Supporting information

A tropane-based ibogaine analog rescues folding-deficient SERT and DAT

Shreyas Bhat[‡1], Daryl A. Guthrie[‡2], Ameya Kasture[3], Ali El-Kasaby[1], Jianjing Cao[2], Alessandro Bonifazi[2], Therese Ku[2], JoLynn B. Giancola[2], Thomas Hummel[3], Michael Freissmuth*[1] and Amy Hauck Newman*[2]

Affiliations: [1]Institute of Pharmacology and the Gaston H. Glock Research Laboratories for Exploratory Drug Development, Center of Physiology and Pharmacology, Medical University of Vienna, Vienna, Waehringerstrasse 13a, Vienna, Austria; [2]Molecular Targets and Medications Discovery Branch, National Institute on Drug Abuse, Intramural Research Program, Baltimore, MD 21224, U.S.A.; [3]Department of Neurobiology, University of Vienna, Austria.

[‡]S. Bhat and D. Guthrie contributed equally to this paper.

*Correspondence: Michael Freissmuth (michael.freissmuth@meduniwien.ac.at), Amy Hauck Newman (anewman@intra.nida.nih.gov.)

Table of Contents:

Synthesis

All chemicals and solvents were purchased from chemical suppliers unless otherwise stated and used without further purification. ^{1}H and ^{13}C NMR spectra were acquired using a Varian Mercury Plus 400 spectrometer at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in parts-per-million (ppm) and referenced according to deuterated solvent for ^{1}H NMR spectra ($CDCl_3$, 7.26; D_2O, 4.79 or DMSO-d_6, 2.50) and ^{13}C NMR spectra ($CDCl_3$, 77.2 or DMSO-d_6, 39.52). Gas chromatography-mass spectrometry (GC/MS) data were acquired (where obtainable) using an Agilent Technologies (Santa Clara, CA) 7890B 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 5977B 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 (70 °C) was held for 1 min and then increased to 300 °C at 20 °C/min over 11.5 min, and finally maintained at 300 °C for 4 min. All column chromatography was performed using a Teledyne Isco CombiFlash RF flash chromatography system. Combustion analyses were performed by Atlantic Microlab, Inc. (Norcross, GA) and agree with ± 0.4% of calculated values. HRMS (mass error within 5 ppm) and MS/MS fragmentation analysis were performed on a LTQ-Orbitrap Velos (Thermo-Scientific, San Jose, CA) coupled with an ESI source in positive ion mode to confirm the assigned structures and regiochemistry. All melting points were determined on an OptiMelt automated melting point system and are uncorrected. On the basis of NMR and combustion data, all final compounds are >95% pure.

3-(2-(8-azabicyclo[3.2.1]octan-8-yl)ethyl)-1H-indole ***(3a)***. 8-Azabicyclo[3.2.1]octane (**1**) (222.4 mg, 2 mmol), 3-(2-bromoethyl)-1H-indole (448.2 mg, 2 mmol), K_2CO_3 (1.1 g, 8 mmol) and acetonitrile (24 mL) were added in a sealed bottle (100 mL). The reaction mixture was stirred at 100 °C overnight and filtered. The filtrate was evaporated and purified by flash column chromatography (DCM/MeOH/NH_4OH = 95 : 5 : 0.5) to give the product (470 mg, 92% yield) as a yellow oil. The free base was converted to the HCl salt and recrystallized from methanol to give a white solid. Mp 247-248 °C; GC/MS (EI) *m/z* 254 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.62-7.63 (m, 1H), 7.34-7.36 (m, 1H), 7.02-7.19 (m, 3H), 3.34 (m, 2H), 2.95-2.99 (m, 2H), 2.68-2.72 (m, 2H), 1.94-1.99 (m, 2H), 1.76-1.85 (m, 2H), 1.35-1.64 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 127.6, 121.9, 121.4, 119.2, 118.9, 114.9, 111.1, 59.6, 53.4, 30.7, 26.5, 25.0, 16.7, ; Anal. ($C_{17}H_{22}N_2 \cdot HCl$) C, H, N.

*3-(3-(8-azabicyclo[3.2.1]octan-8-yl)propyl)-1H-indole (**3b**).* 3-(1H-indol-3-yl)propanoic acid (378.4 mg, 2 mmol) was dissolved in THF (20 mL), CDI (1 equiv) was added and stirred for 2 h at rt followed by adding 8-azabicyclo[3.2.1]octane (**1**) (222.4 mg, 2 mmol) in THF (13 mL). The reaction mixture was stirred overnight at rt. The solvent was removed *in vacuo* and residue was diluted with $CHCl_3$ (50 mL) and washed with saturated aq Na_2CO_3 solution (2 x 30 mL). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (DCM/MeOH/NH_4OH = 97 : 3 : 0.5) to give the amide as yellow oil. The amide was dissolved in anhydrous THF (5.6 mL) and added dropwise to the suspension of LAH (110 mg, 2.84 mmol) in THF (2 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 3 h. H_2O (0.3 mL) was added carefully at 0 °C, followed by the addition of 0.5 mL of aq NaOH (2 M). The resulting mixture was filtered, and the filtrate was dried (K_2CO_3) filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography (DCM/MeOH/NH_4OH = 95 : 5 : 0.5) to give the product (250 mg, 47% yield over two steps) as a yellow oil. The free base was converted to the HCl salt and recrystallized from methanol to give a tan foam; GC/MS (EI) *m/z* 268 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.60-7.62 (m, 1H), 7.33-7.35 (m, 1H), 6.99-7.19 (m, 3H), 3.20 (m, 2H), 2.76-2.80 (m, 2H), 2.42-2.46 (m, 2H), 1.87-1.95 (m, 4H), 1.41-1.78 (m, 6H), 1.26-1.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 127.6, 121.8, 121.0, 119.0, 116.7, 111.0, 59.4, 52.3, 30.7, 29.2, 26.4, 23.1, 16.8; Anal. ($C_{18}H_{24}N_2 \cdot HCl \cdot 0.5H_2O \cdot 0.25$ *i*-PrOH) C, H, N.

*3-(2-(8-azabicyclo[3.2.1]octan-8-yl)ethyl)-5-fluoro-1H-indole (**3c**).* Compound **3c** was prepared as described for **3b** using 8-azabicyclo[3.2.1]octane (**1**) (111.2 mg, 1 mmol) and 3-(5-fluoro-1H-indol-3-yl)propanoic acid (207.2mg, 1 mmol) to give the product (250 mg, 28% yield over two steps) as a yellow oil. GC/MS (EI) *m/z* 286 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.21-7.24 (m, 2H), 6.89-6.96 (m, 2H), 3.22-3.24 (m, 2H), 2.70-2.74 (m, 2H) 2.43-2.47 (m, 2H), 1.73-1.94 (m, 6H), 1.30-1.58 (m, 6H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 156.4, 132.8, 128.1, 128.0, 123.0, 116.7, 116.6, 111.6, 111.5, 110.1, 110.0, 103.9, 103.6, 59.5, 52.2, 30.6, 29.1, 26.4, 23.0, 16.7; Anal. ($C_{18}H_{23}FN_2 \cdot 0.5H_2O$) C, H, N.

