Supporting Information

Synthesis and activity of functionalizable derivatives of the serotonin (5-HT) 5-HT_{2A} receptor (5-HT_{2A}R) antagonist M100907

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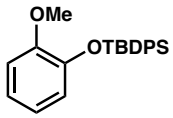
1. General Methods

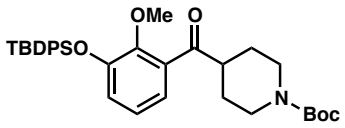
All starting materials and reagents were purchased from Sigma-Aldrich, Acros, AstaTech and Aapptec and used without further purification. Thin layer chromatography (TLC) was performed on Silicycle glass backed plates (extra hard layer, 250 μm thick, 60 Å, with F-254 indicator) and components were visualized by UV light (254 nm) and/or *p*-anisaldehyde, basic permanganate ($KMnO_4$) solution, or ninhydrin solution. Flash column chromatography was performed using Silicycle silica gel (particle size 40-63 μm, 230-400 mesh). NMR spectra were obtained using JEOL ECX-400 spectrometer (400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR) or JEOL ECA-500 spectrometer (500 MHz for ^1H NMR and 125 MHz for ^{13}C NMR). Chemical shifts were referenced to the residual chloroform-H peak at 7.26 ppm (^1H) and 77 ppm (^{13}C) in $CDCl_3$ or to DMSO-H peak at 2.5 ppm (^1H) and 40 ppm (^{13}C) in DMSO-d_6. Chemical shifts were reported in parts per million (ppm, δ). Multiplicity were indicated as s for singlet, d for doublet, t for triplet, d for quartet, m for multiplet, br for broad resonance and the coupling constants (*J*) were reported in Hz. High resolution mass spectra were recorded on an Agilent 6530 Accurate Mass Q-TOF LC/MS (high resolution ESI) from University of Texas at Austin, Mass Spectrometry Facility (MSF) of Department of Chemistry and Biochemistry.

Experimental Procedures

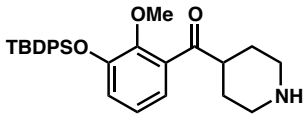


***tert*-butyl(2-methoxyphenoxy)diphenylsilane (6):** TBDPSCl (33.2 g, 120.8 mmol) was dissolved in 120 mL of anhydrous dichloromethane, followed by addition of imidazole (21.9 g, 322.2 mmol), which resulted in a suspension. The mixture was cooled to 0 °C in ice bath for 20 minutes and then guaiacol (10 g, 80.6 mmol) and DMAP (254 mg, 1.6 mmol) were added sequentially. The reaction was warmed to room temperature and stirred at room temperature for 13 hours. Water was used to quench the reaction and the reaction was extracted with water and dichloromethane three times. The organic layers were combined and dried over Na_2SO_4. The material was purified by column chromatography (5% EtOAc in hexanes) to afford the product as a colorless oil (28.6 g, 78.8 mmol, 98%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 8.0, 1.6 Hz, 4H), 7.43–7.31 (m, 6H), 6.83 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.76 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.72

(dd, J = 8.0, 1.6 Hz, 1H), 6.65 (dd, J = 8.1, 1.6 Hz, 1H), 3.56 (s, 1H), 1.11 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.47, 144.97, 135.27, 133.56, 129.51, 127.42, 121.52, 120.57, 120.19, 112.23, 55.09, 26.64, 19.72.

