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SUPPORTING INFORMATION

Hybrid dopamine uptake blocker-serotonin releaser ligands: a new twist on transporter-focused therapeutics

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Synthetic Chemistry

General Preparation of Hybrid Analogs – 2-(Cyclopropylamino)-1-(3'-Tolyl)-1-oxopropane Fumarate (3c): The following is a typical procedure used to synthesize the hybrid analogs. 3'-Methylpropiophenone (3 g, 20.2 mmol) was dissolved in DCM (70 mL) and treated with bromine (3.56 g, 22.3 mmol) and stirred at room temperature for 30 minutes. The reaction was quenched with saturated aqueous $NaHCO_3$, the organic phase was separated, washed with brine, dried ($MgSO_4$) and concentrated to yield a quantitative amount of **5c** as a yellow oil, which required no further purification. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 7.87-7.79 (m, 2 H), 7.48-7.34 (m, 2 H), 5.31 (q, 1 H, J = 3 Hz, 6 Hz), 2.43 (s, 3 H), 1.92 (d, 3 H, J = 6 Hz).

A solution of **5c** (1.1 g, 4.8 mmol) and cyclopropylamine (0.85 mL, 12.3 mmol) in THF (30 mL) was sealed in a glass reactor with Teflon cap and heated to 50 C for 18 h. The reaction mixture was concentrated and the residue was taken up into ethyl acetate and washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated. The crude product was purified by automated flash chromatography (silica gel, 4/1 hexane/ethyl acetate) to yield 442 mg (45%) of yellow oil. The fumarate salt was prepared and recrystallized to yield 149 mg (22%) of pure **3c**. (Generally the fumarate salt was prepared, but occasionally, the hydrochloride salt could be obtained). Mp = 129-130 C (dec.); ^{1}H NMR (d_6-DMSO, 300 MHz) δ 7.96-7.80 (m, 2 H), 7.50-7.41 (m, 2 H), 6.61 (s, 2 H), 4.50 (q, 1 H, J = 6.9 Hz), 2.39 (s, 3 H), 2.11-2.08 (m, 1 H), 1.19 (d, 3 H, J = 7.2 Hz), 0.40-0.32 (m, 4 H); ESI-MS, calculated for $C_{13}H_{17}NO$ $(M+H)^+$ 204.3; observed 204.6; Anal. Calculated for $C_{17}H_{21}NO_5$; C, 63.94; H, 6.63; N, 4.39. Found: C, 63.93; H, 6.62; N, 4.47.

Free Base: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 7.81-7.76 (m, 2 H), 7.42-7.38 (m, 2 H), 4.42 (q, 1 H, J = 6 Hz), 2.44 (s, 3 H), 2.39 (br s, 1 H), 2.12-2.06 (m, 1 H), 1.29 (d, 3 H, J = 9 Hz), 0.47-0.35 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.0, 138.6, 135.8, 134.0, 128.7, 125.5, 57.8, 28.7, 21.3, 19.9, 6.6, 6.3.

2-(Cyclopropylamino)-1-(3'-Bromophenyl)-1-oxopropane hydrochloride (3b): Mp = 183-184 C (dec.); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.23 (s, 1 H), 8.06 (d, 1 H, J = 6 Hz), 7.91 (d, 1 H, J = 9 Hz), 7.54 (t, 1 H, J = 9 Hz), 5.24 (q, 1 H, J = 6 Hz, 9 Hz), 2.84-2.75 (m, 1 H), 1.60 (d, 3 H, J = 9 Hz), 0.95-0.87 (m, 4 H); ^{13}C NMR (d_6-DMSO, 75 MHz) δ 131.2, 128.5, 102.0, 58.3, 28.1, 16.0, 5.5, 4.8; ESI-MS, calculated for $C_{12}H_{13}BrNO$ $(M+H)^+$ 269.2; observed 268.1; Anal. Calculated for $C_{12}H_{14}BrClNO$; C, 47.32; H, 4.96; N, 4.60. Found: C, 47.25; H, 4.97; N, 4.53.