*3-(2-(8-azabicyclo[3.2.1]octan-8-yl)ethyl)-5-methoxy-1H-indole (**3d**).* Compound **3d** was prepared as described for **3b** using 8-azabicyclo[3.2.1]octane (**1**) (222.4 mg, 2 mmol) and 2-(5-methoxy-1H-indol-3-yl)acetic acid (410.0 mg, 2 mmol) to give the product (380 mg, 49% yield over two steps) as a brown oil. The free base was converted to the HCl salt and recrystallized from methanol to give a tan foam; GC/MS (EI) *m/z* 284 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.22-7.24 (m, 1H), 7.07 (s, 1H), 7.00 (s, 1H), 6.83-6.86 (m, 1H),

3.86 (s, 3H), 3.34-3.35 (m, 2H), 2.91-2.95 (m, 2H), 2.67-2.70 (m, 2H), 1.95-1.99 (m, 2H), 1.78-1.85 (m, 2H), 1.46-1.61 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 131.3, 128.0, 122.2, 114.6, 112.1, 111.8, 100.8, 59.6, 55.9, 53.3, 30.7, 26.5, 25.0, 16.7 ; Anal. ($C_{18}H_{24}N_2O \cdot HCl \cdot H_2O$) C, H, N.

*3-(3-(-8-azabicyclo[3.2.1]octan-8-yl)propyl)-5-methoxy-1H-indole (**3e**)*. Compound **3e** was prepared as described in for **3b** using 8-azabicyclo[3.2.1]octane (**1**) (222.4 mg, 2 mmol) and 3-(5-methoxy-1H-indol-3-yl)propanoic acid (438.0 mg, 2 mmol) to give the product (380 mg, 79% yield over two steps) as a tan oil; GC/MS (EI) *m/z* 298 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.21-7.24 (m, 1H), 7.04 (s, 1H), 6.95 (s, 1H), 6.83-6.94 (m, 1H), 3.86 (s, 3H), 3.21-3.23 (m, 2H), 2.73-2.76 (m, 2H), 2.44-2.48 (m, 2H), 1.87-1.94 (m, 4H), 1.72-1.80 (m, 2H), 1.43-1.59 (m, 4H), 1.30-1.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 131.5, 128.0, 121.9, 116.4, 112.0, 111.7, 100.9, 59.4, 56.0, 52.3, 30.7, 29.1, 26.4, 23.1, 16.7; Anal. ($C_{19}H_{26}N_2O \cdot 0.5H_2O$) C, H, N.

*3-(2-(8-azabicyclo[3.2.1]octan-8-yl)ethyl)-1H-indol-5-ol (**3f**)*. Compound **3f** was prepared as described for **3b** using 8-azabicyclo[3.2.1]octane (**1**) (222.4 mg, 2 mmol) and 2-(5-hydroxy-1H-indol-3-yl)acetic acid (382.4 mg, 2 mmol) to give the product (158 mg, 29% yield over two steps) as a tan oil; GC/MS (EI) *m/z* 270 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.11-7.13 (m, 1H), 6.87-6.88 (m, 2H), 6.75-6.78 (m, 1H), 3.34-3.35 (m, 2H), 2.91-2.95 (m, 2H), 2.68-2.72 (m, 2H), 1.84-1.95 (m, 4H), 1.45-1.58 (m, 4H), 1.30-1.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 131.2, 128.1, 122.5, 113.3, 112.8, 111.9, 103.6, 59.5, 52.9, 50.6, 29.8, 26.3, 24.2, 16.4 ; Anal. ($C_{17}H_{22}N_2O \cdot 0.75H_2O$) C, H, N

*2-(2-(1H-indol-3-yl)ethyl)-2-azabicyclo[2.2.2]octane (**4a**)*. Compound **4a** was prepared as described for **3a** using 2-azabicyclo[2.2.2]octane (**2**) (222.4 mg, 2 mmol) and 3-(2-bromoethyl)-1H-indole (448.2 mg, 2 mmol) to give the product (370 mg, 73% yield) as a yellow oil. The free base was converted to the HCl salt and recrystallized from methanol to give a tan solid. Mp 251-253 °C; GC/MS (EI) *m/z* 254 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.63-7.65 (m, 1H), 7.34-7.36 (m, 1H), 7.04-7.20 (m, 3H), 2.93-2.97 (m, 2H), 2.81-2.89 (m, 4H), 2.66-2.67 (m, 1H), 1.96-2.02 (m, 2H) 1.46-1.72 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 127.6, 121.9, 121.4, 119.1, 119.0, 115.0, 111.0, 57.6, 56.8, 49.6, 25.8, 25.0, 24.4, 24.3 ; Anal. ($C_{17}H_{22}N_2 \cdot HCl \cdot 0.25H_2O$) C, H, N.

*2-(3-(1H-indol-3-yl)propyl)-2-azabicyclo[2.2.2]octane (**4b**)*. Compound **4b** was prepared as described for **3b** using 2-azabicyclo[2.2.2]octane (**2**) (180 mg, 1.6 mmol) and 3-(1H-indol-3-yl)propanoic acid (302.7 mg, 1.6 mmol) to give the product (350 mg, 82% yield over two steps) as a yellow oil. The free base was converted to the HCl salt and recrystallized from

methanol to give a tan foam; GC/MS (EI) *m/z* 268 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.61-7.63 (m, 1H), 7.33-7.36 (m, 1H), 7.08-7.20 (m, 2H), 6.98 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 127.6, 121.9, 121.4, 119.1, 119.0, 115.0, 111.0, 57.6, 56.8, 49.6, 25.8, 25.0, 24.4, 24.3 ; Anal. ($C_{18}H_{24}N_2 \cdot HCl \cdot 0.5H_2O$) C, H, N.

*3-(2-(8-azabicyclo[3.2.1]octan-8-yl)ethyl)-5-fluoro-1H-indole (**4c**).* Compound **4c** was prepared as for **3b** using 2-azabicyclo[2.2.2]octane (**2**) (180.0 mg, 1.62 mmol) and 3-(5-fluoro-1H-indol-3-yl)propanoic acid (335.4 mg, 1.62 mmol) to give the product (140 mg, 30% yield over two steps) as a yellow oil. GC/MS (EI) *m/z* 286 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.20-7.26 (m, 2H), 6.88-7.00 (m, 2H), 2.59-3.67 (m, 7H), 1.90-1.96 (m, 4H) 1.44-1.68 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 156.4, 132.8, 128.0, 127.9, 123.2, 116.4, 116.3, 111.6, 110.2, 109.9, 103.8, 103.6, 62.7, 56.3, 56.1, 49.6, 30.0, 27.9, 25.5, 24.6, 23.9, 22.8; Anal. ($C_{18}H_{23}FN_2 \cdot 0.5H_2O$) C, H, N.