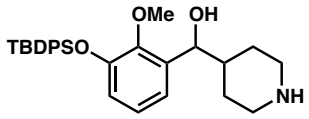


***tert*-butyl 4-(3-(*tert*-butyldiphenylsilyloxy)-2-methoxybenzoyl)piperidine-1-carboxylate (8):** *tert*-butyl(2-methoxyphenoxy)diphenylsilane (17.5 g, 48.3 mmol) was dissolved in anhydrous THF (35 mL) and the solution was cooled to -70 °C for 20 minutes. *n*-BuLi (25 mL of 2.5 M *n*-BuLi in hexanes, 62.8 mmol) and TMEDA (7.2 g, 62.8 mmol) were added. The mixture was warmed to room temperature and stirred for 2.5 hours then cooled to -70 °C and *tert*-butyl 4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate solution in anhydrous THF (12 g, 43.9 mmol in 35 mL of THF) was added. The reaction stirred at room temperature for 20 hours then quenched with saturated NH_4Cl aqueous solution followed by extraction of CH_2Cl_2 three times. The organic layers were combined and dried over Na_2SO_4. The material was purified by column chromatography (5% EtOAc in hexanes) to afford the product as a colorless oil (21.3 g, 37.1 mmol, 77%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, J = 7.2 Hz, 4H), 7.43–7.32 (m, 6H), 6.86 (dd, J = 7.0, 1.8 Hz, 1H), 6.71–6.63 (m, 2H), 4.19–3.96 (m, 2H), 3.93 (s, 3H), 3.21 (dd, J = 10.9, 3.5 Hz, 1H), 2.85 (br, 2H), 1.80 (d, J = 11.2 Hz, 2H), 1.57 (dd, J = 21.2, 9.8 Hz, 2H), 1.46 (s, 9H), 1.14 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 205.70, 154.47, 148.71, 148.39, 135.27, 134.49, 132.03, 129.91, 127.65, 123.80, 123.38, 120.78, 79.21, 61.82, 47.57, 28.26, 27.62, 26.38, 19.28.

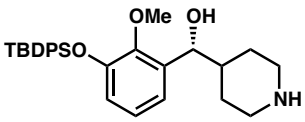


(3-(*tert*-butyldiphenylsilyloxy)-2-methoxyphenyl)(piperidin-4-yl)methanone (9): *tert*-butyl 4-(3-(*tert*-butyldiphenylsilyloxy)-2-methoxybenzoyl)piperidine-1-carboxylate (8 g, 13.9 mmol) was dissolved in TFA (15 mL) and the reaction was stirred at room temperature for 1 hour. The

reaction was diluted with 50 mL of diethyl ether and the pH was adjusted to greater than 10 with ammonium hydroxide. The mixture was extracted with diethylether. The organic layers were combined and dried over $MgSO_4$. Filtration and concentration yielded the crude residue, which was purified by column chromatography (10% methanol in dichloromethane) to afford the product as a white foam (6.5 g, 13.8 mmol, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75−7.69 (m, 4H), 7.46–7.33 (m, 6H), 6.91 (dd, *J* = 6.9, 2.4 Hz, 1H), 6.74–6.68 (m, 2H), 3.93 (s, 3H), 3.44 (s, 1H), 3.41–3.34 (m, 3H), 3.06 (ddd, *J* = 13.4, 10.4, 3.4 Hz, 2H), 2.13–2.04 (m, 2H), 2.00–1.90 (m, 2H), 1.14 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.86, 148.82, 148.64, 135.36, 133.22, 131.98, 130.04, 127.76, 124.23, 124.17, 121.16, 61.95, 44.41, 42.94, 26.43, 24.41, 19.36.



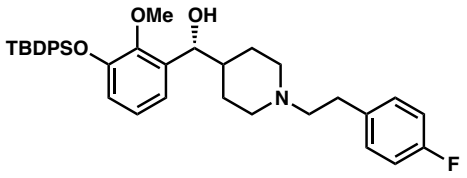
(3-(*tert*-butyldiphenylsilyloxy)-2-methoxyphenyl)(piperidin-4-yl)methanol (10): The solution of (3-(*tert*-butyldiphenylsilyloxy)-2-methoxyphenyl)(piperidin-4-yl)methanone (2.9 g, 5.3 mmol) in methanol (28 mL) was cooled to 0 °C for 10 minutes. $NaBH_4$ (1.2 g, 31.7 mmol) was added portionwise. The reaction was warmed to room temperature and stirred for another 18 hours. The solvent was removed completely and water and dichloromethane were added to suspend the material. The mixture was extracted with ammonium hydroxide and dichloromethane. The organic layers were combined and dried over $MgSO_4$. Filtration and concentration yielded the crude product as a white solid (2.7 g, 5.6 mmol, 92%), which was used directly for the chiral resolution step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79–7.69 (m, 4H), 7.45–7.29 (m, 6H), 6.82 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.63 (t, *J* = 7.9 Hz, 1H), 6.43 (dd, *J* = 8.1, 1.4 Hz, 1H), 4.62 (d, *J* = 7.9 Hz, 1H), 3.97 (s, 3H), 3.08 (d, *J* = 12.1 Hz, 1H), 2.97 (d, *J* = 12.1 Hz, 1H), 2.53 (td, *J* = 12.2, 2.0 Hz, 1H), 2.46 (td, *J* = 11.9, 3.1 Hz, 1H), 2.00 (d, *J* = 12.6 Hz, 1H), 1.77–1.67 (m, 1H), 1.31–1.15 (m, 3H), 1.13 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.33, 148.07, 137.13, 135.43, 135.41, 132.68, 132.35, 129.85, 129.83, 127.67, 127.62, 123.42, 120.03, 119.54, 73.64, 60.96, 46.33, 43.19, 29.82, 29.70, 26.51, 19.39.



