Experimental Section.

Chemistry. Melting points were taken on a Mel-Temp apparatus and are uncorrected. ^{1}H-NMR spectra were recorded using a 500 MHz Varian VXR-500S spectrometer. Chemical shifts are reported in δ values ppm relative to tetramethylsilane as an internal reference (0.03%, v/v) for those spectra obtained in $CDCl_3$, and relative to the HDO resonance, assigned the value of 4.630 ppm, for those spectra obtained in D_2O. Elemental analyses were performed by the Purdue University Microanalysis Laboratory and are within 0.4% (absolute) of the calculated values. Most reactions were carried out under an inert atmosphere of dry argon or nitrogen.

***N*-Trifluoroacetyl-1-(2,3,6,7-tetrahydrobenzo[1,2-*b*:4,5-*b*′]difuran-4-yl)-2-aminopropane (5).** A solution of 0.372 g (1.70 mmol) of **4**[5] and 0.25 mL of triethylamine in 38 mL of CH_2Cl_2 was placed in a flask under argon and cooled to 0 °C. Trifluoroacetic anhydride (0.48 mL) was added dropwise via syringe. The ice bath was removed and the reaction mixture was stirred a further two hours. Volatiles were removed by rotary evaporation and the resulting solid residue was partitioned between 100 mL of CH_2Cl_2 and 100 mL of water. The organic phase was washed with 1 M HCl, water, and brine, dried with $MgSO_4$, filtered, and evaporated, leaving 0.520 g of crude product as an off-white solid. Chromatography on silica (EtOAc:hexane, 2:5) gave 0.463 g (87%) of **5** as a white solid: mp 149-150 °C. ^{1}H NMR ($CDCl_3$) δ 1.27 (d, 3, CH_3, J = 6.6 Hz), 2.75 (d, 2, ArCH_2CH, J = 6.5 Hz), 3.09 (t, 2, ArCH_2CH_2O, J = 8.7 Hz), 3.18 (t, 2, ArCH_2CH_2O, J = 8.7 Hz), 4.14 (septet, 1, ArCH_2CH, J = 6.5 Hz), 4.55 (m, 4, overlapping ArCH_2CH_2O), 6.56 (s, 1, ArH), 7.73 (bs, 1, NH). Anal. ($C_{15}H_{16}F_3NO_3$) C, H, N.

***N*-Trifluoroacetyl-1-(8-bromo-2,3,6,7-tetrahydrobenzo[1,2-*b*:4,5-*b*']difuran-4-yl)-2-aminopropane (6).** A solution of 75 mg (0.238 mmol) of **5** in 4.5 mL of acetic acid in a flask open to the air was cooled in a water bath at 15 °C. A solution of 38 mg (0.238 mmol) of Br_2 in 1 mL of acetic acid was added dropwise with a glass pipet. The water bath was removed and the flask was closed with a septum containing a needle for pressure equalization. The reaction mixture was allowed to warm slowly to room temperature and was stirred for a total of 5 h. Volatiles were removed by rotary evaporation, and the crude product was recrystallized from EtOAc-hexane to give 67 mg (71%) of **6** as fine white crystals: mp 191-192 °C. ^{1}H NMR ($CDCl_3$) δ 1.27 (d, 3, CH_3, J = 6.8 Hz), 2.71 (m, 2, ArCH_2CH), 3.21 (t, 4, ArCH_2CH_2O, J = 8.5 Hz), 4.13 (septet, 1, $ArCH_2CH$, J = 6.4 Hz), 4.60 (dt, 2, $ArCH_2CH_2O$, J = 2.9, 8.5 Hz), 4.66 (t, 2, $ArCH_2CH_2O$, J = 8.5 Hz), 7.47 (bs, 1, NH). Anal. ($C_{15}H_{15}BrF_3NO_3$) C, H, N.

***N*-Trifluoroacetyl-1-(8-bromobenzo[1,2-*b*:4,5-*b*']difuran-4-yl)-2-aminopropane (7).** A suspension of 400 mg (1.02 mmol) of **6** and 624 mg (2.75 mmol) of dichlorodicyanobenzoquinone (DDQ) in 40 mL of dry toluene was placed in a flask under argon and heated at reflux with stirring for 10 h. An additional 100 mg of DDQ was then added and heating at reflux was resumed for 30 min. The mixture was cooled to room temperature and 250 mL of 5% aqueous Na_2SO_3 was added. Diethyl ether (150 mL) was then added and the organic phase was separated. The aqueous phase was extracted twice more with Et_2O. The organic fractions were combined, dried with $MgSO_4$, and filtered. The solvents were evaporated, and the solid residue was dissolved in 4 mL of tetrahydrofuran. Hexane (4 mL) was added and, before precipitation could occur, the material was immediately chromatographed on a column of silica (THF:hexane, 3:7), yielding 354 mg (89%) of 7 as a clingy white solid: mp 203-204 °C. ^{1}H NMR ($CDCl_3$) δ 1.26 (d,