*Nortropidene (**6**).* Nortropine (**5**; 10.0 g, 78.6 mmol) was added portion wise to sulfuric acid (10 mL) cooled in an ice bath, then stirred at 160 °C for 4 h. Once cooled to rt, the reaction mixture was diluted with 50 mL H_2O, 50 mL NaOH (12.5 M), and extracted with Et_2O (3x 75 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give the title compound as a light orange oil (4.0 g, 47% yield). The free base proved unstable overtime. Thus, it was converted to the HCl salt for long term storage by dissolving in EtOH/conc. HCl, concentrated *in vacuo*, and triturated with DCM/Et_2O to give a white solid. ^{1}H NMR (400 MHz, D_2O) δ 6.01 (m, 1H), 5.81 (m, 1H), 4.22 (m, 2H), 2.81 (d, *J* = 24 Hz, 1H), 2.27 (m, 3H), 2.13 (m, 1H), 1.96 (m, 1H). HRMS: found m/z = 110.0964 (MH^+), calcd for $C_7H_{12}N$ (MH^+).

*1-(8-azabicyclo[3.2.1]oct-2-en-8-yl)-2-(1H-indol-3-yl)ethan-1-one (**7a**).* To a solution of indole-3-acetic acid (1.75 g, 10 mmol) in THF (50 mL) was added CDI (1.95 g, 12 mmol), and the reaction stirred at rt for 2 h. A solution of **6** (1.09 g, 10 mmol) in THF (1 mL) was added to the reaction mixture and stirring continued overnight. The reaction mixture was concentrated, diluted with EtOAc (100 mL), and successively washed with 1N HCl (2x 50 mL), sat. $NaHCO_3$ (1x 50 mL), and brine (1x 50 mL). The extract was dried over $MgSO_4$, concentrated *in vacuo*, re-dissolved in minimal DCM and precipitated with hexane to give the title compound as an off-white powder and mixture of two diastereomers (A:B, 0.45:0.55) (2.08 g, 78% yield). Diastereomer A: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.61 (d, *J* = 8 Hz, 1H), 7.33 (d, *J* = 8 Hz, 1H), 7.12 (m, 3H), 5.99 (m, 1H), 5.47 (m, 1H), 4.89 (m, 1H), 4.33 (m, 1H), 3.79 (m, 2H), 2.43 (d, *J* = 20 Hz, 1H), 2.08 (m, 1H), 1.87 (m, 3H), 1.68 (m, 1H). Diastereomer B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.61 (d, *J* = 8 Hz, 1H),

7.33 (d, *J* = 8 Hz, 1H), 7.12 (m, 3H), 5.81 (m, 1H), 5.47 (m, 1H), 4.79 (m, 1H), 4.33 (m, 1H), 3.79 (m, 2H), 2.82 (d, *J* = 20 Hz, 1H), 2.08 (m, 1H), 1.87 (m, 3H), 1.68 (m, 1H). HRMS: found m/z = 267.1494 (MH^+), calcd for $C_{17}H_{19}N_2O$ (MH^+).

*1-(8-azabicyclo[3.2.1]oct-2-en-8-yl)-2-(5-fluoro-1H-indol-3-yl)ethan-1-one (**7b**).* To a solution of 5-fluoro-indole-3-acetic acid (0.976 g, 5.05 mmol) in THF (25 mL) was added CDI (0.973 g, 6 mmol), and the reaction stirred at rt for 2 h. The HCl salt of **6** (0.874 g, 6 mmol) was added as a solid, followed by *N*,*N*-diisopropylethylamine (1.05 mL, 6 mmol) and stirring continued overnight. The reaction mixture was diluted with EtOAc (100 mL), and successively washed with 1N HCl (3x 50 mL), sat. $NaHCO_3$ (1x 50 mL), and brine (1x 50 mL). The product was purified by column chromatography (100% DCM to DCM/MeOH/NH_4OH = 90 : 10 : 1) to give the title compound as a light peach-colored solid and mixture of two diastereomers (A:B, 0.4:0.6) (1.174 g, 82% yield). Diastereomer A: ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.25 (m, 2H), 7.14 (d, *J* = 8 Hz, 1H), 6.92 (t, *J* = 8 Hz, 1H), 6.01 (m, 1H), 5.49 (m, 1H), 4.87 (m, 1H), 4.34 (m, 1H), 3.72 (m, 2H), 2.46 (d, *J* = 20 Hz, 1H), 2.12 (m, 1H), 1.90 (m, 3H), 1.72 (m, 1H). Diastereomer B: ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.25 (m, 2H), 7.14 (d, *J* = 8 Hz, 1H), 6.92 (t, *J* = 8 Hz, 1H), 5.84 (m, 1H), 5.49 (m, 1H), 4.79 (m, 1H), 4.34 (m, 1H), 3.72 (m, 2H), 2.83 (d, *J* = 20 Hz, 1H), 2.12 (m, 1H), 1.90 (m, 3H), 1.72 (m, 1H). HRMS: found m/z = 285.1402 (MH^+), calcd for $C_{17}H_{18}N_2OF$ (MH^+).

*1-(8-azabicyclo[3.2.1]oct-2-en-8-yl)-2-(5-methoxy-1H-indol-3-yl)ethan-1-one (**7c**).* To a solution of 5- methoxy-indole-3-acetic acid (0.371 g, 1.81 mmol) in THF (10 mL) was added CDI (0.352 g, 2.17 mmol), and the reaction stirred at rt for 2 h. A solution of **6** (0.236 g, 2.17 mmol) in THF (1 mL) was added to the reaction mixture and stirring continued overnight. The reaction mixture was diluted with EtOAc (40 mL), and successively washed with 1N HCl (3x 25 mL), sat. $NaHCO_3$ (1x 25 mL), and brine (1x 25 mL). The extract was dried over $MgSO_4$, concentrated *in vacuo*, and the residue was purified by column chromatography (100% DCM to DCM/MeOH/NH_4OH = 90 : 10 : 1) to give the title compound as an off-white solid and mixture of two diastereomers (A:B, 0.4:0.6) (0.412 g, 77% yield). Diastereomer A: ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.24 (m, 1H), 7.06 (m, 2H), 6.85 (m 1H), 6.00 (m, 1H), 5.49 (m, 1H), 4.88 (m, 1H), 4.33 (m, 1H), 3.86 (s, 3H), 3.75 (m, 2H), 2.43 (d, *J* = 20 Hz, 1H), 2.11 (m, 1H), 1.88 (m, 3H), 1.66 (m, 1H). Diastereomer B: ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.24 (m, 1H), 7.06 (m, 2H), 6.85 (m 1H), 5.81 (m, 1H), 5.49 (m, 1H), 4.80 (m, 1H), 4.33 (m, 1H), 3.86 (s, 3H), 3.75 (m, 2H), 2.83 (d, *J* = 20 Hz, 1H), 2.11 (m, 1H),

1.88 (m, 3H), 1.66 (m, 1H). HRMS: found m/z = 297.1601 (MH^+), calcd for $C_{18}H_{21}N_2O_2$ (MH^+).