2-(Cyclopropylamino)-1-(3'-Methoxyphenyl)-1-oxopropane hydrochloride (3d): The product was isolated as a white solid in 41% yield (57 mg), mp = 205-206 C (dec.); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.67 (d, 1 H, J = 9 Hz), 7,58 (s, 1 H), 7.52 (t, 1 H, J = 9 Hz), 7.31 (dd, 1 H, J = 3 Hz, 6 Hz), 5.25 (q, 1 H, J = 6 Hz, 9 Hz), 3.88 (s, 3 H), 2.83-2.76 (m, 1 H), 1.61 (d, 3 H, J = 6 Hz), 0.94-0.89 (m, 4 H); ESI-MS, calculated for $C_{13}H_{17}NO_2$ $(M+H)^+$ 220.3; observed 220.5; Anal. Calculated for $C_{13}H_{18}ClNO_2$; C, 61.05; H, 7.09; N, 5.48. Found: C, 60.81; H, 7.03; N, 5.47.

Free Base: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 7.58 (d, 1 H, J = 6 Hz), 7.53 (s, 1 H), 7.41 (dd, 1 H, J = 6 Hz, 9 Hz), 7.16-7.12 (m, 1 H), 4.41 (q, 1 H, J = 6 Hz, 9 Hz), 3.88 (s, 3 H), 2.37-2.09 (m, 2

H), 1.29 (d, 3 H, J = 6 Hz), 0.47-0.34 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.5, 127.8, 126.9, 121.0, 120.2, 116.7, 112.0, 107.0, 103.0, 53.3, 9.8, 8.4, 4.5.

2-(Cyclopropylamino)-1-(4'-Chlorophenyl)-1-oxopropane fumarate (3e): The product was isolated as a white solid in 26% yield (127 mg), mp = 163-164 C (dec.); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.08-8.04 (m, 2 H), 7.62-7.58 (m, 2 H), 6.70 (s, 2 H), 4.96 (q, 1 H, J = 6 Hz, 9 Hz), 2.58-2.51 (m, 1 H), 1.49 (d, 3 H, J = 9 Hz), 0.75 (d, 4 H, J = 3 Hz); ^{13}C NMR (d_6-DMSO, 75 MHz) δ 166.0, 138.2, 134.0, 128.9, 115.9, 57.4, 28.2, 18.3, 6.2, 5.9; ESI-MS, calculated for $C_{12}H_{14}ClNO$ $(M+H)^+$ 224.7; observed 224.3; Anal. Calculated for $C_{16}H_{18}ClNO_5$; C, 56.56; H, 5.34; N, 4.12; Cl, 10.43. Found: C, 56.62; H, 5.41; N, 4.11; Cl, 10.52.

Free Base: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 7.95 (dd, 2 H, J = 3 Hz), 7.47 (dd, 2 H, J = 3 Hz), 4.37 (q, 1 H, J = 6 Hz), 2.36 (br s, 1 H), 2.11-2.08 (m, 1 H), 1.29 (d, 3 H, J = 9 Hz), 0.44-0.36 (m, 4 H).

2-(Cyclopropylamino)-1-(4'-Tolyl)-1-oxopropane Fumarate (3f): The fumarate salt was prepared and recrystallized to yield 162 mg (26%) of pure **2a** (Generally the fumarate salt was prepared, but occasionally, the hydrochloride salt could be obtained). Mp = 159-160 C (dec.); ^{1}H NMR (CD_3OD 300 MHz) δ 7.96 (d, 2 H, J = 6 Hz), 7.40 (d, 2 H, J = 9 Hz), 6.70 (s, 2 H), 5.00 (q, 1 H, J = 6 Hz, 9 Hz), 2.62-2.55 (m, 1 H), 2.44 (s, 3 H), 1.50 (d, 3 H, J = 6 Hz), 0.80-0.73 (m, 4 H); ESI-MS, calculated for $C_{13}H_{17}NO$ $(M+H)^+$ 204.3; observed 204.8; Anal. Calculated for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.88; H, 6.59; N, 4.42.

