compound **18** (58 mg, 0.165 mmol) in acetic acid (2.0 mL) was added 35% H_2O_2 (16.3 μL) at room temperature. After stirring at room temperature for 3 h, the solvent was evaporated under vacuum. The crude product was purified by preparative TLC using a mixture of EtOAc/Et_3N (10/1) as the developing solvent to provide the product as a colorless oil (35.4 mg, 66%); in addition, 7 mg of the starting material was recovered. R_f(EtOAc/Et_3N 10/1) 0.30;. $[\alpha]^{25}_D$ +81.4° (*c* 0.42, $CHCl_3$); ^{1}H NMR) δ 1.82-1.94 (m, 2 H), 1.96-2.16 (m, 2 H), 2.26-2.44 (m, 1 H), 2.35 (s, 3 H), 2.36 (s, 3 H), 2.46-2.54 (m, 1 H),

2.58-2.76 (m, 2 H), 2.94-3.06 (m, 1 H), 3.24-3.36 (m, 1 H), 3.99 (dd, J = 13.8 and 14.1 Hz, 1 H), 4.12 (dd, J = 2.7, 14.0 Hz, 1 H), 7.10 (dd, J = 5.7, 8.4 Hz, 2 H), 7.27 (dd, J = 3.9, 8.4 Hz, 2 H); ^{13}C NMR δ 11.6 (1 C), 34.2, 34.7 (1 C), 37.2, 39.4 (1 C), 46.3 (1 C), 47.0, 47.7 (1 C), 48.2, 48.3 (1 C), 55.4, 55.5 (1 C), 55.8, 55.9 (1 C), 60.5, 61.2 (1 C), 129.1, 129.2 (1 C), 129.3, 129.5 (1 C), 132.8, 132.9 (1 C), 141.3, 141.4 (1 C), 167.8, 167.9 (1 C), 169.9 (1 C); MS (EI) *m/z* (%) 350 (M^+ - 17, 3), 270 (10), 220 (100), 129 (13), 128 (14), 127 (12), 125 (21), 116 (29), 115 (45), 103 (11); Anal. Calcd for $C_{17}H_{22}ClN_3O_2S \cdot H_2O$: C, 52.91; H, 6.27; N, 10.89. Found: C, 53.02; H, 6.01; N, 10.58.

(+)-[[(3*R*,4*S*)-4-(4-Chlorophenyl)piperidin-3-yl]methylsulfanyl]acetic Acid Methyl Ester (20). To a solution of compound **6** (342 mg, 1.04 mmol) in anhydrous CH_2Cl_2 (10 mL) were added 1,8-bis(dimethylamino)naphthalene (proton sponge, 123 mg, 0.57 mmol) and α-chloroethyl chloroformate (0.85 mL, 1.12 g, 7.83 mmol) at room temperature. The resulting mixture was stirred at reflux for 2.5 h and then cooled to room temperature. To the reaction mixture was added 1 M anhydrous hydrogen chloride solution in ether (10 mL). The suspension was filtered through a silica gel plug, and the residue was rinsed with CH_2Cl_2 (2 × 10 mL). The filtrate was concentrated and mixed with 15 mL of MeOH. The resulting mixture was stirred at reflux for 1 h and then evaporated under vacuum. The residue was mixed with a 0.5 M solution of KOH (4 mL) and extracted with EtOAc (3 × 25 mL). The combined organic extract was washed with brine, dried over Na_2SO_4, concentrated and purified by column chromatography on silica gel with EtOAc/Et_3N (98:2) to EtOAc/MeOH/Et_3N (90:5:5) as the eluent to yield the product as a colorless oil (261 mg, 80%): R_f(EtOAc/MeOH/Et_3N 8:1:1) 0.37; $[\alpha]^{25}_D$ +76.4° (*c* 0.34, $CHCl_3$); ^{1}H NMR δ 1.56-1.72 (m, 2 H), 1.78-1.92 (m, 1 H), 2.08 (dd, J = 9.3, 12.9 Hz, 1 H), 2.24-2.43 (m, 3 H), 2.60 (dt, J = 3.0, 10.6 Hz, 1 H), 2.94 and 3.02 (ABq, J = 14.4 Hz, 2 H),

3.02-3.12 (m, 1 H), 3.39 (dd, J = 3.6, 12.0 Hz, 1 H), 3.53 (s, 3 H), 7.05 (d, J = 8.7 Hz, 2 H), 7.20 (d, J = 8.7 Hz, 2 H); ^{13}C NMR δ 34.0, 34.9, 35.5, 42.0, 47.0, 48.1, 51.5, 52.3, 128.8, 128.9, 132.1, 142.7, 170.7; MS (EI) *m/z* (%) 313 (M^+, 13), 242 (37), 240 (100), 208 (55), 194 (53), 151 (12), 129 (18), 128 (21), 125 (36), 116 (35), 115 (60), 103 (22); Anal. Calcd for $C_{15}H_{20}ClNO_2S \cdot 2/5H_2O$: C, 56.12; H, 6.53; N, 4.36. Found: C, 56.05; H, 6.18; N, 4.24.

