

Supplementary Materials: Novel Enantiopure Sigma Receptor (SR) Modulators: Quick (Semi)-Preparative Chiral Resolution via HPLC and Absolute Configuration Assignment

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1. Materials and Methods

1.1. General

Optical rotation values were measured on a Jasco photoelectric polarimeter DIP 1000 using a 0.5-dm cell and a sodium and mercury lamp ($\lambda = 589$ nm, 435 nm, 405 nm); sample concentration values (c) are given in 10^{-2} g·mL⁻¹.

Proton nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 500 spectrometer operating at 500 MHz. Proton chemical shifts (δ) are reported in ppm with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard (CDCl₃, $\delta = 7.26$ ppm). The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal, dd = doublet-doublet, td = triplet-doublet. The coupling constant values are reported in Hz. ¹³C-NMR spectra were recorded on a 500-MHz spectrometer, with complete proton decoupling. Carbon chemical shifts (δ) are reported in ppm relative to TMS with the respective solvent resonance as the internal standard (CDCl₃, $\delta = 77.23$ ppm). UPLC-UV-ESI/MS analyses were carried out on an Acquity UPLC Waters LCQ FLEET system using an ESI source operating in positive ion mode, controlled by ACQUITY PDA and 4 MICRO (Waters S.A.S., Saint-Quentin En Yvelines Cedex, France). Analyses were run on a ACQUITY BEH C18 (Waters S.A.S). 50 × 2.1 mm, 1.7 μ m) column, at room temperature, with gradient elution (Solvent A: water containing 0.1% of formic acid; Solvent B: methanol containing 0.1% of formic acid; gradient: 10% B in A to 100% B in 3 min, followed by isocratic elution 100% B for 1.5 min, return to the initial conditions in 0.2 min) at a flow rate of 0.5 mL·min⁻¹. All of the final compounds had 95% or greater purity.

1.2. Compound Characterization

(+)-(S)-4-(4-Benzyl-piperidin-1-yl)-2-naphthalen-2-yl-butan-2-ol, [(+)-(S)-1]: White solid; $[\alpha]_D^{20} = +40.5$ (c 0.2, CH₃OH). IR (cm⁻¹): 3434, 2918, 1653, 1438, 1156, 1112, 820; ¹H-NMR (500 MHz) (CDCl₃) δ (ppm): 8.01 (s, 1H), 7.86–7.81 (m, 3H), 7.47–7.45 (m, 3H), 7.28 (t, $J = 7.8$ Hz, 2H), 7.19 (t, $J = 7.0$ Hz, 1H), 7.13 (d, $J = 7.1$ Hz, 2H), 3.19 (d, 1H), 2.54–2.50 (m, 3H), 2.31 (m, 1H), 2.22–2.14 (m, 2H), 1.92 (d, 1H), 1.84 (m, 1H), 1.76 (m, 1H), 1.68 (m, 1H), 1.60 (m, 1H), 1.57 (s, 3H), 1.50 (m, 1H), 1.31 (m, 2H); ¹³C-NMR (500 MHz) (CDCl₃) δ (ppm): 146.3, 140.5, 133.3, 132.0, 129.1, 128.2, 128.1, 127.6, 127.4, 125.8, 125.4, 123.8, 123.6, 75.7, 55.1, 54.8, 52.6, 43.1, 37.8, 37.4, 32.6, 32.1, 31.4. HPLC: $t_R = 8.5$ min, ee 96.0%.

(-)-(R)-4-(4-Benzyl-piperidin-1-yl)-2-naphthalen-2-yl-butan-2-ol, [(-)-(R)-1]: White solid; $[\alpha]_D^{20} = -42.3$ (c 0.2, CH₃OH). The IR and NMR spectra are identical to that of (+)-(S)-1. HPLC: $t_R = 11.1$ min, ee 97.0%.

(+)-(S)-4-Benzyl-1-(3-naphthalen-2-yl-butyl)-piperidine, [(+)-(S)-2]: Yellow oil; $[\alpha]_D^{20} = +6.1$ (c 0.2, CH₃OH). IR (cm⁻¹): 3025, 2924, 2508, 1631, 1602, 1542, 1496, 1453; ¹H-NMR (500 MHz) (CDCl₃) δ (ppm): 7.79–7.77 (t, $J = 8.7$ Hz, 3H), 7.59 (s, 1H), 7.45–7.42 (m, 2H), 7.32 (d, $J = 8.8$ Hz, 1H), 7.25 (m, 2H), 7.17 (m, 1H), 7.08 (m, 2H), 3.30 (broad peak, 2H), 2.90 (m, 1H), 2.76 (m, 1H), 2.55 (d, $J = 7.4$ Hz, 2H), 2.46 (m, 1H), 2.27–2.13 (m, 4H), 1.82–1.71 (m, 4H), 1.59 (m, 1H), 1.36 (d, $J = 6.5$ Hz, 3H); ¹³C-NMR (500 MHz) (CDCl₃) δ (ppm): 142.4, 139.3, 133.4, 132.3, 128.9, 128.5, 128.3, 127.6, 127.5, 126.1, 125.5, 125.3, 124.8, 56.1, 52.4, 41.9, 38.3, 36.5, 31.8, 29.1, 22.7. HPLC: $t_R = 7.7$ min, ee 95.0%.