3, CH_3, J = 6.7 Hz), 3.35 (two nearly-merged dd's, 2, $ArCH_2$, J_{ac} = 6.4 Hz, J_{bc} = 6.1 Hz, J_{ab} = 13.9 Hz), 4.46 (septet, 1, $ArCH_2CH$, J = 6.8 Hz), 6.41 (bs, 1, NH), 6.92 (d, 1, ArH, J = 2.3 Hz), 6.99 (d, 1, ArH, J = 2.2 Hz), 7.69 (d, 1, ArH, J = 2.2 Hz), 7.73 (d, 1, ArH, J = 2.3 Hz). Anal. ($C_{15}H_{11}BrF_3NO_3$) C, H, N.

1-(8-bromobenzo[1,2-*b*:4,5-*b*']difuran-4-yl)-2-aminopropane hydrochloride (3). A solution of 2.4 g of NaOH in 12 mL of H_2O was added to a solution of 0.239 g of **7** in 50 mL of methanol. The mixture was stirred under argon overnight at room temperature. The methanol was removed by rotary evaporation at 30 °C and the remaining liquid was partitioned between Et_2O and H_2O. The Et_2O phase was separated, dried with $MgSO_4$, filtered, and evaporated, giving 0.168 g of a viscous yellow oil. The oil was dissolved in 5 mL of ethanol and acidified with 0.5 mL of 2 M anhydrous ethanolic HCl. Et_2O was added slowly until crystallization occurred. Yield 0.175 g (86%) of **3** as fine off-white crystals: mp >240 °C (dec.) ^{1}H NMR (D_2O) δ 1.12 (d, 3, CH_3, J = 6.3 Hz), 3.18 (d, 2, $ArCH_2$, J = 6.8 Hz), 3.67 (sextet, 1, $ArCH_2CH$, J = 6.7 Hz), 6.80 (d, 1, ArH, J = 2.0 Hz), 6.91 (d, 1, ArH, J = 2.3 Hz), 7.67 (d, 1, ArH, J = 2.3 Hz), 7.68 (d, 1, ArH, J = 2.3 Hz). Anal. ($C_{13}H_{13}BrClNO_2$) C, H, N.

Pharmacology Methods. Animals. Male Sprague-Dawley rats (Harlan, Indianapolis, IN) weighing 175-200 g were used. Animals were group housed (for *in vitro* experiments) or individually caged (for drug discrimination experiments) in a temperature-controlled room with a 12 h day/night lighting schedule. Animals that were used for *in vitro* experiments were supplied with food (Lab Blox, Purina) and water *ad libitum*.

Drug Discrimination. The procedures for the drug discrimination assays were performed as described previously.[5] Training drugs were (+)-lysergic acid diethylamide tartrate

(LSD, 0.08 mg/kg) and (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride (DOI, 0.40 mg/kg). The drugs were dissolved in 0.9% saline and were injected intraperitoneally in a volume of 1 mL/kg, 30 min before the sessions.

None of the rats had previously received drugs or behavioral training. Water was freely available in the individual home cages and a rationed amount of supplemental feed (Purina Lab Blox) was made available after experimental sessions to maintain approximately 80% of free-feeding weight. Lights were on from 0700 to 1900. The laboratory and animal facility temperature was 22-24 °C and the relative humidity was 40-50%. Experiments were performed between 0830 and 1700 each day, Monday-Friday.

Six standard operant chambers (model E10-10RF, Coulbourn Instruments, Lehigh Valley, PA) consisted of modular test cages enclosed within sound-attenuated cubicles with fans for ventilation and background white noise. A white house light was centered near the top of the front panel of the cage, which was also equipped with two response levers, separated by a food hopper (combination dipper pellet trough, model E14-06, module size 1/2), all positioned 2.5 cm above the floor. Solid state logic in an adjacent room, interfaced through a Med Associates interface to a 486-based microcomputer, controlled reinforcement and data acquisition with locally-written software.

Briefly, a fixed ratio (FR) 50 schedule of food reinforcement (Bioserv 45 mg dustless pellets) in a two-lever paradigm was used. At least one drug and one saline session separated each test session. Rats were required to maintain an 85% correct responding criterion on training days in order to be tested. In addition, test data were discarded when the accuracy criterion of 85% was not achieved on the two training sessions following a test session. Test sessions were

run under conditions of extinction, with rats removed from the operant chamber when 50 presses were emitted on one lever. If 50 presses on one lever were not completed within 5 min the session was ended and scored as a disruption. Treatments were randomized at the beginning of the study.

