Supporting information:

Synthesis and Evaluation of Fluorinated Aporphines: Potential Positron Emission Tomography Ligands for D_2 Receptors

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Experimental Section

General Synthetic Methods. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively using $CDCl_3$ or CD_3OD as solvent, on a Varian Mercury 300 spectrometer. Chemical shifts are given as δ value (ppm) downfield from tetramethylsilane as an internal reference. Melting points were determined on a Thomas-Hoover capillary tube apparatus and are reported uncorrected. Elemental analyses, performed by Atlantic Microlabs, Atlanta, GA, were within ±0.4% of theoretical values. Analytical thin-layer chromatography (TLC) was carried out on 0.2-mm Kieselgel 60F-254 silica gel aluminum sheets (EMD Science, Newark, NJ). Flash chromatography was used for the routine purification of reaction products.

Inhibition of [^{3}H]domperidone binding to dopamine D_2 and D_3 receptors

The potencies of the compounds on the high-affinity and low-affinity states of the dopamine D_2 receptor (or D_2^{High}) was measured by competition with [^{3}H]domperidone, using rat striatal tissue and human cloned D_3 receptors.

Rat brains were used (Sprague-Dawley; 275-300 g, male, 60-65 days of age, euthanized by a CO_2 atmosphere at Rockland Immunochemicals, Gilbertsville, PA; Certified by the U.S. Department of Agriculture, OLANIH-assured [Office of Laboratory Animals, National Institutes of Health, Bethesda, MD]). The brains were stored at -70 ˚C until used, at which time the striata were removed. The striata were homogenized in buffer (4 mg frozen tissue per ml buffer), using a teflon-glass homogenizer (with the piston rotating at 500 rpm) and 10 up and down strokes of the glass container. The buffer contained 50 mM Tris-HC1 (pH 7.4 at 20 ˚C), 1 mM EDTA, 5 mM KCl, 1.5 mM $CaC1_2$, 4 mM $MgC1_2$ and 120 mM NaCl. The homogenate was not washed, centrifuged, or pre-incubated because previous work found that 30-50% of the D_2 receptors were lost by these procedures.

The dopamine D_2 receptors in the rat striatum were measured with a final concentration of 2 nM [^{3}H]domperidone (68 Ci/mmol, custom-synthesized by PerkinElmer Life Sciences Inc., Boston, MA, and 41.4 Ci/mmol, custom-synthesized by Moravek Biochemicals, Inc., Brea, CA). Each incubation tube (12 x 75 mm, glass) received, in the following order, 0.25 ml of competing drug, 0.25 ml buffer, and with or without a final concentration of 10 µM S-sulpiride to define nonspecific binding to the dopamine D_2 receptors), 0.25 ml [^{3}H]domperidone, and 0.25 ml of tissue homogenate. The tubes, containing a total volume of 1 ml, were incubated for 2 h at room temperature (20 ˚C), after which the incubates were filtered, using a 12-well cell harvester (Titertek, Skatron, Lier, Norway) and buffer-presoaked glass fiber filter mats (Whatman GF/C). After filtering the incubate, the filter mat was rinsed with buffer for 15 s (7.5 ml buffer). The filters were pushed out and placed in scintillation minivials (7 ml, 16 x 54 mm; Valley Container Inc., Bridgeport, Conn.). The minivials received 4 ml each of scintillant (Research Products International Corp., Mount Prospect, IL), and were monitored 6 h later for tritium in a Beckman LS5000TA scintillation spectrometer at 52% efficiency. The specific binding of [^{3}H]domperidone was defined as total binding minus that in the presence of 10 µM S-sulpiride.