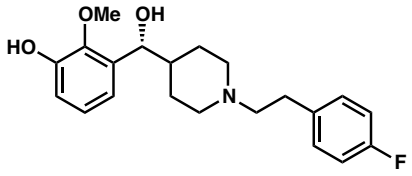
***(R)*-(3-(*tert*-butyldiphenylsilyloxy)-2-methoxyphenyl)(piperidin-4-yl)methanol ((R)-10):** The racemic mixture (9.3 g, 19.6 mmol) and (R)-mandelic acid (3.3 g, 21.5 mmol) were mixed together and 62 mL of methanol and 124 mL of acetonitrile were added. The mixture were warmed to 80 °C and stirred for 18 hours. The stir bar and heat were removed. The sample was capped tightly with septum and cooled gradually. First generation of crystals were resolved to 77% *ee* (4.8 g). The crystals were again added to 57 mL of methanol and 57 mL of acetonitrile and the mixture was warmed to 80 °C until crystals fully dissolved generating a light yellowish solution. The heat source and stir bar were removed. The sample was capped tightly with septum and cooled gradually. Second generation of crystals were formed to give a one diastereomer salt of 1:1 ratio of M100907:(R)-mandelic acid as white crystal (4.44 g, 7.1 mmol, 36% yield, > 95% *ee*).

Enantiomeric selectivity determination

The resolved diastereomeric salt was partitioned between ammonium hydroxide and dichloromethane. The ammonium hydroxide layers were extracted two more times with dichloromethane. The combined organic layer was dried over Na_2SO_4 and evaporated to dryness. The enantiomeric purity was determined by adding same weight of (R)-(-)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate to the free-based material and proton NMR was performed. $CDCl_3$ was used as NMR solvent and calibrated to 7.26 ppm as internal standard. The benzylic proton of *(R)*-(3-(*tert*-butyldiphenylsilyloxy)-2-methoxyphenyl)(piperidin-4-yl)methanol would shift to 4.4 ppm for (R)-form in the presence of (R)-(-)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate while the benzylic proton of racemic mixture is at 4.6 ppm. While the benzylic proton of *(S)*-(3-(*tert*-butyldiphenylsilyloxy)-2-methoxyphenyl)(piperidin-4-yl)methanol would shift to 4.5 ppm for (S)-form in the presence of (R)-(-)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate.