Free Base: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 7.91 (d, 2 H, J = 9 Hz), 7.31-7.26 (m, 2 H), 4.43 (q, 1 H, J = 6 Hz), 2.43 (s, 3 H), 2.11-2.05 (m, 1 H), 1.28 (d, 3 H, J = 6 Hz), 0.46-0.34 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.3, 144.1, 133.2, 129.4, 128.4, 57.6, 28.7, 21.6, 10.3, 6.6, 6.3.

2-(Cyclopropylamino)-1-(3',4'-Dichlorophenyl)-1-oxopropane hydrochloride (3g): The product was isolated as a white solid in 36% yield (146 mg), mp = 209-210 C (dec.); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.26 (s, 1 H), 8.01 (dd, 1 H, J = 6 Hz, 9 Hz), 7.80 (d, 1 H, J = 9 Hz), 5.27 (q, 1 H, J = 6 Hz, 9 Hz), 2.83-2.79 (m, 1 H), 1.62 (d, 3 H, J = 9 Hz), 0.98-0.93 (m, 4 H); ^{13}C NMR (d_6-DMSO, 75 MHz) δ 132.3, 131.5, 130.7, 128.9, 58.2, 28.1, 15.5, 3.7; ESI-MS, calculated for $C_{12}H_{13}Cl_2NO$ $(M+H)^+$ 259.1; observed 258.5; Anal. Calculated for $C_{12}H_{14}Cl_3NO$; C, 48.92; H, 4.79; N, 4.75; Cl, 36.10. Found: C, 48.80; H, 4.70; N, 4.66; Cl, 36.12.

Free Base: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 8.08 (s, 1 H), 7.83 (d, 1 H, J = 6 Hz), 7.58 (d, 1 H, J = 9 Hz), 4.33 (q, 1 H, J = 6 Hz), 2.12-2.05 (m, 2 H), 1.29 (d, 3 H, J = 6 Hz), 0.45-0.37 (m, 4 H).

2-(Cyclopropylamino)-1-(3'-Chloro-4'-Methylphenyl)-1-oxopropane hydrochloride (3h): The product was isolated as a white solid in 29% yield (20 mg), mp = 197-198 C (dec.); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.08 (s, 1 H), 7.92 (dd, 1 H, J = 3 Hz, 6 Hz), 7.55 (d, 1 H, J = 9 Hz), 5.19 (q, 1 H, J = 6 Hz, 9 Hz), 2.79-2.72 (m, 1 H), 2.48 (s, 3 H), 1.59 (d, 3 H, J = 9 Hz), 0.92-0.89 (m, 4 H); ESI-MS, calculated for $C_{13}H_{16}ClNO$ $(M+H)^+$ 238.7; observed 238.2; Anal. Calculated (with 0.1 mol water) for $C_{13}H_{17}Cl_2NO$; C, 56.58; H, 6.28; N, 5.08. Found: C, 56.44; H, 6.27; N, 5.06.

Free Base: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 7.97 (s, 1 H), 7.79 (dd, 1 H, J = 3 Hz, 6 Hz), 7.36 (d, 1 H, J = 9 Hz), 4.36 (q, 1 H, J = 6 Hz, 9 Hz), 2.45 (s, 3 H), 2.28-2.09 (m, 2 H), 1.28 (d, 3 H, J = 6 Hz), 0.46-0.37 (m, 4 H);

(S)-2-(Cyclopropylamino)-1-(3'-chlorophenyl)-1-oxopropane hydrochloride ((-)-3a): (R)-1-(3'-chlorophenyl)-2-hydroxypropanone was prepared and converted to **(-)-3a**, as described by Lukas, et al. (J. Med. Chem. 2010, 53(12), 4731-4748) by using cyclopropylamine as the required amine. The crude material was purified via silica gel on an automated chromatography system using 15% ethyl acetate from hexane to yield 70 mg (29%) of yellow oil. This oil was dissolved in diethyl ether and treated with 2 N HCl/ether. The resulting hydrochloride salt was recrystallized from methanol/diethyl ether to yield 27 mg (33%) of **(-)-3a**. Mp = 167-168 C (dec.); ^{1}H-NMR (CD_3OD 300 MHz) δ 8.09 (s, 1 H), 8.03 (d, 1 H, J = 6 Hz), 7.77 (dd, 1 H, J = 3 Hz, 6 Hz), 7.61 (dd, 1 H, J = 6 Hz, 9 Hz), 5.28 (q, 1 H, J = 6 Hz, 9 Hz), 2.88-2.78 (m, 1 H), 1.62 (d, 3 H, J = 6 Hz), 1.03-0.89 (m, 4 H); ESI-MS, calculated for $C_{12}H_{14}ClNO$ $(M+H)^+$ 224.7; observed 224.3; Anal. calculated for $C_{12}H_{15}Cl_2NO$: C, 55.40; H, 5.81; N, 5.38. Found: C, 55.25; H, 5.80; N, 5.36.