*(3R,4R,12S,12aR)-2,3,6,11,12,12a-hexahydro-3,12-ethanopyrrolo[1',2':1,2]azepino[4,5-b]indol-5(1H)-one (**8a**)*. A 25 mL Schlenk tube in an argon atmosphere was charged with **7a** (0.266 g, 1.00 mmol) and $Pd(CH_3CN)_4(BF_4)_2$ (0.577 g, 1.30 mmol). Anhyd acetonitrile (10 mL) was added resulting in a dark red solution, which was stirred at rt overnight, maintaining its appearance throughout the time of reaction. The flask was equipped with a deflated balloon, converted to static argon, and a solution of $NaBH_4$ (0.113 g, 3 mmol) in 4 mL EtOH was added dropwise over 10 min, precipitating Pd(0) black and filling the balloon with H_2 gas. The reaction continued to stir for 1 h, where most of the H_2 was consumed and the product precipitated along with the Pd(0) black. The reaction was diluted with 50 mL 20% MeOH/DCM, vacuum filtered (Pd(0)), and the filtrate successively washed with 1N HCl (1x 20 mL) and brine (1x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was separated from byproducts by taking up in minimal DCM, diluted with Et_2O, and filtered to give the title compound as an off-white solid (0.169 g, 63% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (s, 1H), 7.47 (d, *J* = 8 Hz, 1H), 7.25 (d, *J* = 8 Hz, 1H), 7.03 (t, *J* = 8 Hz, 1H), 6.97 (t, *J* = 8 Hz, 1H), 4.57 (d, *J* = 8 Hz, 1H), 4.27 (d, *J* = 8 Hz, 1H), 3.92 (d, *J* = 16 Hz, 1H), 3.41 (d, *J* = 16 Hz, 1H), 2.98 (d, *J* = 8 Hz, 1H), 2.24 (m, 2H), 2.00 (m, 2H), 1.80 (m, 2H), 1.53 (m, 1H), 1.21 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.35, 136.57, 134.78, 127.28, 120.74, 118.39, 117.32, 110.62, 103.88, 55.91, 53.03, 38.29, 32.58, 28.69, 26.92, 25.78, 22.69. HRMS: found m/z = 267.1483 (MH^+), calcd for $C_{17}H_{19}N_2O$ (MH^+).

*(3R,4R,12S,12aR)-8-fluoro-2,3,6,11,12,12a-hexahydro-3,12-ethanopyrrolo[1',2':1,2]azepino[4,5-b]indol-5(1H)-one (**8b**)*. Compound **8b** was prepared as described for **8a** using **7b** (0.142 g, 0.50 mmol) and $Pd(CH_3CN)_4(BF_4)_2$ (0.289 g, 0.65 mmol) to give the title compound (0.990 g, 70% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (s, 1H), 7.26 (m, 2H), 6.86 (m, 1H), 4.56 (d, *J* = 8 Hz, 1H), 4.27 (d, *J* = 8 Hz, 1H), 3.90 (d, *J* = 16 Hz, 1H), 3.38 (d, *J* = 16 Hz, 1H), 2.98 (d, *J* = 8 Hz, 1H), 2.23 (m, 2H), 1.99 (m, 2H), 1.79 (m, 2H), 1.51 (m, 1H), 1.18 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.19, 156.88 (d, $J_{c,f}$ = 230 Hz), 138.83, 131.39, 127.61 (d, $J_{c,f}$ = 10 Hz), 111.46 (d, $J_{c,f}$ = 9 Hz), 108.63, (d, $J_{c,f}$ = 25 Hz), 104.38, (d, $J_{c,f}$ = 4 Hz), 102.34, (d, $J_{c,f}$ = 23 Hz), 55.79, 53.02, 38.36, 32.57, 28.64, 26.93, 25.78, 22.70. HRMS: found m/z = 285.1397 (MH^+), calcd for $C_{17}H_{18}N_2OF$ (MH^+).

*(3R,4R,12S,12aR)-8-methoxy-2,3,6,11,12,12a-hexahydro-3,12-ethanopyrrolo[1',2':1,2]azepino[4,5-b]indol-5(1H)-one (**8c**)*. Compound **8c** was prepared as

for **8a** using **7c** (0.260 g, 0.88 mmol) and $Pd(CH_3CN)_4(BF_4)_2$ (0.506 g, 1.14 mmol) to give the title compound (0.210 g, 81% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74 (s, 1H), 7.13 (d, *J* = 8 Hz, 1H), 6.99 (s, 1H), 6.67 (d, *J* = 8 Hz, 1H), 4.56 (d, *J* = 8 Hz, 1H), 4.27 (m, 1H), 3.89 (d, *J* = 16 Hz, 1H), 3.76 (s, 3H), 3.41 (d, *J* = 16 Hz, 1H), 2.95 (m, 1H), 2.25 (m, 2H), 2.00 (m, 2H), 1.78 (m, 2H), 1.52 (m, 1H), 1.21 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.40, 153.18, 137.25, 129.81, 127.62, 111.26, 110.73, 103.78, 99.48, 55.91, 55.37, 52.99, 38.37, 32.64, 28.69, 26.92, 25.79, 22.78. HRMS: found m/z = 297.1586 (MH^+), calcd for $C_{18}H_{21}N_2O_2$ (MH^+).

