Supplementary Information

SARs at the Monoamine Transporters for a Novel Series of Modafinil Analogues

Jianjing Cao,[§] Thomas Prisinzano,[¥] Oluyomi M. Okunola,[§] Theresa Kopajtic,[≠] Matthew Shook, [≠] Jonathan L. Katz,[≠] and Amy Hauck Newman,[§*]

[§]Medicinal Chemistry and [≠]Psychobiology Sections, National Institute on Drug Abuse – Intramural Research Program, National Institutes of Health, 333 Cassell Drive, Baltimore, MD 21224, [¥]Division of Medicinal & Natural Products Chemistry, College of Pharmacy, The University of Iowa, Iowa City, IA 52242

Experimental Section

Reaction conditions and yields were not optimized, and spectroscopic data and yields refer to the free base unless otherwise described for each compound. Flash chromatography was performed using silica gel (EMD Chemicals, Inc.; 230-400 mesh, 60 Å). ^{1}H and ^{13}C NMR spectra were acquired using a Varian Mercury Plus 400 spectrometer. Chemical shifts are reported in parts-per-million (ppm) and referenced according to deuterated solvent for ^{1}H spectra ($CDCl_3$, 7.26, CD_3OD, 3.31 or DMSO-d_6, 2.50), and ^{13}C spectra ($CDCl_3$, 77.2, CD_3OD, 49.0 or DMSO-d_6, 39.5). Gas chromatography-mass spectrometry (GC/MS) data were acquired using an Agilent Technologies (Santa Clara, CA) 6890N GC equipped with an HP-5MS column (cross-linked 5% PH ME siloxane, 30 m × 0.25 mm i.d. × 0.25 μm film thickness) and a 5973 mass-selective ion detector in electron-impact mode. Ultrapure grade helium was used as the carrier gas at a flow rate of 1.2 mL/min. The injection port and transfer line temperatures were 250 and 280 °C, respectively, and the oven temperature gradient used was as follows: the initial temperature (100 °C) was held for 3 min and then increased to 295 °C at 15 °C/min over 13 min, and finally maintained at 295 °C for 10 min. Combustion analysis was performed by Atlantic Microlab, Inc. (Norcross, GA) and agrees within 0.5% of calculated values. Melting point determination was conducted using a Thomas-Hoover melting point apparatus and are uncorrected. On the basis of NMR, GC-MS, and combustion data, all final compounds are >95% pure.

2-(Bis(4-fluorophenyl)methylthio)acetic acid (3b). A mixture of bis (4-fluorophenyl)methanol (2.20 g, 10 mmol) and thioglycolic acid (0.92 g, 10 mmol) in trifluoroacetic acid (11 mL) was stirred at r.t. overnight. The solvent was removed, the mixture was washed with H_2O (5 mL) and hexane (15 mL) to obtain the product as a white solid (2.8 g), which was carried to the next step without further purification.

2-(Bis(4-chlorophenyl)methylthio)acetic acid (3c) was prepared as described for **3b** using bis(4-chlorophenyl)methanol (2.53 g, 10 mmol) to give the product as a brown solid (3.1 g).

2-(Bis(4-bromophenyl)methylthio)acetic acid (3d) was prepared as described for **3b** using bis(4-bromophenyl)methanol (5.0 g, 14.9 mmol), which was prepared by the reduction of bis(4-bromophenyl)methanone with $NaBH_4$ in EtOH, to give the desired product as a white solid (6.0 g).

2-(Bis(4-fluorophenyl)methylthio)acetamide (4b; JJC6-034). A mixture of **3b** (883 mg, 3 mmol), K_2CO_3 (0.6 g) and CH_3I (0.6 g, 4.4 mmol) in acetone (51 mL) was stirred at reflux overnight. The solvent was removed, H_2O (20 mL) was added to the residue, followed by extraction with CH_2Cl_2 (3 X 20 mL). The combined organic layer was dried over $MgSO_4$, and the solvent was removed to yield the ester (1.2 g, 97.4%) as a yellow oil. A mixture of the ester (1.2 g, 3.9 mmol), NH_4Cl (283 mg, 5.3 mmol), concentrated NH_4OH (20 mL) and MeOH (5.7

mL) was stirred at 50 °C for 72 h. MeOH was removed and the reaction mixture was diluted with H_2O (50 mL), extracted with ethyl acetate (3 X 50 mL), and dried with Na_2SO_4. The solvent was removed to afford crude product which was purified by flash column chromatography (1:1 hexane:ethyl acetate) to give the pure product as a light yellow oil (800 mg, 91%); ^{1}H NMR ($CDCl_3$): δ 3.03 (s, 2H), 5.21 (s, 1H), 7.01-7.03 (m, 4H), 7.33-7.37 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 35.8, 53.2, 116.1, 130.1, 136.1, 161.1, 163.5, 171.9; GC/MS (EI) *m/z* 293 (M^+); Anal. Calc.: C, 61.42, H, 4.47, N, 4.78. Found: C, 61.50; H, 4.38, N, 4.80.