Free Base: ^{1}H-NMR ($CDCl_3$ 300 MHz) δ 7.97 (s, 1 H), 7.88 (d, 1 H, J = 9 Hz), 7.57 (dd, 1 H, J = 3 Hz, 6 Hz), 7.44 (dd, 1 H, J = 6 Hz, 9 Hz), 4.43-4.34 (m, 1 H), 2.35 (br s, 1 H), 2.14-2.08 (m, 1 H), 1.29 (d, 3 H, J = 6 Hz), 0.49-0.33 (m, 4 H); ^{13}C-NMR ($CDCl_3$ 75 MHz) δ 132.2, 131.3, 129.9, 129.2, 129.0, 127.8, 103.2, 72.7, 35.1, 13.9, 10.9, 7.6; [α] = - 13.7 (c = 3.35/$CHCl_3$).

(R)-2-(Cyclopropylamino)-1-(3'-chlorophenyl)-1-oxopropane hydrochloride ((+)-3a): (S)-1-(3'-chlorophenyl)-2-hydroxypropanone was prepared (using AD-Mix-α) and converted to (+)-**3a**, as described by Lukas, et al. (J. Med. Chem. 2010, 53(12), 4731-4748) by using cyclopropylamine as the required amine. The crude material was purified via silica gel on an automated chromatography system using 15% ethyl acetate from hexane to yield 335 mg (28%) of yellow oil. This oil was dissolved in diethyl ether and treated with 2 N HCl/ether. The resulting hydrochloride salt was recrystallized from methanol/diethyl ether to yield 149 mg (38%) of **(+)-3a**. Mp = 169-170 C (dec.); ^{1}H-NMR (D_2O 300 MHz) δ 7.95 (s, 1 H), 7.84 (d, 1 H, J = 6 Hz), 7.67 (dd, 1 H, J = 3 Hz, 6 Hz), 7.48 (dd, 1 H, J = 6 Hz, 9 Hz), 5.13 (q, 1 H, J = 6 Hz, 9 Hz), 2.77-2.69 (m, 1 H), 1.53 (d, 3 H, J = 9 Hz), 0.93-0.79 (m, 4 H); ESI-MS, calculated for $C_{12}H_{14}ClNO$ $(M+H)^+$ 224.7; observed 224.3; Anal. calculated for $C_{12}H_{15}Cl_2NO$: C, 55.40; H, 5.81; N, 5.38. Found: C, 55.29; H, 5.71; N, 5.37.

Free Base: ^{1}H-NMR ($CDCl_3$ 300 MHz) δ 7.97 (s, 1 H), 7.88 (d, 1 H, J = 9 Hz), 7.55 (d, 1 H, J = 6 Hz), 7.44 (dd, 1 H, J = 6 Hz, 9 Hz), 4.43-4.36 (m, 1 H), 2.31 (br s, 1 H), 2.15-2.07 (m, 1 H), 1.29 (d, 3 H, J = 6 Hz), 0.50-0.34 (m, 4 H); ^{13}C-NMR ($CDCl_3$ 75 MHz) δ 135.1, 133.2, 130.0, 128.4, 126.4, 58.1, 28.7, 19.6, 6.7, 6.3; [α] = + 23.7 (c = 2.7/$CHCl_3$).