(+)-2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)piperidin-3-yl]methylsulfanyl]acetamide (21). To a solution of compound **6** (152.5 mg, 0.486 mmol) in *t*-BuOH (3 mL), which was contained in a tube that was cooled with a dry ice-acetone bath was introduced an excess of ammonia gas. Then the tube was capped, and the reaction mixture was stirred at room temperature for 72 h (Caution! Use adequate shielding.). The tube was recooled and opened, and the solvent was evaporated under vacuum. The crude product was purified by column chromatography on silica gel using EtOAc/MeOH/Et_3N (6/2/2) as the eluent to give the product as a pale yellow oil, which was further purified by HPLC (conditions see below) to afford the desired product as a colorless oil (130 mg, 90%). R_f(EtOAc/MeOH/Et_3N 6/2/2) 0.24;. $[\alpha]^{25}_D$ +45.5° (*c* 0.31, CH_3OH); ^{1}H NMR (CD_3OD) δ 1.84-2.04 (m, 2 H), 2.24-2.40 (m, 2 H), 2.48-2.60 (m, 1 H), 2.70 (td, J = 3.9, 18.3 Hz, 1 H), 2.90 (t, J = 11.7 Hz, 1 H), 3.00-3.14 (m, 3 H), 3.44-3.54 (m, 1 H), 3.76-3.84 (m, 1 H), 7.24 (dd, J = 1.2, 8.7 Hz, 2 H), 7.37 (dd, J = 1.2, 8.7 Hz, 2 H); ^{13}C NMR (CD_3OD) δ 32.2, 34.8, 36.3, 39.7, 45.6, 46.4, 48.9, 130.2, 130.3, 134.2, 142.0, 174.9; MS (EI) *m/z* (%) 298 (M^+, 7), 240 (74), 208 (85), 194 (100), 151 (18), 128 (26), 125 (48), 116 (41), 115 (68), 103 (22), 102 (46). HPLC conditions: Waters μBondapak C_{18} (300 × 7.8 mm); flow rate 2.8 mL/min; UV detection at 280 nm; linear gradient from 10% acetonitrile in water (0.05% CF_3COOH) to 40% acetonitrile in water (0.05% CF_3COOH) in 30 min followed by 30 min of the last-named solvent; t_R 26.6 min; purity (by peak area) 98.0%.

(+)-2-[[(3*R*,4*S*)-4-(4-Chlorophenyl)piperidin-3-yl]methanesulfinyl]acetamide (22). To a solution of compound **21** (68 mg, 0.228 mmol) in acetic acid (2.0 mL) was added 35% H_2O_2 (22.6 μL) at room temperature. After stirring at room temperature for 2.5 h, the solvent was evaporated under vacuum. The crude product was purified by preparative TLC using EtOAc/MeOH/Et_3N/NH_3 aq. (60/19/19/2) as the developing solvent to afford the product as a colorless oil, which was further purified by HPLC to give the desired product as a white solid (52 mg, 73%). R_f(EtOAc/MeOH/Et_3N /NH_3 aq. 60/19/19/2) 0.27; $[\alpha]^{25}_D$ +35.1° (*c* 0.23, CH_3OH); ^1H NMR (CD_3OD) δ 1.84-2.12 (m, 2 H), 2.58-2.92 (m, 4 H), 2.94-3.22 (m, 2 H), 3.46-3.70 (m, 3 H), 3.74-3.84 (m, 1 H), 7.27 (dd, J = 2.7, 8.4 Hz, 2 H), 7.37 (dd, J = 2.7, 8.4 Hz, 2 H); ^{13}C NMR (CD_3OD) δ 32.1, 32.4 (1 C), 35.6, 37.4 (1 C), 45.3, 45.5 (1 C), 46.0, 46.8 (1 C), 48.4, 49.3 (1 C), 54.4, 54.7 (1 C), 58.1, 58.6 (1 C), 130.5, 130.6 (1 C), 130.6, 130.7 (1 C), 134.5, 134.6 (1 C), 141.3, 141.5 (1 C), 168.5, 168.6 (1 C); MS (EI) *m/z* (%) 297 (M^+ - 17, 4), 256 (7), 206 (100), 125 (16), 116 (15), 115 (25). HPLC conditions: Waters μBondapak (C_{18} 300 × 7.8 mm); flow rate 2.8 mL/min; UV detection at 280 nm; linear gradient from 10% acetonitrile in water (0.05% CF_3COOH) to 40% acetonitrile in water (0.05% CF_3COOH) in 30 min followed by 30 min of the last-named solvent; t_R 21.7 min; purity 97%.