(-)-(R)-4-Benzyl-1-(3-naphthalen-2-yl-butyl)-piperidine, [(-)-(R)-2]: Yellow oil; $[\alpha]_{\text{D}}^{20} = -6.3$ (c 0.2, CH₃OH). The IR and NMR spectra are identical to that of (+)-(S)-2. HPLC: $t_{\text{R}} = 9.0$ min, ee 95.0%.

(+)-(S)-4-(4-Benzyl-piperidin-1-yl)-2-phenyl-butan-2-ol, [(+)-(S)-3]: Yellow oil; $[\alpha]_{\text{D}}^{20} = +10.5$ (c 0.6, CH₃OH). IR (cm⁻¹): 3184, 3125, 1602, 1369, 1343, 1156, 846, 699; ¹H-NMR (500 MHz) (CDCl₃) δ (ppm): 7.45 (d, $J = 8.9$ Hz, 2H), 7.33 (t, $J = 8.1$ Hz, 2H), 7.27 (t, $J = 7.4$ Hz, 2H), 7.21–7.19 (m, 2H), 7.13 (d, $J = 7.0$ Hz, 2H), 3.15 (d, 1H), 2.54 (m, 1H), 2.52 (m, 2H) 2.30 (m, 1H), 2.22 (m, 1H), 2.07 (m, 1H), 1.86 (m, 1H), 1.80 (m, 1H) 1.75 (m, 1H), 1.67 (m, 1H) 1.60 (m, 1H), 1.50 (m, 1H), 1.49 (s, 3H) 1.31 (m, 2H); ¹³C-NMR (500 MHz) (CDCl₃) δ (ppm): 148.9, 140.5, 129.1, 127.9, 128.2, 126.0, 125.8, 125.0, 75.5, 55.1, 54.8, 52.6, 43.1, 37.8, 37.7, 32.6, 32.1, 31.4. HPLC: $t_{\text{R}} = 3.4$ min, ee 99.9%.

(-)-(R)-4-(4-Benzyl-piperidin-1-yl)-2-phenyl-butan-2-ol, [(-)-(R)-3]: Yellow oil; $[\alpha]_{\text{D}}^{20} = -9.2$ (c 0.6, CH₃OH). The IR and NMR spectra are identical to that of (+)-(S)-3. HPLC: $t_{\text{R}} = 4.2$ min, ee 98.0%.

(+)-(S)-4-Benzyl-1-(3-phenyl-butyl)-piperidine, [(+)-(S)-4]: Yellow oil; $[\alpha]_{\text{D}}^{20} = +8.2$ (c 0.3, CH₃OH). IR (cm⁻¹): 3682, 3019, 2929, 2856, 2434, 2400, 1230; ¹H-NMR (500 MHz) (CDCl₃) δ (ppm): 7.28–7.27 (m, 4H), 7.17 (m, 4H), 7.13 (d, $J = 7.0$ Hz, 2H), 2.86 (broad peak, 2H), 2.71 (m, 1H), 2.52 (d, $J = 6.6$ Hz, 2H), 2.26 (m, 1H), 2.14 (m, 1H), 1.87–1.72 (m, 4H), 1.61 (d, 2H), 1.49 (m, 1H), 1.29 (m, 2H), 1.24 (d, $J = 7.3$ Hz, 3H); ¹³C-NMR (500 MHz) (CDCl₃) δ (ppm): 147.3, 140.7, 129.1, 128.3, 128.1, 126.9, 125.9, 125.7, 57.3, 54.1, 53.9, 43.2, 38.4, 37.9, 35.4, 32.1, 22.6. HPLC: $t_{\text{R}} = 3.7$ min, ee 99.9%.

(-)-(R)-4-Benzyl-1-(3-phenyl-butyl)-piperidine, [(-)-(R)-4]: Yellow oil; $[\alpha]_{\text{D}}^{20} = -8.3$ (c 0.3, CH₃OH). The IR and NMR spectra are identical to that of (+)-(S)-4. HPLC: $t_{\text{R}} = 5.3$ min, ee 99.9%.