2-(Bis(4-chlorophenyl)methylthio)acetamide (4c; JJC6-036) was prepared as described for **4b** using **3c** (1.1 g, 3.2 mmol) to give the product as a white solid (900 mg, 92%). Mp 112-113 °C; ^{1}H NMR ($CDCl_3$): δ 3.06 (s, 2H), 5.16 (s, 1H), 7.30-7.33 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 35.6, 53.4, 129.3, 129.8, 133.9, 138.5, 171.1; GC/MS (EI) *m/z* 325 (M^+); Anal. Calc.: C, 55.22, H, 4.02, N, 4.29. Found: C, 55.24, H, 4.00; N, 4.17.

2-(Bis(4-bromophenyl)methylthio)acetamide (4d; JJC6-049) was prepared as described for **4b** using **3d** (832.26 mg, 2 mmol) to give the product as a white solid (600 mg, 62%). Mp 128-129 °C; ^{1}H NMR ($CDCl_3$): δ 3.05 (s, 2H), 5.13 (s, 1H), 7.24-7.26 (m, 4H), 7.44-7.46 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 35.6, 53.5, 122.1, 130.1, 130.3, 132.1, 132.2, 139.0, 171.4; GC/MS (EI) *m/z* 415 (M^+).

2-(Bis(4-fluorophenyl)methylsulfinyl)acetamide (5b; JJC5-083). Compound **4b** (1 g, 3.41 mmol) was dissolved in a solution of 3.4 mL acetic acid in 10.2 mL MeOH, followed by H_2O_2 (0.34 mL). The reaction mixture was stirred at 40 °C overnight. The solvent was removed and the reaction residue was purified by flash column chromatography (1:1 CH_2Cl_2:Ethyl acetate to 95:5 CH_2Cl_2:MeOH) to give the product as a white solid (700 mg, 66%). Mp 78-80 °C; ^{1}H NMR ($CDCl_3$): δ 3.08-3.12 (d, *J* = 14.0 Hz, 1H), 3.49-3.53 (d, *J* = 14.0 Hz, 1H), 5.23 (s, 1H), 7.08-7.14 (m, 4H), 7.40-7.46 (m, 4H); Anal. Calc.: C, 55.04, H, 4.62, N, 4.53. Found: C, 55.06; H, 4.57, N, 4.36.

2-(Bis(4-chlorophenyl)methylsulfinyl)acetamide (5c; JJC5-086) was prepared as described for **5b** using **4c** (1.0 g, 3.07 mmol) to give the product as a white solid (800 mg, 76%). Mp 90-92 °C; ^{1}H NMR ($CDCl_3$): δ 3.06 (s, 2H), 5.16 (s, 1H), 7.28-7.33 (m, 8H); Anal. Calc.: C, 52.64, H, 3.83, N, 4.09. Found: C, 52.37, H, 3.85, N, 3.97.

2-(Bis(4-bromophenyl)methylsulfinyl)acetamide (5d; JJC6-050) was prepared as described for **5b** using **4d** (520 mg, 1.25 mmol) to give the product as a white solid (400 mg, 74.1%). Mp 92-94 °C; ^{1}H NMR ($CDCl_3$): δ 3.09-3.13 (d, *J* = 14.1 Hz, 1H), 3.51-3.55 (d, *J* = 14.1 Hz, 1H), 5.17 (s, 1H), 7.44-7.46 (m, 4H), 7.53-7.57 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 51.8, 69.7, 123.6, 130.6, 131.2, 132.4, 133.0, 166.0; Anal. Calc.: C, 41.79, H, 3.04, N, 3.25. Found: C, 41.57; H, 3.05, N, 3.20.