Synaptosomal Uptake of [^{3}H]Dopamine, [^{3}H]5-Hydroxytryptamine, and [^{3}H]Norepinephrine. Compounds were tested as the free base. The effect of candidate compounds in antagonizing biogenic amine high-affinity uptake was determined as previously described.[1] Striatum, midbrain, and parietal/occipital cortex were dissected and used as a source of rat DAT, SERT, and NET, respectively. These brain regions were homogenized with a Teflon-glass pestle in ice-cold 0.32 M sucrose and centrifuged for 10 min at 1000*g*. The supernatant was centrifuged at 17500*g* for 20 min. This P_2 synaptosomal pellet was resuspended in 30 volumes of

ice-cold modified KRH buffer consisting of (in mM) NaCl (125), KCl (4.8), $MgSO_4$ (1.2), $CaCl_2$ (1.3), KH_2PO_4 (1.2), glucose (5.6), nialamide (0.01), and HEPES (25) (pH 7.4). An aliquot of the synaptosomal suspension was preincubated with the buffer and drug for 30 min at 4 °C and then for 15 min at 37 °C before uptake was initiated by the addition of [^{3}H]biogenic amine (~5 nM for [^{3}H]DA and [^{3}H]5-HT, 9 nM for [^{3}H]NE, final concentration). After 5 min, uptake was terminated by adding 5 mL of cold buffer containing glucosamine as a substitute for NaCl and then finally by rapid vacuum filtration over GF/C glass-fiber filters, followed by washing with two 5 mL volumes of ice-cold, sodium-free buffer. The bound and free [^{3}H]biogenic amines were separated by rapid vacuum filtration over Whatman GF/C filters, using a Brandel M24R cell harvester, followed by two washes with 5 mL of cold buffer. Radioactivity on the filters was then extracted by allowing the filters to sit overnight with 5 mL of scintillation fluid. The vials were vortexed and counted. Specific uptake of [^{3}H]DA was defined as that which is sensitive to inhibition by 30 μM cocaine. 10 μM Fluoxetine and 3 μM desipramine, respectively, were used to define the specific uptake of [^{3}H]5-HT and [^{3}H]NE. In each instance, it was virtually identical to that calculated by subtracting the mean of identical tubes incubated at 0 °C. IC_{50} values were determined using the computer program LIGAND. The Cheng-Prusoff equation for classic, competitive inhibition was used for calculating K_i from IC_{50} values in uptake experiments. The K_m values used were 67 nM for [^{3}H]DA, 53 nM for [^{3}H]5-HT, and 54 nM for [^{3}H]NE. Even though uptake is a non-equilibrium process, K_i determinations are thought to be appropriate estimates of affinity between these compounds and the biogenic amine transporters because it is likely that the relatively long (45 min) period of incubation of the drug before addition of the [^{3}H] amine is adequate time for equilibrium between the test compound the biogenic amine transporter to occur.

Table 1. ClogP Data of the New Ligands[a]

compound	ClogP 'Daylight'	ClogP 'KowWin'
5	4.41	4.85
6	3.15	3.72
7	1.64	2.58
8	2.81	3.21
9	1.95	1.07
10	3.41	3.91
11	1.76	1.77
12	3.71	4.21
13	2.85	2.07
14	5.46	5.67
15	4.55	3.53
16a	2.19	2.84
16b	1.87	2.71
16c	2.29	3.30
16d	2.89	3.52
16e	3.13	4.21
16f	3.80	4.88
17a	1.46	1.05
17b	1.14	0.92
17c	0.78	1.51
17d	2.16	1.72
17e	1.62	2.42
17f	3.08	3.08
18	3.31	4.17
19	1.56	2.03
20	2.87	3.51
21	1.75	2.63
22	0.24	0.84

[a]ClogP calculated by using web sites 1) http://www.daylight.com/daycgi/clogp; and 2) http://esc.syrres.com/interkow/kowdemo.htm.

References

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