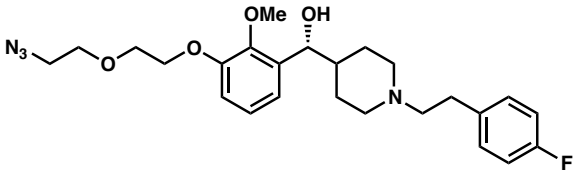


(*R*)-(3-(*tert*-butyldiphenylsilyloxy)-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanol (12): *(R)*-(3-(*tert*-butyldiphenylsilyloxy)-2-methoxyphenyl)(piperidin-4-yl)methanol (1.5 g, 3.1 mmol), 4-fluorophenethyl 4-methylbenzenesulfonate (1 g, 3.4 mmol), and $NaHCO_3$ (389 mg, 4.6 mmol) were mixed in anhydrous DMF (30 mL). The mixture was stirred at 80 °C for 2.5 hours. Extraction of the reaction was performed with water and EtOAc. The organic layers were combined and dried over $MgSO_4$. Filtration and concentration yielded the crude residue, which was purified by column chromatography (5% methanol in dichloromethane) to afford the product as a white foam (1.7 g, 2.8 mmol, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77–7.70 (m, 4H), 7.46–7.33 (m, 6H), 7.18–7.13 (m, 2H), 6.99–6.93 (m, 2H), 6.80 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.64 (t, *J* = 7.9 Hz, 1H), 6.43 (dd, *J* = 8.1, 1.5 Hz, 1H), 4.63 (d, *J* = 8.2 Hz, 1H), 3.99 (s, 3H), 3.10 (d, *J* = 11.5 Hz, 1H), 2.96 (d, *J* = 12.1 Hz, 1H), 2.82–2.76 (m, 2H), 2.58–2.50 (m, 2H), 2.10 (dd, *J* = 12.8, 2.4 Hz, 1H), 2.00 (td, *J* = 11.8, 2.5 Hz, 1H), 1.96–1.89 (m, 1H), 1.68 (dtt, *J* = 15.4, 7.8, 3.7 Hz, 1H), 1.50 (qd, *J* = 12.3, 3.9 Hz, 1H), 1.39 (qd, *J* = 12.4, 3.9 Hz, 1H), 1.30–1.24 (m, 1H), 1.13 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.29, 160.35, 148.42, 148.10, 136.77, 135.43, 135.41, 132.61, 132.34, 130.02, 129.96, 129.88, 127.71, 127.67, 123.50, 120.04, 119.77, 115.18, 115.01, 73.91, 61.02, 60.43, 53.54, 42.50, 32.38, 28.26, 26.52, 19.41.



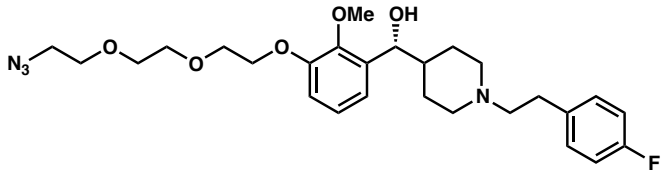
(*R*)-3-((1-(4-fluorophenethyl)piperidin-4-yl)(hydroxy)methyl)-2-methoxyphenol: (*R*)-(3-(*tert*-butyldiphenylsilyloxy)-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanol (185.6 mg, 0.3 mmol) solution in methanol (7 mL) was added NH_4F (34.5 mg, 0.9 mmol). The reaction was refluxed at 70 °C for 20 minutes. The solvent was removed and the residue was

extracted with water and dichloromethane. The organic layers were combined and dried over Na_2SO_4. Filtration and concentration yielded the crude residue, which was purified by column chromatography (5% methanol in dichloromethane) to afford the product as an off-white foam (105.7 mg, 0.3 mmol, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12–7.07 (m, 2H), 6.98 (t, *J* = 7.9 Hz, 1H), 6.96–6.91 (m, 2H), 6.84 (ddd, *J* = 9.7, 8.0, 1.5 Hz, 2H), 4.62 (d, *J* = 8.1 Hz, 1H), 3.81 (s, 3H), 3.14 (d, *J* = 11.3 Hz, 1H), 2.98 (d, *J* = 11.1 Hz, 1H), 2.84–2.75 (m, 2H), 2.63–2.53 (m, 2H), 2.13–2.02 (m, 2H), 1.97 (t, *J* = 11.0 Hz, 1H), 1.76–1.65 (m, 1H), 1.51 (qd, *J* = 12.5, 2.2 Hz, 1H), 1.40 (qd, *J* = 12.5, 3.1 Hz, 1H), 1.30 (d, *J* = 12.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.29, 160.36, 149.37, 145.54, 136.10, 135.32, 129.97, 129.90, 124.60, 118.57, 116.04, 115.20, 115.03, 73.27, 61.08, 60.47, 53.43, 42.34, 32.13, 28.18, 27.91.