2-(Benzhydrylthio)-*N*,*N*-dimethylacetamide (6a; JJC6-004). CDI (360 mg, 2 mmol) was added to **3a**[26] (516.14 mg, 2 mmol) in THF (16 mL). The reaction mixture was stirred at r.t. for 2h followed by the addition of dimethylamine (1 mL, 2M in THF). The reaction mixture was stirred overnight and solvent was removed. The reaction residue was diluted with H_2O (30 mL), basified with NH_4OH, extracted with ethyl acetate (3 X 30 mL), and dried (Na_2SO_4). After filtration, the solvent was removed to give the crude product, which was purified by flash column chromatography (1:1 CH_2Cl_2:Ethyl acetate) to give the product as a white solid (570 mg, 100%). Mp 104-105 °C; ^{1}H NMR ($CDCl_3$): δ 2.89 (s, 3H), 2.90 (s, 3H), 3.16 (s, 2H), 5.41 (s, 1H), 7.21-7.32 (m, 6H), 7.45-7.47 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 33.6, 35.9, 38.0, 54.0, 127.6, 128.7, 141.1, 169.1; GC/MS (EI) *m/z* 285 (M^+); Anal. Calc.: C, 71.54, H, 6.71, N, 4.91. Found: C, 71.58; H, 6.76, N, 4.94.

2-(Bis(4-fluorophenyl)methylthio)-*N*,*N*-dimethylacetamide (6b; JJC6-005) was prepared as described for **6a** using **3b** (588.64 mg, 2 mmol) to give the product as a yellow oil (640 mg, 100%). ^{1}H NMR ($CDCl_3$): δ 2.91 (s, 3H), 2.96 (s, 3H), 3.14 (s, 2H), 5.40 (s, 1H), 6.97-7.01 (m, 4H) 7.37-7.41 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 33.3, 35.9, 38.0, 52.3, 115.6, 130.2, 136.6, 160.9, 163.4, 169.0 ; Anal. Calc.: C, 63.53, H, 5.33, N, 4.36. Found: C, 63.78; H, 5.31, N, 4.45.

2-(Bis(4-chlorophenyl)methylthio)-*N*,*N*-dimethylacetamide (6c; JJC6-006) was prepared as described for **6a** using **3c** (654.46 mg, 2 mmol) to give the product as a yellow oil (708.5 mg, 100%). ^{1}H NMR ($CDCl_3$): δ 2.91 (s, 3H), 2.96 (s, 3H), 3.14 (s, 2H), 5.38 (s, 1H), 7.28-7.36 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 33.3, 36.0, 38.1, 52.4, 127.6, 129.1, 130.0, 133.5, 139.1, 168.9; GC/MS (EI) *m/z* 354 (M^+); Anal. Calc.: C, 57.63, H, 4.84, N, 3.95. Found: C, 57.62, H, 4.97; N, 4.05.

2-(Bis(4-bromophenyl)methylthio)-*N*,*N*-dimethylacetamide (6d; JJC6-044) was prepared as described for **6a** using **3d** (2.08 mg, 5 mmol) to give the product as a yellow oil (1.7 g, 77%). ^{1}H NMR ($CDCl_3$): δ 2.91 (s, 3H), 2.96 (s, 3H), 3.15 (s, 2H), 5.35 (s, 1H), 7.28-7.31 (m, 4H), 7.43-7.47 (m, 4H); GC/MS (EI) *m/z* 443 (M^+); Anal. Calc.: C, 46.07, H, 3.87, N, 3.16. Found: C, 46.08, H, 3.76, N, 3.17.

2-(Benzhydrylthio)-*N*-methylacetamide (6e; JJC6-058) was prepared as described for **6a** using **3a**[26] (775.02 mg, 3 mmol) and methylamine (1.5 mL, 2 M in THF) to give the product as a white solid (514 mg, 63%). ^{1}H NMR ($CDCl_3$): δ 2.74-2.76 (m, 3H), 3.12 (s, 2H), 5.11 (s, 1H), 7.24-7.41 (m, 10H); GC/MS (EI) *m/z* 271 (M^+).

2-(Bis(4-chlorophenyl)methylthio)-*N*-methylacetamide (6f; JJC6-052) was prepared as described for **6a** using **3c** (654.46 mg, 2 mmol) and methylamine (1 mL, 2 M in THF) to give the product as a white solid (390 mg, 57.3%). ^{1}H NMR

($CDCl_3$): δ 2.78-2.80 (m, 3H), 3.08 (s, 2H), 5.12 (s, 1H), 7.30 (m, 8H); GC/MS (EI) *m/z* 340 (M^+).

2-(Bis(4-bromophenyl)methylthio)-*N*-methylacetamide (6g; JJC6-054) was prepared as described for **6a** using **3d** (832.26 mg, 2 mmol) and methylamine (1 mL, 2 M in THF) to give the product as a white solid (280 mg, 32.9%). ^{1}H NMR ($CDCl_3$): δ 2.77-2.78 (m, 3H), 3.07 (s, 2H), 5.10 (s, 1H), 7.22-7.25 (m, 4H), 7.44-7.45 (m, 4H).