Radioligand Competition Assays in Rat Brain Homogenate. The procedure of Johnson *et al.*[10] was employed with minor modifications. Briefly, 50 male Sprague Dawley whole rat brains (unstripped) were purchased from Harlan Bioproducts for Science, Inc. and dissected over dry ice. The frontal cortex tissue was homogenized (Kinematica Polytron, setting "4," 2 x 20 seconds) in 4 volumes (w/v) of ice-cold 0.32 M sucrose and centrifuged at 36,000 x g for 10 minutes at 4 °C. The pellet was again suspended in the same volume of sucrose, homogenized (Kinematica Polytron, setting "4," 20 seconds), separated into aliquots of 4.5 mL, and stored at -70 °C.

For each experiment one aliquot of frontal cortex tissue was thawed and diluted with 25 volumes (w/v) of 50 mM Tris (Aldrich Chemicals) buffer, adjusted to pH 7.4 by HCl. The tissues were homogenized (Kinematica Polytron, setting "4," 20 seconds) and incubated for 10 minutes at 37 °C in a shaking water bath. The homogenate was then centrifuged twice at 36,000 x g at 4 °C for 10 minutes, with the pellet being resuspended in 25 volumes of Tris-HCl buffer in between. The supernatant was discarded and the pellet was resuspended with 25 volumes of Te Pac buffer (0.5 mM Na_2EDTA, 10.0 μM pargyline, 5.7 mM $CaCl_2$, 0.1% $Na_2Ascorbate$), homogenized using the Kinematica as above, and incubated for 10 minutes at 37 °C in a shaking water bath. The homogenate was then placed in an ice bath to cool. Binding was initiated by adding 800 μL of homogenate tissue to assay tubes containing 100 μL of [^{3}H]MDL 100,907 (0.2 nM) and 100 μL of the competing drug solution or H_2O. Non-specific binding was determined

in the presence of cinanserin (10 μM). Binding assays were incubated for 15 minutes at 37 °C in a shaking water bath. Incubation was stopped by rapid vacuum filtration through GF/C filters using a Brandel Cell Harvester (Brandel Instruments, Gaithersburg, MD, USA). The filters were washed twice with 5 mL aliquots of ice-cold Tris-HCl buffer, allowed to air dry and placed into scintillation vials containing 10 mL of Ecolite scintillation cocktail (ICN Biomedicals). Eight hours later the radioactivity was measured using liquid scintillation spectroscopy (Packard model 4430) at 37% efficiency. EC_{50} (nM) values were calculated from at least three experiments, each done in triplicate, using GraphPad PRISM™.

Radioligand Competition Experiments Using Cloned Human Receptors. These assays were peformed exactly as previously described.[5]

Statistical Analysis. Data from the drug-discrimination studies were scored in a quantal fashion, with the lever on which the rat first emitted 50 presses in a test session scored as the "selected" lever. The percentage of rats selecting the drug lever (%SDL) for each dose of compound was determined. The degree of substitution was determined by the maximum % SDL for all doses of the test drug. "No substitution" (NS) is defined as 59% SDL or less, and "partial" substitution is 60-79% SDL. If the compound was one that completely substituted for the training drug (at least one dose resulted in a % SDL = 80% or higher), the ED_{50} values and 95% confidence intervals (95% CI) were then determined from quantal dose-response curves according to the procedure of Litchfield and Wilcoxon.[7] If the percentage of rats disrupted (% D) was 50% or higher, the ED_{50} value was not determined, even if the % SDL of nondisrupted animals was higher than 80%.

Materials. (±)-DOI, as the hydrochloride salt, was synthesized in our laboratory. (+)-LSD tartrate was obtained from NIDA. For drug-discrimination experiments, drugs were dissolved in 0.9% saline and injected intraperitoneally in a volume of 1 mL/kg, 30 min before the session.

Appendix — Elemental Analyses

Elemental Analysis Data for New Compounds Synthesized

#	Molecular Formula	Calculated (% C, H, N)	Found (% C, H, N)	δ (% C, H, N)
3.HCl	$C_{13}H_{13}BrClNO_2$	47.23, 3.96, 4.24	47.00, 4.06, 4.08	0.23, 0.10, 0.16
5	$C_{15}H_{16}F_3NO_3$	57.14, 5.11, 4.44	57.26, 5.06, 4.27	0.12, 0.05, 0.17
6	$C_{15}H_{15}BrF_3NO_3$	45.71, 3.84, 3.55	45.70, 3.64, 3.42	0.01, 0.20, 0.13
7	$C_{15}H_{11}BrF_3NO_3$	46.18, 2.84, 3.59	46.12, 3.20, 3.33	0.06, 0.36, 0.26