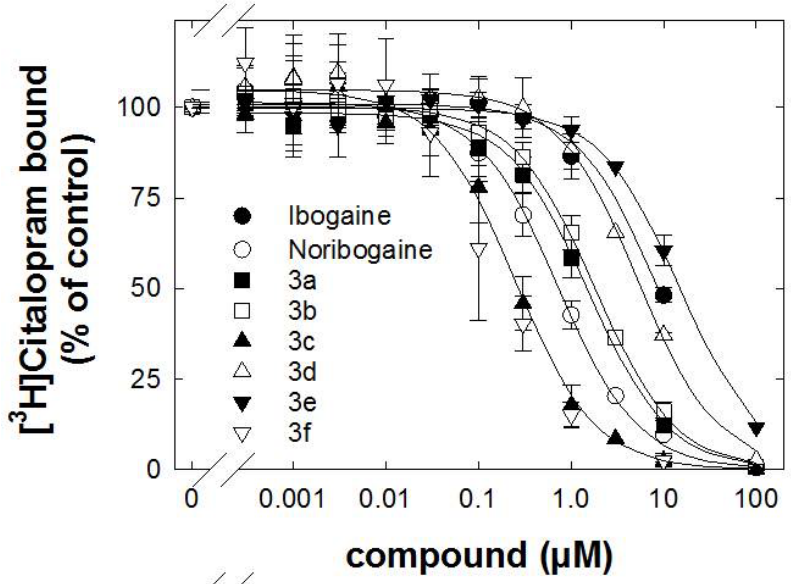
*(3R,4R,12S,12aR)-1,2,3,5,6,11,12,12a-octahydro-3,12-ethanopyrrolo[1',2':1,2]azepino[4,5-b]indole (**9a**).* To a suspension of **8a** (0.030 g, 0.11 mmol) in 3 mL THF at rt was added BMS (0.20 mL, 2.1 mmol) and the reaction was stirred at reflux for 1 h. Once cooled to rt, the reaction was slowly quenched with MeOH and concentrated *in vacuo*. The reaction was then taken up in 3 M HCl (5 mL) and stirred at reflux overnight to ensure hydrolysis of the boron complex with the product. The reaction was basified with 1 M NaOH and extracted with DCM (3 x 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (100% DCM to DCM/MeOH/NH_4OH = 90 : 10 : 1) to give the title compound as a white solid (0.019 g, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.50 (m, 1H), 7.26 (m, 1H), 7.12 (m, 2H), 3.91 (d, *J* = 4 Hz, 1H), 3.49 (m, 1H), 3.38 (m, 2H), 3.17 (m, 1H), 3.03 (m, 1H), 2.80 (d, *J* = 8 Hz, 1H), 2.29 (m, 1H), 2.09 (m, 3H), 1.75 (m, 3H), 1.08 (dd, *J* = 8, 16 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 139.23, 134.91, 128.27, 120.04, 117.92, 117.17, 111.39, 110.30, 56.25, 56.00, 47.98, 38.39, 29.18, 28.29, 23.88, 23.51, 21.82. HRMS: found m/z = 253.1698 (MH^+), calcd for $C_{17}H_{21}N_2$ (MH^+).

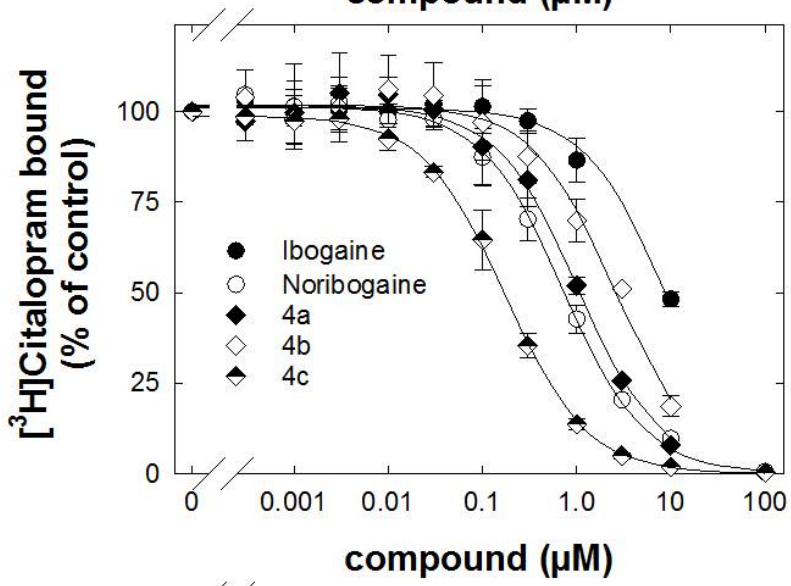
*(3R,4R,12S,12aR)-8-fluoro-1,2,3,5,6,11,12,12a-octahydro-3,12-ethanopyrrolo[1',2':1,2]azepino[4,5-b]indole (**9b**).* Compound **9b** was prepared as described for **9a** using **8b** (0.028 g, 0.10 mmol) and BMS (0.20 mL, 2.1 mmol) to give the title compound as a white solid (0.019 g, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.15 (m, 2H), 6.86 (m, 1H), 3.88 (d, *J* = 8 Hz, 1H), 3.48 (m, 1H), 3.38 (m, 2H), 3.09 (m, 1H), 2.97 (m, 1H), 2.77 (d, *J* = 8 Hz, 1H), 2.29 (m, 1H), 2.10 (m, 3H), 1.74 (m, 3H), 1.09 (dd, *J* = 8, 16 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.74 (d, $J_{c,f}$ = 229 Hz), 141.23, 131.56, 128.46 (d, $J_{c,f}$ = 10 Hz), 111.77 (d, $J_{c,f}$ = 5 Hz), 111.08 (d, $J_{c,f}$ = 9 Hz), 107.88 (d, $J_{c,f}$ = 25 Hz), 102.11 (d, $J_{c,f}$ = 23 Hz), 56.36, 56.22, 47.89, 38.24, 28.85, 27.96, 23.54, 23.20, 21.72. HRMS: found m/z = 271.1604 (MH^+), calcd for $C_{17}H_{20}N_2F$ (MH^+).

*(3R,4R,12S,12aR)-8-methoxy-1,2,3,5,6,11,12,12a-octahydro-3,12 ethanopyrrolo[1',2':1,2]azepino[4,5-b]indole (**9c**)*. Compound **9c** was prepared as described for **9a** using **8c** (0.444 g, 1.5 mmol) and BMS (1.50 mL, 15.8 mmol) in THF (40 mL) without the 3 M HCl reflux step to give the title compound as a white solid (0.365 g, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.16 (d, *J* = 8 Hz, 1H), 6.96 (s, 1H), 6.79 (d, *J* = 8 Hz, 1H), 3.89 (m, 1H), 3.86 (s, 3H), 3.44 (m, 1H), 3.39 (m, 2H), 3.13 (m, 1H), 2.98 (m, 1H), 2.77 (m, 1H), 2.28 (m, 1H), 2.08 (m, 3H), 1.75 (m, 3H), 1.08 (m, 1H). HRMS: found m/z = 283.1804 (MH^+), calcd for $C_{18}H_{23}N_2O$ (MH^+).

*(3R,4R,12S,12aR)-1,2,3,5,6,11,12,12a-octahydro-3,12-ethanopyrrolo[1',2':1,2]azepino[4,5-b]indol-8-ol (**9d**)*. Compound **9d** was prepared as described for **9a** using **8c** (0.450 g, 1.5 mmol) and BMS (1.50 mL, 15.8 mmol) in THF (40 mL) with the 3 M HCl reflux step (12 mL, overnight) to give the title compound as a tan solid (0.078 g, 19% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.11 (d, *J* = 8 Hz, 1H), 6.90 (s, 1H), 6.69 (d, *J* = 8 Hz, 1H), 3.88 (d, *J* = 8 Hz, 1H), 3.47 (m, 1H), 3.38 (m, 2H), 3.06 (m, 1H), 2.96 (m, 1H), 2.77 (d, *J* = 8 Hz, 1H), 2.28 (m, 1H), 2.10 (m, 3H), 1.75 (m, 3H), 1.08 (dd, *J* = 8, 16 Hz, 1H). HRMS: found m/z = 269.1654 (MH^+), calcd for $C_{17}H_{21}N_2O$ (MH^+).