2-(Benzhydrylthio)-*N*-(3-phenylpropyl)acetamide (6h; JJC6-073) was prepared as described for **6a** using **3a**[26] (3.1 g, 12 mmol) and 3-phenylpropan-1-amine (1.6 g, 12 mmol) to give the product as a yellow oil (3.9 g , 87%). ^{1}H NMR ($CDCl_3$): δ 1.80-1.81 (m, 2H), 2.63-2.67 (m, 2H), 3.10 (s, 2H), 3.21-3.27 (m, 2H), 5.10 (s, 1H), 7.16-7.40 (m, 15H).

2-(Bis(4-chlorophenyl)methylthio)-*N*-(3-phenylpropyl)acetamide (6i; JJC6-074) was prepared as described for **6a** using **3c** (981.69 mg, 3 mmol) and 3-phenylpropan-1-amine (405.63 mg, 3 mmol) to give the product as a yellow oil (1 g, 75%). ^{1}H NMR ($CDCl_3$): δ 1.82-1.83 (m, 2H), 2.64-2.67 (m, 2H), 3.04 (s, 2H), 3.24-3.29 (m, 2H), 5.10 (s, 1H), 7.16-7.33 (m, 13H).

2-(Bis(4-bromophenyl)methylthio)-*N*-(3-phenylpropyl)acetamide (6j; JJC6-078) was prepared as described for **6a** using **3d** (832.26 mg, 2 mmol) and 3-

phenylpropan-1-amine (270.42 mg, 2 mmol) to give the product as a yellow oil (1 g, 94%). ^{1}H NMR ($CDCl_3$): δ 1.80-1.84 (m, 2H), 2.63-2.67 (m, 2H), 3.03 (s, 2H), 3.23-3.28 (m, 2H), 5.07 (s, 1H), 7.15-7.46 (m, 13H).

2-(Benzhydrylsulfinyl)-*N*,*N*-dimethylacetamide (7a; JJC6-012) was prepared as described for **5b** using **6a** (570 mg, 2 mmol) to give the product as a white solid (502 mg, 83%). Mp 129-130 °C; ^{1}H NMR ($CDCl_3$): δ 2.85 (s, 3H), 2.93 (s, 3H), 3.46-3.49 (d, *J* = 14.1 Hz, 1H), 3.56-3.60 (d, *J* = 14.5 Hz, 1H), 5.38 (s, 1H), 7.29-7.56 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 33.8, 38.053.3, 69.8, 128.4, 128.7, 128.9, 129.2, 129.3, 130.2, 133.9, 136.4, 165.0; Anal. Calc.: C, 67.74; H, 6.35, N, 4.65. Found: C, 67.60, H, 6.30, N, 4.64.

2-(Bis(4-fluorophenyl)methylsulfinyl)-*N*,*N*-dimethylacetamide (7b; JJC6-011) was prepared as described for **5b** using **6b** (642.76 mg, 2 mmol) to give the product as a yellow oil (581 mg, 86%). ^{1}H NMR ($CDCl_3$): δ 2.94 (s, 3H), 2.98 (s, 3H), 3.46-3.50 (d, *J* = 14.4 Hz, 1H), 3.56-3.59 (d, *J* = 14.4 Hz, 1H), 5.44 (s, 1H), 7.05-7.13 (m, 4H), 7.46-7.54 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 35.8, 38.1, 52.9, 67.5, 115.8, 116.1, 116.2, 116.4, 129.2, 129.3, 130.9, 131.0, 132.0, 132.1, 132.2, 161.5, 162.0, 164.0, 164.4, 164.8; Anal. Calc.: C, 60.52; H, 5.08, N, 4.15. Found: C, 60.77, H, 5.10, N, 4.23.

2-(Bis(4-chlorophenyl)methylsulfinyl)-*N*,*N*-dimethylacetamide (7c; JJC6-015) was prepared as described for **5b** using **6c** (670 mg, 2 mmol) to give the product as a yellow oil (600 mg, 81%). ^{1}H NMR ($CDCl_3$): δ 2.95 (s, 3H), 2.98 (s, 3H), 3.47-3.51 (d, *J* = 14.4 Hz, 1H), 3.57-3.61 (d, *J* = 14.8 Hz, 1H), 5.43 (s, 1H), 7.35-7.49 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 35.8, 38.1, 52.9, 67.7, 129.2, 129.5, 130.5, 131.6, 134.6, 135.1, 164.7; Anal. Calc.: C, 55.14, H, 4.63, N, 3.78. Found: C, 55.05, H, 4.49, N, 3.79.