(+)-(S)-6-[3-(4-Benzyl-piperidin-1-yl)-1-hydroxy-1-methyl-propyl]-naphthalen-2-ol, [(+)-(S)-5]: Yellow oil; $[\alpha]_{\text{D}}^{20} = +24.2$ (c 0.1, CH₃OH). IR (cm⁻¹): 3452, 2925, 1633, 1605, 1560, 1454, 1381; ¹H-NMR (500 MHz) (CDCl₃) δ (ppm): 7.91 (s, 1H), 7.72 (d, $J = 8.4$ Hz, 1H), 7.60 (d, $J = 8.4$ Hz, 1H), 7.40 (d, $J = 8.8$ Hz, 1H), 7.25 (t, $J = 6.9$ Hz, 2H), 7.18–7.14 (m, 3H), 7.07 (d, $J = 8.0$ Hz, 2H), 3.20 (broad peak, 1H), 2.61 (broad peak, 1H), 2.46 (d, $J = 6.5$ Hz, 2H), 2.34 (m, 2H), 2.18 (m, 1H), 1.96 (broad peak, 1H), 1.88 (broad peak, 1H), 1.80 (broad peak, 1H), 1.66 (broad peak, 2H), 1.59 (s, 1H), 1.49 (broad peak, 1H), 1.34 (broad peak, 2H); ¹³C-NMR (500 MHz) (CDCl₃) δ (ppm): 154.0, 143.0, 140.3, 133.3, 129.8, 129.0, 128.5, 128.2, 126.2, 125.8, 124.1, 123.4, 118.3, 109.2, 75.8, 55.0, 54.7, 52.6, 42.9, 37.6, 37.4, 31.7, 31.3. HPLC: $t_{\text{R}} = 4.0$ min, ee 99.9%.

(-)-(R)-6-[3-(4-Benzyl-piperidin-1-yl)-1-hydroxy-1-methyl-propyl]-naphthalen-2-ol, [(-)-(R)-5]: Yellow oil; $[\alpha]_{\text{D}}^{20} = -24.8$ (c 0.1, CH₃OH). The IR and NMR spectra are identical to that of (+)-(S)-5. HPLC: $t_{\text{R}} = 5.0$ min, ee 99.9%.

(+)-(S)-6-[3-(4-Benzyl-piperidin-1-yl)-1-methyl-propyl]-naphthalen-2-ol, [(+)-(S)-6]: Yellow oil; $[\alpha]_{\text{D}}^{20} = +11.8$ (c 0.3, CH₃OH). IR (cm⁻¹): 3297, 2924, 2349, 2309, 1604, 1453, 1376, 1269; ¹H-NMR (500 MHz) (CDCl₃) δ (ppm): 7.42 (d, $J = 9.0$ Hz, 1H), 7.37 (s, 1H), 7.24 (t, 2H), 7.17 (d, $J = 8.0$ Hz, 1H), 7.17 (m, 1H), 7.06 (m, 3H), 6.98 (d, $J = 9.0$ Hz, 1H), 6.81 (s, 1H), 3.26 (broad peak, 1H), 3.10 (broad peak, 1H), 2.73 (m, 1H), 2.50–2.49 (broad peak, 4H), 2.14–2.12 (m, 2H), 2.04 (m, 2H), 1.67 (m, 2H), 1.60–1.54 (m, 3H), 1.28 (overlapped peak, 3H); ¹³C-NMR (500 MHz) (CDCl₃) δ (ppm): 154.6, 139.5, 133.6, 129.0, 128.3, 126.8, 126.0, 125.1, 125.0, 118.7, 109.2, 56.5, 53.7, 52.9, 42.3, 38.1, 37.0, 33.2, 30.0, 22.9. HPLC: $t_{\text{R}} = 4.9$ min, ee 99.9%.

(-)-(R)-6-[3-(4-Benzyl-piperidin-1-yl)-1-methyl-propyl]-naphthalen-2-ol, [(-)-(R)-6]: Yellow oil; $[\alpha]_{\text{D}}^{20} = -12.0$ (c 0.3, CH₃OH). The IR and NMR spectra are identical to that of (+)-(S)-6. HPLC: $t_{\text{R}} = 5.7$ min, ee 99.9%.