Supplementary figures





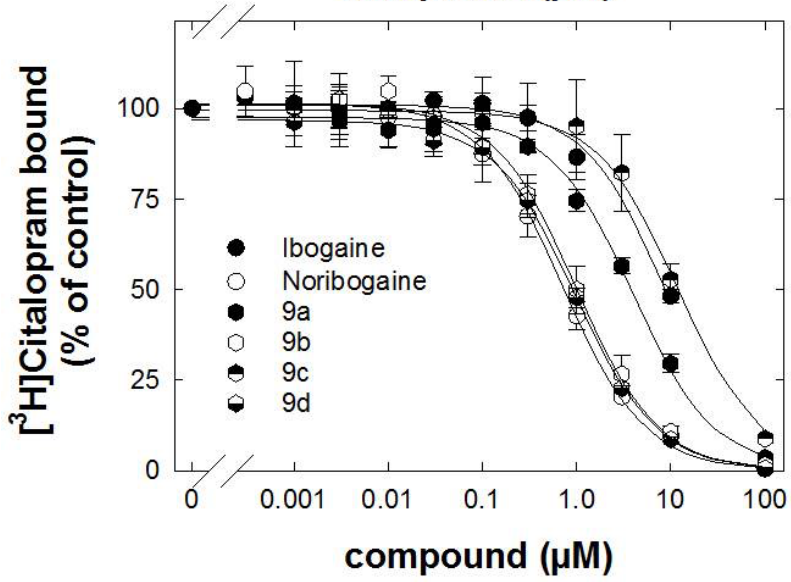


Figure S-1. Inhibition by ibogaine analogs of [^{3}H]citalopram binding to rat SERT. Brain stem membranes were dissected and prepared from male Sprague–Dawley rat brains (see Methods). Membranes binding was conducted in 96-well polypropylene plates containing 50 µL of various concentrations of the inhibitor, diluted using 30% DMSO vehicle, 300 µL of Tris buffer (SERT), 50 µL of [^{3}H]citalopram solution (final concentration 1.5 nM) and 100 µL of tissue (2.0 mg/well original wet weight) for 60 min at room temperature (SERT). Nonspecific binding was determined using 10 µM fluoxetine, which was <10% of specific binding. Data are represented as the means $\pm$ S.D. (error bars) from at least three independent experiments, each performed in triplicate. Specific binding (between 3000 and 5000 cpm) was set to 100% to normalize for inter-assay variation. The solid curves were drawn by fitting the data to the equation for a monophasic inhibition. K_i-values were calculated from the IC_{50} values using the Cheng-Prusoff equation (see **Table 1)**.

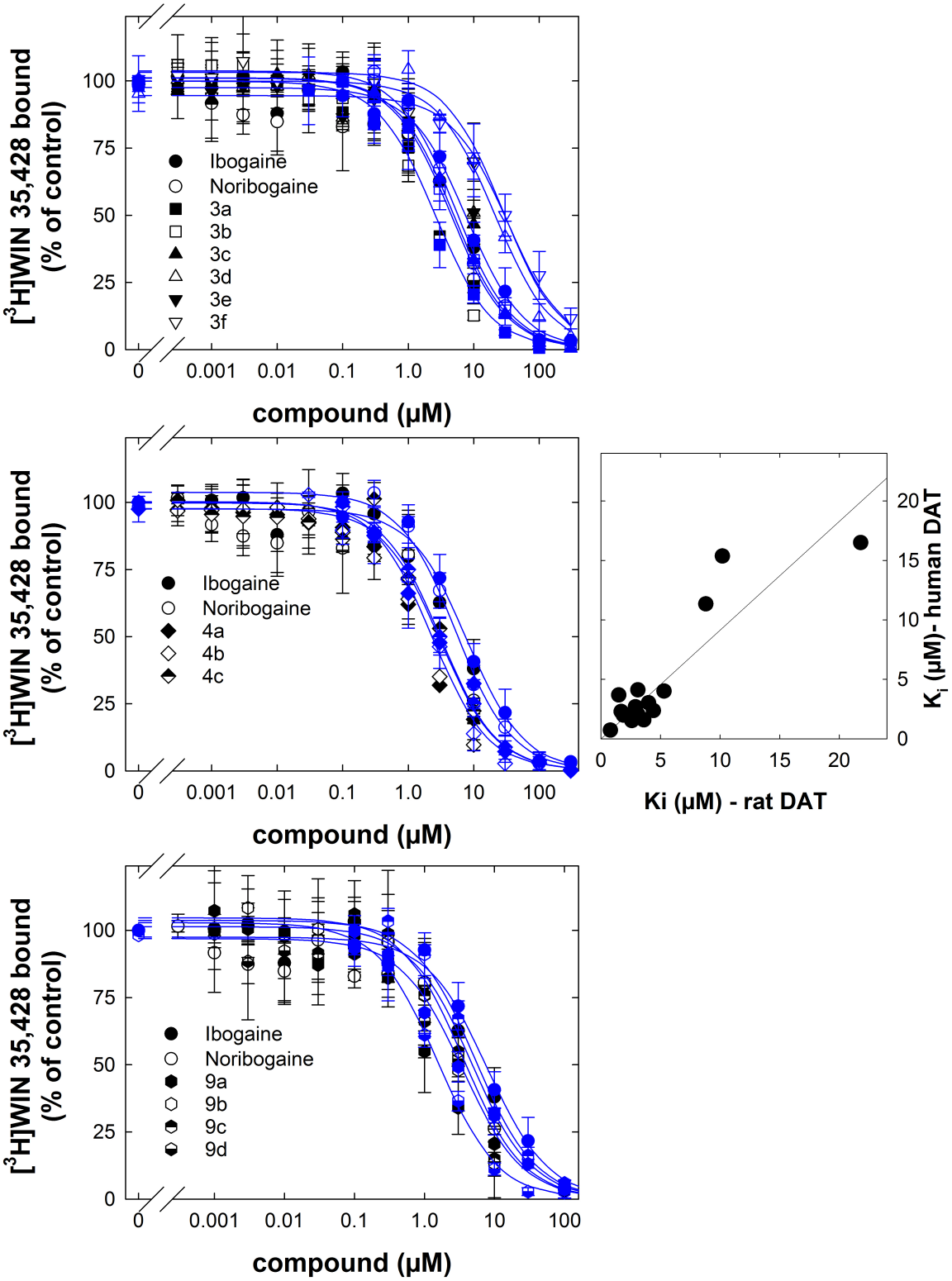
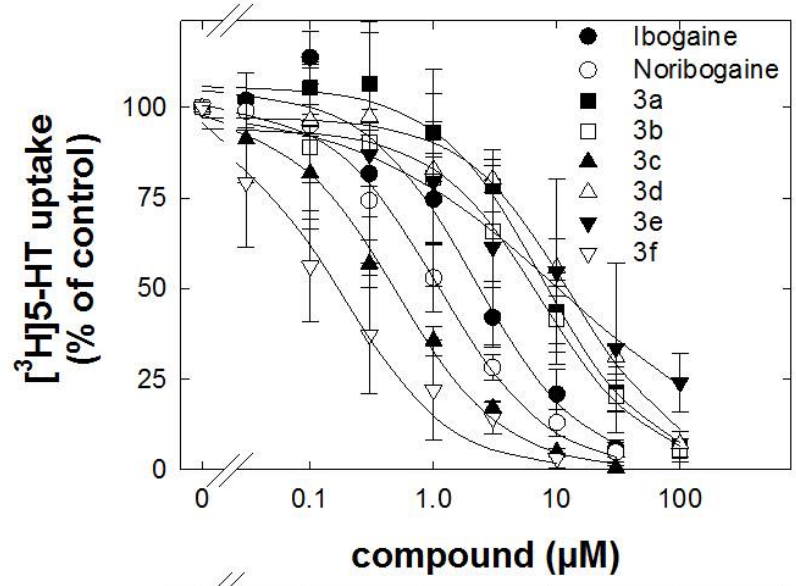
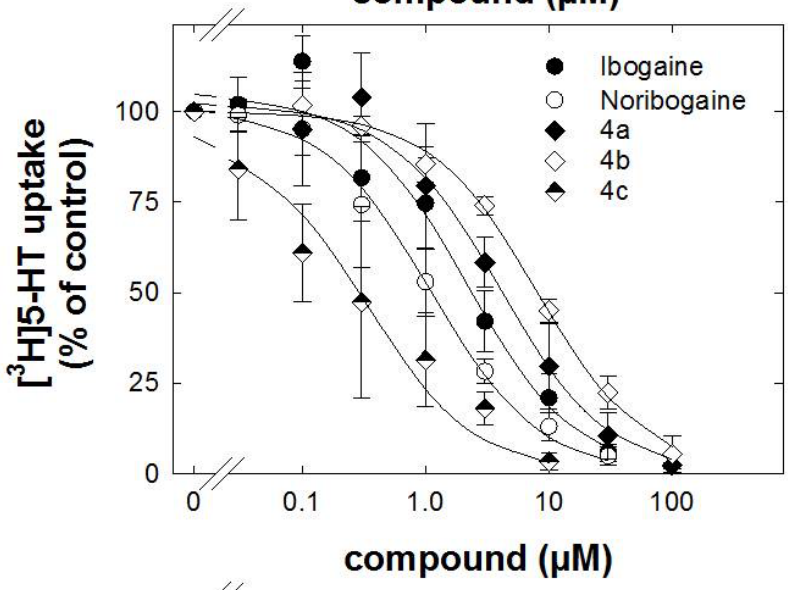