2-(Bis(4-bromophenyl)methylsulfinyl)-*N*,*N*-dimethylacetamide (7d; JJC6-045) was prepared as described for **5b** using **6d** (642.76 mg, 2 mmol) to give the product as a yellow oil (443 mg, 81%). ^{1}H NMR ($CDCl_3$): δ 2.71-2.72(m, 6H), 3.32-3.46 (d, *J* = 14.2 Hz, 1H), 3.61-3.65 (d, *J* = 14.6 Hz, 1H), 5.21 (s, 1H), 7.22-7.25 (m, 4H), 7.36-7.39 (m, 4H); ^{13}C NMR (CD_3OD): δ 38.41, 40.70, 57.6, 72.3, 126.2, 126.5, 134.3, 135.4, 135.6, 136.0, 136.8, 138.8, 169.2; Anal. Calc.: C, 44.47, H, 3.73, N, 3.05. Found: C, 44.43, H, 3.72, N, 2.88.

2-(Benzhydrylsulfinyl)-*N*-methylacetamide (7e; JJC6-059) was prepared as described for **5b** using **6e** (500 mg, 1.84 mmol) to give the product as a yellow oil (427 mg, 81%). ^{1}H NMR ($CDCl_3$): δ 2.82-2.83 (m, 3H), 3.12-3.15 (d, *J* = 14.0 Hz, 1H), 3.42-3.46 (d, *J* = 14.0 Hz, 1H), 5.18 (s, 1H), 7.35-7.50 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 26.7, 52.3, 71.7, 128.9, 129.0, 129.1, 129.6, 129.7, 134.2, 134.9, 164.9; Anal. Calc.: C, 63.87, H, 6.20, N, 4.66. Found: C, 64.15, H, 5.83, N, 4.63.

2-(Bis(4-chlorophenyl)methylsulfinyl)-*N*-methylacetamide (7f; JJC6-053) was prepared as described for **5b** using **6f** (390 mg, 1.15 mmol) to give the product as a white solid (318 mg, 77.6%). Mp 121-123 °C; ^{1}H NMR ($CDCl_3$): δ 2.82-2.83 (m, 3H), 3.10-3.14 (d, *J* = 13.6 Hz, 1H), 3.44-3.48 (d, *J* = 12.4 Hz, 1H), 5.21 (s, 1H), 7.38-7.39 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 26.8, 52.6, 69.3, 129.4, 129.9, 130.4, 131.1, 132.1, 133.2, 135.2, 135.3, 164.4; Anal. Calc.: C, 50.55, H, 3.98, N, 3.63. Found: C, 50.06, H, 3.95, N, 3.57.

2-(Bis(4-bromophenyl)methylsulfinyl)-*N*-methylacetamide (7g; JJC6-056) was prepared as described for **5b** using **6g** (280 mg, 0.66 mmol) to give the product as a white solid (242 mg, 82%). Mp 88-90 °C; ^{1}H NMR ($CDCl_3$): δ 2.84-2.85 (m, 3H), 3.10-3.13 (d, *J* = 14.0 Hz, 1H), 3.44-3.48 (d, *J* = 14.8 Hz, 1H), 5.15 (s, 1H), 7.380-7.33 (m, 4H), 7.52-7.56 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 26.8, 52.4, 69.6, 123.5, 130.7, 131.3, 132.3, 132.5, 132.9, 133.5, 164.4; Anal. Calc.: C, 42.31, H, 3.55, N, 3.08. Found: C, 42.24, H, 3.28, N, 2.97.

2-(Benzhydrylsulfinyl)-*N*-(3-phenylpropyl)acetamide (7h; JJC6-017) was prepared as described for **6a** using (±)-2-(benzhydrylsulfinyl)acetic acid[26] (1.1 g, 4 mmol) and 3-phenylpropan-1-amine (541 mg, 4 mmol) to give the product as a yellow oil (1.56 g, 100%) . ^{1}H NMR ($CDCl_3$): δ 1.76-1.86 (m, 2H), 2.61-2.66 (m, 2H), 3.09-3.13 (m, 1H), 3.26-3.31 (m, 2H), 3.39-3.42 (d, *J* = 14.0 Hz, 1H), 5.19

(s, 1H), 7.14-7.48 (m, 15H); ^{13}C NMR ($CDCl_3$): δ 31.2, 33.4, 39.6, 52.6, 71.7, 126.2, 128.6, 128.7, 128.9, 129.0, 129.1, 129.6, 129.8, 134.2, 135.0, 141.5, 141.9, 164.3; Anal. Calc.: C, 73.62, H, 6.44, N, 3.58. Found: C, 73.53, H, 6.68, N, 4.02.