3-Chloroamphetamine hydrochloride (8): To a stirred mixture of ammonium acetate (1.31 g, 17.0 mmol) in nitroethane (25 mL) was added 3-chlorobenzaldehyde (2.4 g, 17.1 mmol); this mixture was refluxed under nitrogen for 7 hours. Upon cooling to room temperature, the reaction was concentrated and the residue was dissolved in a solution of 10% DCM in diethyl ether (30 mL) and washed with brine and 1 M HCl. The organic layer was dried (Na_2SO_4), filtered and concentrated. The crude product was purified via flash chromatography (silica gel,

5% ethyl acetate/hexanes) affording 1.59 g (47%) of pure **1**-(3'-chlorophenyl)-2-nitropropene. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 8.01 (s, 1 H), 7.36 (m, 2 H), 7.33 (m, 2 H), 2.45 (s, 3 H).

A solution of 1-(3'-chlorophenyl)-2-nitropropene (1.59 g, 8.0 mmol) in DCM (9.2 mL), under nitrogen, was treated dropwise with 1.0 M $LiAlH_4$/THF solution (18.7 mL, 18.7 mmol); this reaction was refluxed for 18 h. Upon cooling, the reaction was quenched via dropwise addition of water. A saturated aqueous Rochelle's salt (potassium sodium tartrate tetrahydrate) solution (85 mL) was added and the mixture stirred for 2 h, under nitrogen. This mixture was extracted with 3:1 DCM/THF. The organic layer was then dried (Na_2SO_4), filtered and concentrated affording 1.40 g (100%) of crude **8**. The crude material was purified via flash chromatography (silica gel, 2% NH_4OH/ethyl acetate) affording 856 mg (63%) of yellow oil. This material was converted to the hydrochloride salt and recrystallized from ethyl acetate/methanol. MP = 181-3 C (dec.). ^{1}H NMR (CD_3OD 300 MHz) δ 7.36 (m, 3 H), 7.23 (d, 1 H, J = 7.0 Hz), 3.55 (m, 1 H), 2.98-2.83 (m, 2 H), 1.28 (d, 3 H, J = 6.6 Hz); ESI-MS, calculated for $C_9H_{12}ClN$ $(M+H)^+$ 170.6; observed 170.1; Anal. Calculated for $C_9H_{13}Cl_2N$; C, 52.45; H, 6.36; N, 6.80. Found: C, 52.60; H, 6.38; N, 6.73.

2-(Methylamino)-1-(3'-Chlorophenyl)-1-oxopropane hydrochloride (9): 3-Chloropropiophenone (25 g, 148.2 mmol) was dissolved in DCM (600 mL) and treated with bromine (26.1 g, 163.1 mmol) and stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the organic phase was separated, washed with brine, dried ($MgSO_4$) and concentrated to yield 37.6 g (100%) of product as a yellow oil, which required no further purification. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 8.00 (s, 1 H), 7.90 (d, 1 H, J = 6 Hz), 7.57 (d, 1 H, J = 6 Hz), 7.44 (dd, 1 H, J = 6 Hz, 9 Hz), 5.28-5.21 (m, 1 H), 1.91 (d, 3 H, J = 6 Hz).

A solution of 2-Bromo-1-(3'-Chlorophenyl)-1-oxopropane (37.6 g, 148.2 mmol) and N-benzylmethylamine (38.2 mL, 296 mmol) in THF (600 mL) was refluxed for 18 h. The reaction mixture was concentrated and the residue was taken up into ethyl acetate and washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated. The crude product was purified by automated flash chromatography (silica gel, 4/1 hexane/ethyl acetate) to yield 37.2 g (87%) of 2-(N-Benzyl-N-methylamino)-1-(3'-chlorophenyl)-1-oxopropane as a yellow oil. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 7.99 (s, 1 H), 7.85 (d, 1 H, J = 9 Hz), 7.54-7.50 (m, 1 H), 7.39-7.22 (m, 6 H), 4.37-4.27 (m, 1 H), 3.63 (s, 2 H), 2.19 (s, 3 H), 1.29 (d, 3 H, J = 6 Hz).