Figure S-2. Inhibition by ibogaine analogs of [^{3}H]WIN 35,428 binding to rat and human DAT. Striatum membranes were dissected and prepared from male Sprague–Dawley rat brains (see

Methods). Membranes binding was conducted in 96-well polypropylene plates containing 50 µL of various concentrations of the inhibitor, diluted using 30% DMSO vehicle, 300 µL of sucrose phosphate buffer, 50 µL of [^{3}H]-WIN35,428 solution (final concentration 1.5 nM) and 100 µL of tissue (2.0 mg/well original wet weight) for 120 min at 0-4 °C. Nonspecific binding was determined using 10 µM indatraline, which was <10% of specific binding. Binding assays were also done with membranes prepared from HEK293 cells, which stably expressed human DAT (see Methods). The black and blue symbols represent data obtained with rat and human DAT, respectively. Data are represented as the means $\pm$ S.D. (error bars) from at least three independent experiments, each performed in triplicate. Specific binding (between 3000 and 5000 cpm for rat DAT, 1000 - 1500 cpm for human DAT) was set to 100% to normalize for inter-assay variation. The blue solid curves were drawn by fitting the data obtained for human DAT to the equation for a monophasic inhibition. For the sake of clarity, the fit to rat data was omitted. Ki-values were calculated from the IC50 values using the Cheng-Prusoff equation (see Table 1). The right hand, graph visualizes the correlation between K_i-values obtained for rat and human DAT. The slope of the line (0.91) is reasonably close to unity (=the line of identity).


Ibogaine
Noribogaine
3a
3b
3c
3d
3e
3f
[3H]5-HT uptake
(% of control)
100
75
50
25
0
0
0.1
1.0
10
100
compound (μM)


Ibogaine
Noribogaine
4a
4b
4c
[3H]5-HT uptake
(% of control)
100
75
50
25
0
0
0.1
1.0
10
100
compound (μM)