2-(Bis(4-bromophenyl)methylsulfinyl)-*N*-(3-phenylpropyl)acetamide (7j; JJC6-080) was prepared as described for **5b** using **6j** (220 mg, 0.41 mmol) to give the product as a clear oil (100 mg, 44%) . ^{1}H NMR ($CDCl_3$): δ 1.85-1.89 (m, 2H), 2.65 -2.69 (m, 2H), 3.04-3.07 (d, *J* = 14.0 Hz, 1H), 3.30-3.32 (m, 2H), 3.40-3.44 (d, *J* = 14.4 Hz, 1H), 5.13 (s, 1H), 7.16-7.31 (m, 9H), 7.51-7.55 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 31.2, 33.4, 39.7, 52.4, 69.7, 123.5, 126.3, 128.6, 128.7, 130.7, 131.3, 132.3, 132.6, 132.9, 133.4, 141.3, 163.7; Anal. Calc.: C, 51.63, H, 4.33, N, 2.50. Found: C, 51.27, H, 4.08, N, 2.52.

2-(Benzhydrylsulfinyl)-1-(piperidin-1-yl)ethanone (7k; JJC6-016) was prepared as described for **6a** using (±)-2-(benzhydrylsulfinyl)acetic acid[26] (548.7 mg, 2 mmol) and piperidine (170.3 mg, 2 mmol) to give the product as a white solid (280 mg, 74%). Mp 150-151 °C; ^{1}H NMR ($CDCl_3$): δ 1.43-1.61 (m, 6H), 3.20-3.26 (m, 2H), 3.42-3.62 (m, 4H), 5.36 (s, 1H), 7.27-7.56 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 24.4, 25.7, 26.5, 43.2, 47.7, 53.7, 69.8, 128.4, 128.7, 128.9, 129.2, 130.3, 133.9, 136.5, 163.2; Anal. Calc.: C, 69.43, H, 6.85; N, 4.05. Found: C, 69.78, H, 6.70, N, 4.07.

2-(Benzhydrylsulfinyl)-1-morpholinoethanone (7l; JJC6-020) was prepared as described for **6a** using (±)-2-(benzhydrylsulfinyl)acetic acid[26] (1.65 g, 6 mmol) and morpholine (522.72 mg, 6 mmol) to give the product as a white solid (1.2 g, 59%). Mp 142-143 °C; ^{1}H NMR ($CDCl_3$): δ 3.24-3.74 (m, 10H), 5.31 (s, 1H), 7.29-7.54 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 42.5, 47.0, 52.8, 66.7, 66.8, 66.9, 70.6, 128.6, 128.8, 129, 129.2, 129.4, 130.1, 134.0, 136.0, 163.5.

***N*-(2-(benzhydrylthio)ethyl)-3-phenylpropan-1-amine (8a; JJC6-075).** Sulfuric acid (1.87 g, 98%) in THF (4 mL) was added dropwise at 0 °C to $LiAlH_4$ (1.47 g) in THF (20 mL) and stirred for 15 minutes. Compound **6h** (3.6 g, 9.58 mmol) in THF (67 mL) was added dropwise to the reduction mixture at r.t and stirred for 2h. The mixture was quenched with H_2O (0.3 mL) and 15% NaOH (1.4 mL) successively, at 0 °C. The reaction mixture was filtered and washed with THF and evaporated to dryness. The crude product was purified by flash column chromatography ($CHCl_3$/MeOH/NH_4OH= 95/5/0.5) to give the product as a light yellow oil (3.1 g, 89%). ^{1}H NMR ($CDCl_3$): δ 1.73-1.81 (m, 2H), 2.54-2.65 (m, 6H), 2.71-2.74 (m, 2H), 5.16 (s, 1H), 7.16-7.31 (m, 11H), 7.40-7.43 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 31.9, 32.9, 33.8, 48.4, 49.2, 54.3, 126.0, 127.5, 128.5, 128.6, 128.8, 129.0, 141.7, 142.3; GC/MS (EI) *m/z* 361 (M^+).

4-(2-(Benzhydrylthio)ethyl)morpholine (8b; JJC6-021) was prepared as described for **8a** using **7l** (686 mg, 2 mmol) to give the product as a yellow oil

(430 mg, 69%). ^{1}H NMR ($CDCl_3$): δ 2.36-2.38 (m, 4H), 2.52-2.54 (m, 4H), 3.66-3.68 (m, 4H), 5.22 (s, 1H), 7.20-7.32 (m, 6H), 7.41-7.44 (m, 4H); GC/MS (EI) *m/z* 313 (M^+).