A solution of 2-(N-Benzyl-N-methylamino)-1-(3'-chlorophenyl)-1-oxopropane (56.8 g, 197.4 mmol) and 1-chloroethyl chloroformate (43.0 mL, 394.7 mmol) in dichloroethane (1.2 L) was refluxed for 2 h. The reaction mixture was concentrated and the residue was dissolved in methanol (1.2 L) and refluxed for 1 h. The reaction mixture was concentrated and the residue was stirred in diethyl ether (1.2 L) for 18 h. The solids were filtered, washed with ether and dried to obtain a grey solid. The crude material was recrystallized from ethyl acetate/methanol to yield 40.6 g (88%) of **9** as a grey solid. MP = 181-3 C (dec.). ^{1}H NMR (D_2O 300 MHz) δ 7.95 (s, 1 H), 7.83 (d, 1 H, J = 6 Hz), 7.68 (d, 1 H, J = 6 Hz), 7.49 (dd, 1 H, J = 6 Hz, 9 Hz), 4.97 (q, 1 H, J = 7.5 Hz), 2.70 (s, 3 H), 1.57 (d, 3 H, J = 6 Hz); ESI-MS, calculated for $C_{10}H_{12}ClNO$ $(M+H)^+$ 197.7; observed 198.1; Anal. Calculated for $C_{10}H_{13}Cl_2NO$; C, 51.30; H, 5.60; N, 5.98. Found: C, 51.03; H, 5.49; N, 5.79.

2-(Methylamino)-1-phenylbutane hydrochloride (10): A solution of 1-phenyl-2-butanone (2.62 g, 17.7 mmol) and methylamine (0.61 mL, 17.7 mmol) in dichloroethane (61.8 mL) was treated with sodium triacetoxyborohydride (5.24 g, 24.7 mmol); this mixture stirred for 4 days at room temperature, but the reaction never went to completion. The reaction was quenched with 50% aqueous NaOH solution (1.78 mL) and the mixture was diluted with water. This mixture was extracted with 3:1 DCM/THF and the organic layer was concentrated. The residue was dissolved in diethyl ether, washed with water, dried (Na_2SO_4), filtered and concentrated. The crude product was purified via flash chromatography (silica gel, 10% ethyl acetate/hexanes) affording 552 mg (19%) of pure **10**. This material was converted to the hydrochloride salt and recrystallized from ethyl acetate/methanol. MP = 109-110 C. ^{1}H NMR (CD_3OD 300 MHz) δ 7.39 (m, 5 H), 3.42-3.38 (m, 1 H), 3.08-3.02 (m, 1 H), 2.96-2.91 (m, 1 H), 1.68 (q, 2 H, J = 6 Hz, 9 Hz), 1.01 (t, 3 H, J = 6 Hz); Anal. Calculated for $C_{11}H_{18}ClN$; C, 66.15; H, 9.08; N, 7.01. Found: C, 65.95; H, 9.05; N, 6.94.

2-Amino-1-phenylpentane hydrochloride (12): A mixture containing ammonium acetate (0.71 g, 9.1 mmol), benzaldehyde (2.4 g, 17.1 mmol) and nitrobutane (2.3 g, 22.1 mmol) in glacial acetic acid (5 mL) was heated to 100 C for 18 hours. Upon cooling to room temperature, the reaction was diluted with water (20 mL) and basified with concentrated ammonium hydroxide. This mixture was extracted with DCM and the organics were washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified via automated flash chromatography (silica gel, 10% ethyl acetate/hexanes) affording 0.69 mg (38%) of pure 1-phenyl-2-nitro-1-pentene. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 8.30 (s, 1 H), 7.49-7.40 (m, 5 H), 2.82 (dd, 2 H, J = 3 Hz, 6 Hz), 1.74-1.62 (m, 2 H), 1.06-0.98 (m, 3 H).