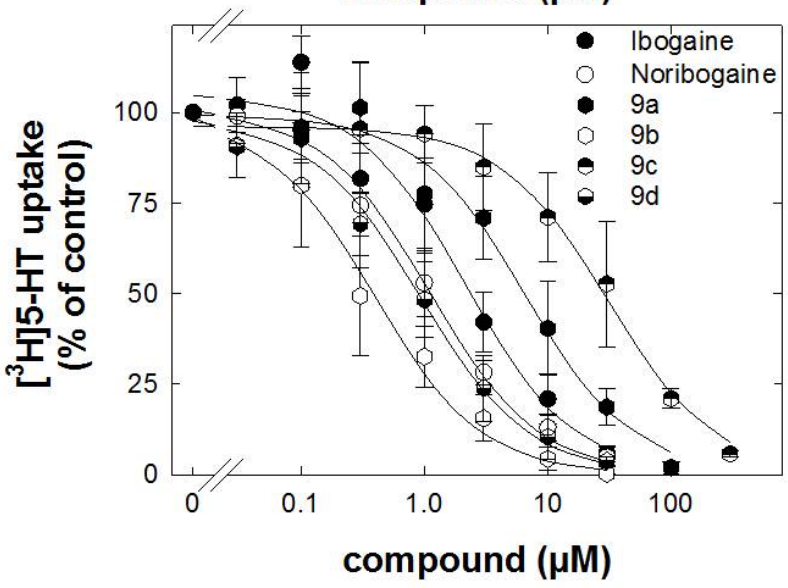
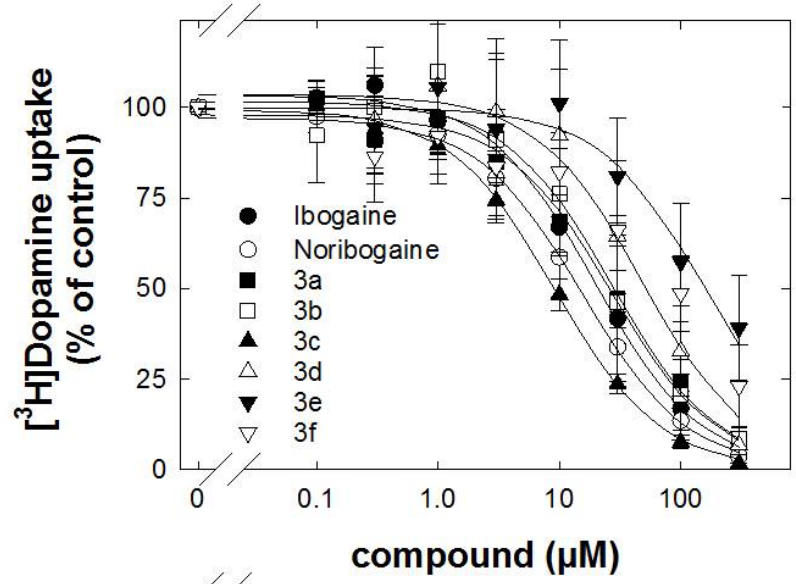
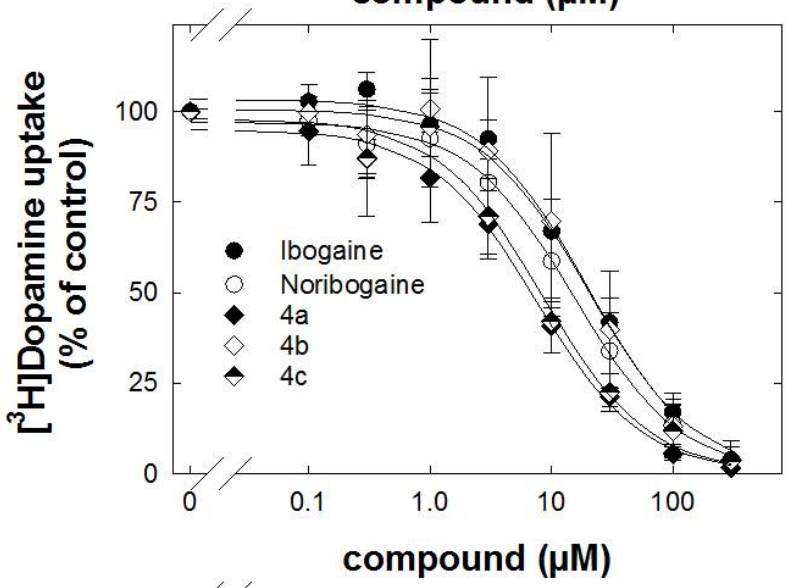

Ibogaine
Noribogaine
9a
9b
9c
9d
[3H]5-HT uptake
(% of control)
100
75
50
25
0
0
0.1
1.0
10
100
compound (μM)

Figure S-3. Inhibition by ibogaine analogs of [^{3}H]5-HT uptake by hSERT. HEK293 cells stably expressing wild-type YFP-hSERT were seeded onto 96-well plates for 24 h. Cells were incubated with logarithmically spaced concentrations (0.003–300 μM) of ibogaine analogs for 10 minutes and subsequently with the same concentration of the ibogaine analogs with 0.4 μM [^{3}H]5-HT for 1 minute. Non-specific uptake was defined as cellular accumulation of radioactivity in the presence of 30 μM paroxetine; this was was <10% of total uptake. Specific uptake is the difference between total and non-specific uptake. Data are the means ± S.D. from three independent experiments done in triplicates. Specific uptake for SERT was 4.46 ± 1.47 pmol·min^{-}10^{-6} cells and was set to 100% to normalize for inter-assay variation. The solid curves were drawn by fitting the data to the equation for a monophasic inhibition. The IC_{50}-values are reported in **Table 1**.


[3H]Dopamine uptake
(% of control)
100
75
50
25
0
Ibogaine
Noribogaine
3a
3b
3c
3d
3e
3f
0
0.1
1.0
10
100
compound (μM)


[3H]Dopamine uptake
(% of control)
100
75
50
25
0
Ibogaine
Noribogaine
4a
4b
4c
0
0.1
1.0
10
100
compound (μM)

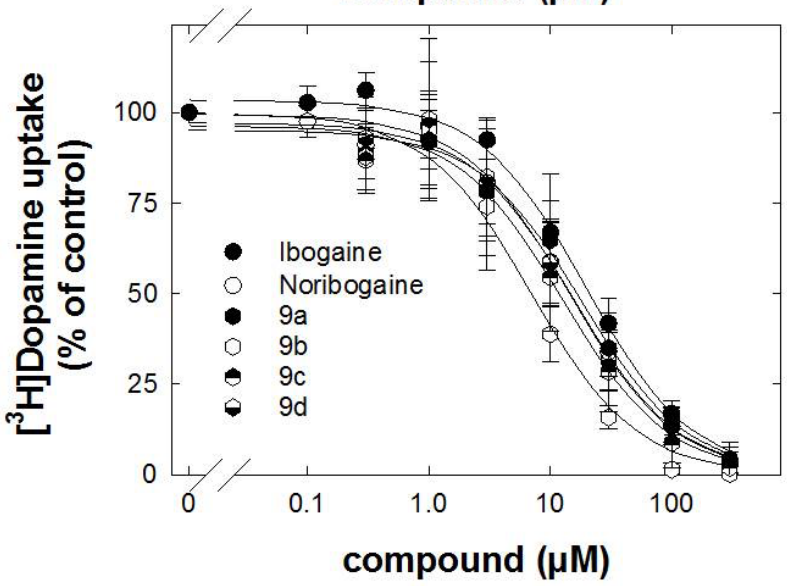

[3H]Dopamine uptake
(% of control)
100
75
50
25
0
Ibogaine
Noribogaine
9a
9b
9c
9d
0
0.1
1.0
10
100
compound (μM)

Figure S-4. Inhibition by ibogaine analogs of [^{3}H]5-DA uptake by hDAT. HEK293 cells stably expressing YFP-hDAT were seeded onto 96-well plates for 24 h. Cells were incubated with logarithmically spaced concentrations (0.003–300 μM) of ibogaine analogs for 10 minutes and subsequently with the same concentration of the ibogaine analogs with 0.4 μM of [^{3}H]DA for 1 minute. Non-specific uptake was defined as cellular accumulation of radioactivity in the presence of 30 μM mazindol; this was <10% of total uptake. Specific uptake is the difference between total and non-specific uptake. Data are the means $\pm$ S.D. from three independent experiments done in triplicates. Specific uptake for DAT was 7.5 $\pm$ 2.1 pmol·min^{-}10^{-6} cells, respectively, and was set to 100% to normalize for inter-assay variation. The solid curves were drawn by fitting the data to the equation for a monophasic inhibition. The IC_{50}-values are reported in **Table 1**.