1.3. (Semi-)Preparative Chromatograms and Analytical Controls

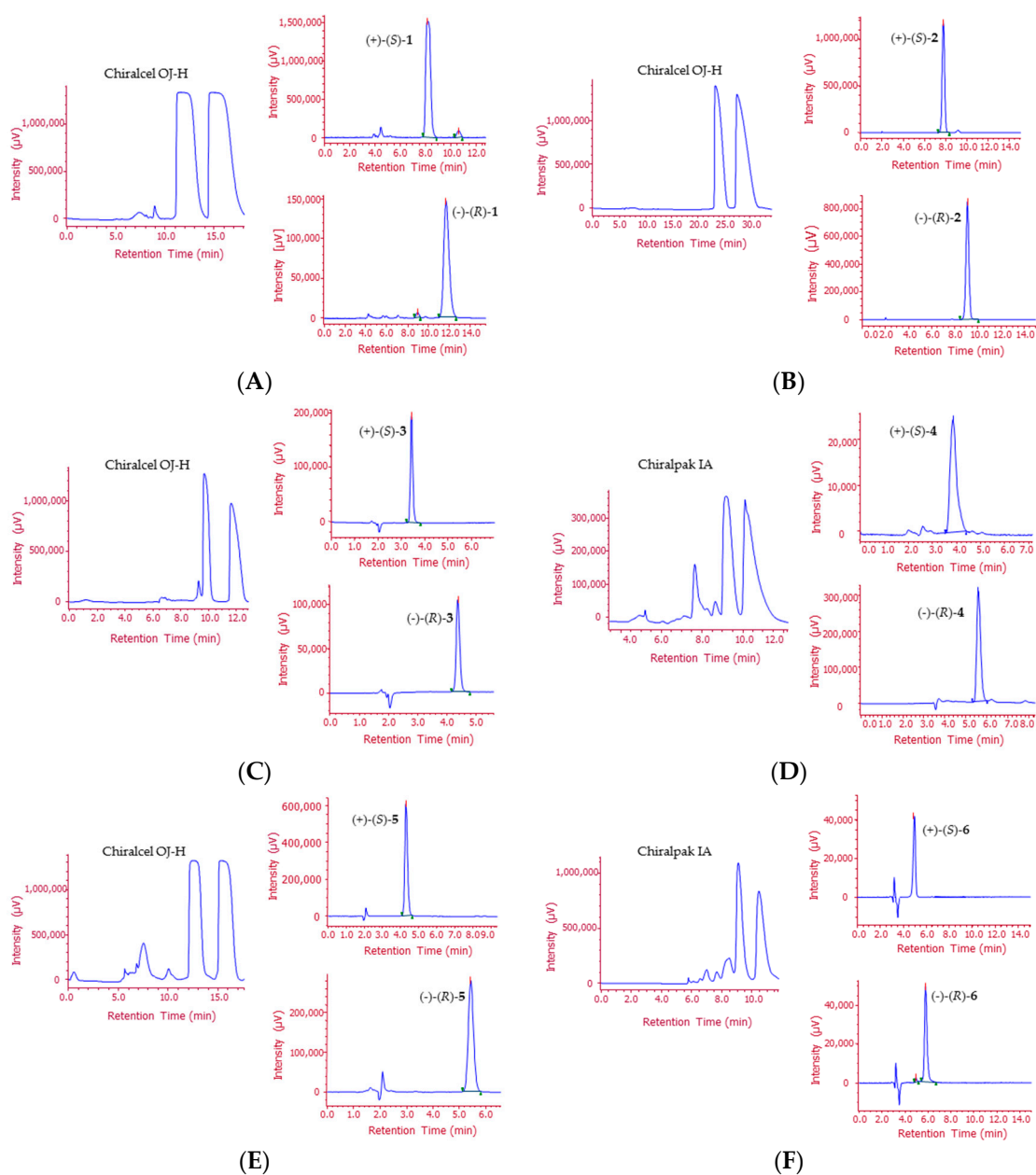


Figure S1. (Semi-)preparative enantiomer separations and analytical enantioselective analysis of first and second collected fractions of (A) **1**, (B) **2**, (C) **3**, (D) **4**, (E) **5**, (F) **6**. Elution conditions: (A) 100% EtOH, DEA 0.1%, flow rate 2.5 mL/min for (semi-)preparative analysis and 0.5 mL/min for analytical analysis; (B, C, E) 100% MeOH, DEA 0.1%, flow rate 2.5 mL/min for (semi-)preparative analysis and 0.5 mL/min for analytical analysis; and (D, F) 100% MeOH, 0.1% DEA, flow rate 2.5 mL/min for (semi-)preparative analysis and 1 mL/min for analytical analysis. Injection volume: 1 mL for (semi-)preparative analysis and 10 μ L for analytical analysis. Detection: 254 nm (Compounds **1**, **2**, **5**, **6**) and 220 nm (Compounds **3**, **4**).