2-(Benzhydrylthio)-*N*,*N*-dimethylethanamine (8c; JJC 6-024) was prepared as described for **8a** using **7a** (1.1g g, 3.65 mmol) to give the product as a yellow oil (800 mg) and used to next step without further purification.

2-(Bis(4-chlorophenyl)methylthio)-*N*,*N*-dimethylethanamine (8d; JJC6-029) was prepared as described for **8a** using **6c** (1.67 g, 4.71 mmol) to give the product as a yellow oil (1.03 g, 64%). ^{1}H NMR ($CDCl_3$): δ 2.18 (s, 6H), 2.45-2.49 (m, 4H), 5.12 (s, 1H), 7.27-7.35 (m, 8H).

***N*-(2-(benzhydrylsulfinyl)ethyl)-3-phenylpropan-1-amine (9a, oxalate salt; JJC6-019)** was prepared as described for **5b** using **8a** (160 mg, 0.44 mmol) to give the product (100 mg, 60%). The free base was converted to oxalate salt and recrystallized from acetone to give a white solid. Mp 170-172 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 1.80-1.88 (m, 2H), 2.59-2.72 (m, 5H), 2.80-2.86 (m, 1H), 3.04-3.10 (m, 1H), 3.17-3.23 (m, 1H), 5.00 (s, 1H), 7.16-7.50 (m, 15H); ^{13}C NMR ($CDCl_3$): δ 22.4, 30.2, 33.4, 43.5, 48.6, 126.3, 128.6, 128.7, 128.8, 128.9, 129.1, 129.2, 129.3, 129.5, 129.6, 130.1, 134.9, 135.4, 141.4, 176.2; Anal. Calc.: C, 64.91, H, 6.39, N, 2.91. Found: C, 64.78, H, 6.26, N, 3.19.

4-(2-(Benzhydrylsulfinyl)ethyl)morpholine (9b, oxalate salt; JJC6-022) was prepared as described for **5b** using **8b** (430 mg, 1.37 mmol) to give the product as a brown oil (270 mg, 60%) and the free base was converted to oxalate salt and recrystallized from acetone to give a white solid. Mp 169-170 °C; ^{1}H NMR ($CDCl_3$): δ 2.36-2.41 (m, 4H), 2.58-2.85 (m, 4H), 3.64-3.69 (m, 4H), 4.95 (s, 1H), 7.31-7.65 (m, 10H); ^{13}C NMR ($CDCl_3$); Anal. Calc.: C, 58.86, H, 6.12, N, 3.27. Found: C, 58.93, H, 5.93, N, 3.45.

2-(Benzhydrylsulfinyl)-*N*,*N*-dimethylethanamine (9c, hydrochloride salt; JJC6-025) was prepared as described for **5b** using **8c** (380 mg, 1.40 mmol) to give the product as a yellow oil (305 mg, 75.9%). The free base was converted to the HCl salt and recrystallized from 2-PrOH to give a white solid. Mp 160-161 °C; ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 6H), 2.62-2.70 (m, 3H), 2.81-2.87 (m, 1H), 4.94 (s, 1H), 7.31-7.51 (m, 10H); Anal. Calc.: C, 60.52, H, 7.02, N, 4.15. Found: C, 60.70, H, 6.91; N, 4.28.

2-(Bis(4-chlorophenyl)methylsulfinyl)-*N*,*N*-dimethylethanamine (9d, hydrochloride salt; JJC6-030) was prepared as described for **5b** using **8d** (630 mg, 1.85 mmol) to give the product as a yellow oil (450 mg, 68%). The free base was converted to the HCl salt and recrystallized from acetone to give a white solid. Mp 153-155 °C; ^{1}H NMR ($CDCl_3$): δ 2.24-2.25 (s, 6H), 2.55-2.71 (m, 3H), 2.79-2.84 (m, 1H), 4.92 (s, 1H), 7.35-7.40 (m, 8H); Anal. Calc.: C, 51.40, H, 5.20, N, 3.53. Found: C, 51.26, H, 5.15, N, 3.57.