A solution of 1-phenyl-2-nitro-1-pentene (0.69 g, 3.6 mmol) in anhydrous THF (30 mL), under nitrogen, was treated dropwise with 1.0 M $LiAlH_4$/THF solution (12 mL, 12 mmol); this reaction was refluxed for 18 h. Upon cooling, the reaction was quenched via dropwise addition of 1:1 water/THF and basified with aqueous 2 N NaOH. The mixture was filtered through Celite, dried ($MgSO_4$), filtered and concentrated. The crude material was purified via automated flash chromatography (silica gel, 20% methanol/ethyl DCM) affording 335 mg (57%) of yellow oil. This material was converted to the hydrochloride salt and recrystallized from ethyl acetate/methanol to yield 56 mg (14%) of **12**. MP = 119-120 C. ^{1}H NMR (CD_3OD 300 MHz) δ 7.39-7.34 (m, 2 H), 7.31-7.25 (m, 3 H), 3.48-3.41 (m, 1 H), 2.92 (dd, 2 H, J = 3 Hz), 1.61-1.54 (m, 4 H), 0.94 (dd, 3 H, J = 6 Ha, 9 Hz); ESI-MS, calculated for $C_{11}H_{17}N$ $(M+H)^+$ 164.2; observed 164.6; Anal. Calculated for $C_{11}H_{18}ClN$; C, 66.15; H, 9.08; N, 7.01. Found: C, 66.11; H, 9.10; N, 7.03.

Biological Assays

Calcium Mobilization Assay – General Procedure.
Cells stably over-expressing the desired human receptor cDNA were plated into 96-well black-walled assay plates in growth medium. After incubating at 37°C, 5% CO_2 overnight, the growth medium was removed and the cells were gently washed with 100 µL of pre-warmed (37°C) assay buffer (1X HBSS, 20 mM HEPES, 2.5 mM probenecid, pH 7.4). The cells were incubated for 45 minutes at 37°C, 5% CO_2 in 200 µL of a calcium-sensitive fluorescent dye (½ the

manufacturer's recommended concentration diluted in assay buffer without probenecid, calcium 5 assay kit, Molecular Devices). During the incubation period, test compounds were prepared at 10X final concentration in assay buffer/1% DMSO and aliquoted into 96-well polypropylene plates. After 45 minutes, 25 µL of pretreatment (assay buffer/10% DMSO) was added to the wells and incubated for 15 minutes at 37°C. Calcium-mediated changes in fluorescence were monitored in a FlexStation II (Molecular Devices) plate reader. Fluorescence intensity was measured every 1.52 seconds over a 60 second time period, with the FlexStation II adding 25 µL of test compound at the 19 second time point (excitation at 485 nm, detection at 525 nm). Peak kinetic reduction (SoftMax, Molecular Devices) relative fluorescent units (RFU) were used to calculate % of control 5-HT E_{MAX}.

5-HT$_{2A,2B,2C}$ HEK293 assay.
The calcium mobilization general procedure was followed using $5HT_{2A}$ HEK293 cells plated at 35,000 cells/well in plates pre-coated with PEI. The growth medium was DMEM-HG supplemented with 10% fetal bovine serum, 100 units of penicillin and streptomycin, 15mM HEPES, and 100 µg/mL normocin™.

5-HT$_{1A}$ Gα16-CHO assay.
The calcium mobilization general procedure was followed using 5-HT_{1A} Gα16-CHO cells plated at 25,000 cells/well. The growth medium was Ham's F12 supplemented with 10% fetal bovine serum, 100 units of penicillin and streptomycin, and 100 µg/mL normocin™.

β-Arrestin Recruitment Assay (PathHunter Detection Kit, DiscoveRx).
CHOk1 cells stably expressing the 5-HT_{2A} receptor cDNA fused to the Prolink gene were plated into 96-well white-walled assay plates at a density of 15,000 cells/well in Cell Plating Reagent (DiscoveRx) and incubated at 37°C, 5% CO_2 overnight. The next day, test compounds were prepared at 10X final concentration in DPBS/1% DMSO and 10 µL was added to the cells. Following a 3 hour incubation at 37°C, detection reagent (prepared according to the manufacturer's specifications) was added to each well. Luminescence was measured at 1 hour post detection reagent addition using a FlexStation III (Molecular Devices, 1000ms integration time). Relative luminescence units (RLU) were used to calculate % of control 5-HT E_{MAX}.