(*R*)-(3-(2-(2-azidoethoxy)ethoxy)-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanol (4): To a cooled suspension of NaH (36 mg, 1.5 mmol) in anhydrous DMF (20 mL) was added (*R*)-3-((1-(4-fluorophenethyl)piperidin-4-yl)(hydroxy)methyl)-2-methoxyphenol. (540.7 mg, 1.5 mmol) The mixture was stirred at room temperature for 30 minutes then cooled to 0 °C for 10 minutes and 2-(2-azidoethoxy)ethyl 4-methylbenzenesulfonate (470.3 mg, 1.7 mmol) solution in DMF (3 mL) was added to the mixture. The reaction was warmed to room temperature and stirred for another 15 hours. The reaction was quenched with water followed by extraction of EtOAc (20 mL for 3 times). The organic layers were combined and dried over $MgSO_4$. Filtration and concentration yielded the crude residue, which was purified by column chromatography (5% methanol in dichloromethane) to afford the product as a light yellowish oil (609.6 mg, 1.3 mmol, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14–7.08 (m, 2H), 7.01 (t, *J* = 7.9 Hz, 1H), 6.96–6.88 (m, 3H), 6.84 (dd, *J* = 8.1, 1.2 Hz, 1H), 4.61 (d, *J* = 8.0 Hz, 1H), 4.15 (t, *J* = 4.8 Hz, 2H), 3.93–3.83 (m, 5H), 3.73 (t, *J* = 4.9 Hz, 2H), 3.39 (t, *J* = 4.9 Hz, 2H), 3.09 (d, *J* = 11.1 Hz, 1H), 2.95 (d, *J* = 11.2 Hz, 1H), 2.82–2.73 (m, 2H), 2.57–2.50 (m, 2H), 2.09–1.98 (m, 2H), 1.97–1.90 (m, 1H), 1.71–1.62 (m, 1H), 1.55–1.45 (m, 1H), 1.46–1.36 (m, 1H), 1.30 (d, *J* = 12.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.23, 160.29, 151.42, 146.73, 136.46, 135.64,

129.97, 129.91, 123.76, 120.15, 115.11, 114.94, 112.91, 74.17, 70.07, 69.70, 68.03, 60.80, 60.54, 53.53, 50.71, 42.56, 32.49, 28.40, 28.34.



(*R*)-(3-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanol: To a cooled suspension of NaH (13.8 mg, 0.58 mmol) in anhydrous DMF (4 mL) was added (*R*)-3-((1-(4-fluorophenethyl)piperidin-4-yl)(hydroxy)methyl)-2-methoxyphenol (188 mg, 0.52 mmol). The mixture was stirred at room temperature for 30 minutes then cooled to 0 °C for 10 minutes and 2-(2-(2-azidoethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (189 mg, 0.58 mmol) solution in DMF (2 mL) was added to the mixture. The reaction was warmed to room temperature and stirred for another 25 hours. The reaction was quenched with water followed by extraction of EtOAc (5 mL for 3 times). The organic layers were combined and dried over $MgSO_4$. Filtration and concentration yielded the crude residue, which was purified by column chromatography (4% methanol in dichloromethane) to afford the product as an oil (142.1 mg, 0.28 mmol, 56%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11–7.06 (m, 2H), 6.98 (t, *J* = 7.9 Hz, 1H), 6.94–6.88 (m, 3H), 6.81 (dd, *J* = 8.1, 1.3 Hz, 1H), 4.59 (d, *J* = 8.0 Hz, 1H), 4.12 (t, *J* = 4.8 Hz, 2H), 3.90–3.83 (m, 5H), 3.74–3.69 (m, 2H), 3.65–3.61 (m, 4H), 3.34 (t, *J* = 3.1 Hz, 2H), 3.03 (d, *J* = 11.2 Hz, 1H), 2.90 (d, *J* = 11.2 Hz, 1H), 2.77–2.69 (m, 2H), 2.53–2.46 (m, 2H), 2.03 (d, *J* = 13.0 Hz, 1H), 1.95 (td, *J* = 11.7, 2.0 Hz, 1H), 1.88 (td, *J* = 11.6, 2.3 Hz, 1H), 1.70–1.57 (m, 1H), 1.52–1.31 (m, 2H), 1.26 (d, *J* = 12.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.11, 160.18, 151.39, 146.63, 136.52, 135.82, 129.89, 129.83, 123.61, 119.96, 114.98, 114.81, 112.69, 73.96, 70.62, 70.57, 69.89, 69.66, 67.91, 60.67, 60.62, 53.54, 50.48, 42.63, 32.57, 28.48.