***R*-(–)-Modafinil (*R*-(–)-1; OMO1-014)** was synthesized as previously described[26] with slight modifications. Briefly, a mixture of *R*-(–)-2-(benzhydrylsulfinyl)acetic acid[26] (2.00 g, 7.29 mmol), K_2CO_3 (1.22 g, 8.83 mmol) and iodomethane (1.75 mL, 3.98 g, 28.0 mmol in two portions) in acetone (120 mL) was heated at reflux overnight. The solvent was removed under reduced pressure and H_2O (100 mL) added to the residue. The aqueous mixture was extracted with CH_2Cl_2 (100 mL). The aqueous layer was washed with additional CH_2Cl_2 (2 x 50 mL). The combined CH_2Cl_2 portion was washed with saturated NaCl (100 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded a crude solid that was recrystallized from diisopropyl ether to afford 1.47 g (70%) of the corresponding methyl ester as a white solid, mp 109-110 °C (lit. 106-108 °C).[26] The methyl ester (1.36 g, 4.72 mmol) and NH_4Cl (0.36 g, 6.71 mmol) were partially dissolved in MeOH (10 mL), after which NH_4OH (28.0-30.0%; 34 mL) was added and the mixture stirred overnight at r.t.. The resulting precipitate was collected by filtration and triturated in diisopropyl ether to afford 1.13 g (57%) of *R*-(–)-modafinil as a white solid. Mp 156-158 °C (lit. 156-157 °C);[26] $[\alpha]_D^{25}$ = –83.4 (c = 1.02, $CHCl_3$); ^{1}H NMR (DMSO-d_6): δ 7.62 (br s, 1H), 7.46 (d, *J* = 7.4 Hz, 4H), 7.37 (t, *J* = 7.6 Hz, 4H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.26 (br s, 1H), 5.29 (s, 1H), 3.32 (d, *J* = 13.7 Hz, 1H), 3.16 (d, *J* = 13.7 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 167.3, 138.2, 135.9, 130.6, 130.0, 129.4, 129.0, 128.9, 69.7, 57.1. Anal. Calc.: C, 65.91, H, 5.53, N, 5.12. Found: C, 65.88; H, 5.45, N, 5.19.

_S_-(+)-Modafinil (_S_-(+)-1; OMO1-020). _S_-(+)-Modafinil was synthesized as previously described[26] with slight modifications. Briefly, a mixture of _S_-(+)-2-(benzhydrylsulfinyl)acetic acid[26] (2.00 g, 7.29 mmol), K_2CO_3 (1.22 g, 8.83 mmol) and iodomethane (1.10 mL, 2.50 g, 17.6 mmol in two portions) in acetone (165 mL) was heated at reflux overnight. The solvent was removed under reduced pressure and H_2O (100 mL) added to the residue. The aqueous mixture was extracted with CH_2Cl_2 (100 mL). The aqueous layer was washed with additional CH_2Cl_2 (2 x 50 mL). The combined CH_2Cl_2 portion was washed with saturated NaCl (100 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded a crude solid that was recrystallized from diisopropyl ether to afford 1.47 g (70%) of the corresponding methyl ester as a white solid, mp 106-108 °C (lit. 106-108 °C).[26] The methyl ester (1.45 g, 5.03 mmol) and NH_4Cl (0.40 g, 7.48 mmol) were partially dissolved in MeOH (4.2 mL), after which NH_4OH (28.0-30.0%; 36 mL) was added and the mixture stirred overnight at r.t.. The resulting precipitate was collected by filtration and triturated in diisopropyl ether to afford 1.18 g (59%) of _S_-(+)-modafinil as a white solid. Mp 152.5-154 °C (lit. 153-154 °C);[26] $[\alpha]_D^{26}$ = +78.5 (c = 1.032, $CHCl_3$); ^{1}H NMR (DMSO-d_6): δ 7.63 (br s, 1H), 7.48 (d, _J_ = 7.0 Hz, 4H), 7.38 (t, _J_ = 7.8 Hz, 4H), 7.32 (t, _J_ = 7.2 Hz, 2H), 7.27 (br s, 1H), 5.30 (s, 1H), 3.33 (d, _J_ = 13.7 Hz, 1H), 3.18 (d, _J_ = 13.7 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 167.3, 138.1, 135.9, 130.6, 130.0, 129.4, 128.9, 128.8, 69.7, 57.1. Anal. Calc.: C, 65.91, H, 5.53, N, 5.12. Found: C, 65.87; H, 5.45, N, 5.07.

Locomotor Activity Assay – Mice were placed one at a time in clear acrylic chambers (40 cm^3) for the assessment locomotor activity on a horizontal plane. The acrylic chambers fit within monitors (Med Associates, St. Albans, VT) which were equipped with light sensitive detectors, spaced 2.5 cm apart along two perpendicular walls. Mounted on the opposing walls and directed at the detectors were infrared light sources. One activity count was registered each time the subject interrupted a single light beam. Mice were injected and immediately placed in the apparatus for 4 hrs, with activity counts totaled each 10 min. Each drug dose was studied in 6 mice, and mice were used only once.