The data for the competition between the compound and [^{3}H]domperidone were analyzed using the GraphPad Prism method (GraphPad Software, Inc., La Jolla, CA 92037). The dissociation constant, Ki, was equal to IC50%/ (1+C/Kd), where IC50% was the concentration that inhibited the binding at either the high- or low-affinity component by 50%, where C was the final molarity of [^{3}H]domperidone (2 nM), and where Kd was the dissociation constant for [^{3}H]domperidone. The Kd for [^{3}H]domperidone was 0.44 nM for D_2 in the rat homogenized striata. Both a two-site fit and a one-site fit were tested, with the two-site fit being statistically better in the absence of guanylylimidodiphosphate.

We used human cloned dopamine D_3 receptors (expressed in mouse CCL1-3 mouse fibroblasts (Sigma Aldrich Canada Ltd., Oakville, Ontario, Canada).

Inhibition of Dopamine D_3 Receptors Using [^{3}H]-Domperidone (11a-d)[21]

Assay Buffers:

Dopamine Binding Buffer (50 mM NaCl, 50 mM HEPES-HCl, 5 mM $MgCl_2$, 0.5 mM EDTA, pH 7.4)

Membrane Fraction Source:

Transiently or stably transfected cell lines (*e.g.*, HEK293, COS, CHO, NIH3T3)

Protocol adapted from Roth *et al*. *Psychopharmacology* 120(3):365-368 (1995).

Experimental Procedure and Data Analysis:

A solution of the compound to be tested is prepared as a 1-mg/ml stock in Dopamine Binding Buffer or DMSO according to its solubility. A similar stock of a reference compound (positive control) is also prepared. Eleven dilutions (5 x assay concentration) of the test and reference (see Table) compounds are prepared in Dopamine Binding Buffer by serial dilution: 0.05 nM, 0.5 nM, 1.5 nM, 5 nM, 15 nM, 50 nM, 150 nM, 500 nM, 1.5 µM, 5 µM, 50 µM (thus, the corresponding assay concentrations span from 10 pM to 10 µM and include semilog points in the range where high-to-moderate affinity ligands compete with radioligand for binding sites).

[^{3}H]Domperidone is diluted to five times the assay concentration in Dopamine Binding Buffer (1.78 nM). Aliquots (50 µl) of radioligand are dispensed into the wells of a 96-well plate containing 100 µl of Dopamine Binding Buffer. Then, duplicate 50-µl aliquots of the test and reference compound dilutions are added. Finally, crude membrane fractions of cells expressing recombinant target (prepared from 10-cm plates by harvesting PBS-rinsed monolayers, resuspending and lysing in chilled, hypotonic 50 mM Tris-HCl, pH 7.4, centrifuging at 20,000 x *g*, decanting the supernatant and storing at -80 degrees centigrade; typically, one 10-cm plate provides sufficient material for 24 wells) are resuspended in 3 ml

of chilled Dopamine Binding Buffer and homogenized by several passages through a 26 gauge needle, then 50 µl are dispensed into each well. The 250-µl reactions are incubated at room temperature and shielded from light (to prevent photolysis of light-sensitive ligands) for 1.5 hours, then harvested by rapid filtration onto Whatman GF/B glass fiber filters pre-soaked with 0.3% polyethyleneimine using a 96-well Brandel harvester. Four rapid 500-µl washes are performed with chilled Standard Binding Buffer to reduce non-specific binding. Filters are placed in 6-ml scintillation tubes and allowed to dry overnight. The next day, 4 ml of EcoScint scintillation cocktail (National Diagnostics) is added to each tube. The tubes are capped, labeled, and counted by liquid scintillation counting. For higher throughput assays, bound radioactivity is harvested onto 0.3% polyethyleneimine-treated, 96-well filter mats using a 96-well Filtermate harvester. The filter mats are dried, then scintillant is melted onto the filters and the radioactivity retained on the filters is counted in a Microbeta scintillation counter. Currently, nearly all of our radioligand binding assays have been adapted to this higher throughput approach. Raw data (dpm) representing total radioligand binding (*i.e.*, specific + non-specific binding) are plotted as a function of the logarithm of the molar concentration of the competitor (*i.e.*, test or reference compound). Non-linear regression of the normalized (*i.e.*, percent radioligand binding compared to that observed in the absence of test or reference compound) raw data is performed in Prism 4.0 (GraphPad Software) using the built-in three parameter logistic model describing ligand competition binding to radioligand-labeled sites:

$$y = \text{bottom} + [(\text{top-bottom})/(1 + 10^{x\text{-log}IC_{50}})]$$

where bottom equals the residual radioligand binding measured in the presence of 10 µM reference compound (*i.e.*, non-specific binding) and top equals the total radioligand binding observed in the absence of competitor. The log IC_{50} (*i.e.*, the log of the ligand concentration that reduces radioligand binding by 50%) is thus estimated from the data and used to obtain the K_i by applying the Cheng-Prusoff approximation:

$K_i = IC_{50}/(1 + [ligand]/K_D)$

where [ligand] equals the assay radioligand concentration and K_D equals the affinity constant of the radioligand for the target receptor.

N-(3-Fluoropropyl)-3-deoxynormorphine (5).

1-bromo-3-fluoropropane (410 mg, 2.91 mmol) was slowly added into the mixture of 3-deoxynormorphine (300 mg, 1.17 mmol) and $NaHCO_3$ (150 mg, 1.78 mmol) in EtOH (25 mL). The resulting mixture was refluxed overnight. Ethanol was removed in vacuo. Water (50 mL) was added into the residue and extracted with EtOAc (30 mL x 3). The combined organic layer was washed with brine (50 mL), dried with Na_2SO_4 and evaporated *in vacuo*. The residue was purified on silica gel column eluting with CH_2Cl_2: MeOH = 40:1 to obtain the product **5** (220 mg) in 60% yield.

(*R*)-(–)-11-Hydroxy-N-(3-fluoropropyl)noraporphine (6)

Under nitrogen atmosphere, a mixture of *N*-(3-fluoropropyl)-3-deoxynormorphine (**5**) (220 mg, 0.69 mmol) in $MeSO_3H$ (8 mL) was stirred for 30 min at 95-100 ºC. After cooling to room temperature, the mixture was poured into ice water and brought to pH = 9-10 with ammonium hydroxide. The mixture was extracted with CH_2Cl_2 (50 mL x 3). The combined organic layer was washed with brine, dried with Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography using hexanes:ethyl acetate (2:1) as eluent to afford **6** (115 mg) as a white foam in 56% yield. The free base was converted to the HCl salt with 1 M HCl in ether to afford 101 mg of a white solid. M.p. (HCl) 195-197 ^oC (decomposed). Anal. calcd. for $C_{19}H_{20}NOF•HCl•0.5H_2O$: C, 66.49; H, 6.41; N, 4.08. Found: C, 66.68; H, 6.40; N, 4.03. ^1H NMR (base, 300 MHz, $CDCl_3$) δ 7.97 (d, J = 7.8

Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.62 (d, *J* = 7.8 Hz, 1H), 4.62 (m, 1H), 4.46 (m, 1H), 3.36 (dd, *J* = 13.5 and 3.0 Hz, 1H), 3.17-3.02 (m, 4H), 2.74 (dd, *J* = 15.0 and 3.3 Hz, 1H), 2.60-2.44 (m, 3H), 2.06-1.89 (m, 2H); ^{13}C NMR (base, 75 MHz, $CDCl_3$) δ 152.8, 138.0, 134.8, 133.1, 131.6, 127.9, 127.4, 126.2, 124.9, 121.4, 120.2, 115.6, 82.48 (d, *J* = 163.2 Hz), 59.6, 50.09 (d, *J* = 4.9 Hz), 48.9, 34.7, 28.9, 27.3 (d, *J* = 19.5 Hz).

General Procedure for the Preparation of (*R*)-(–)-N-alkyl-2-Fluoroalkoxy-norapomorphines 8a-f.

A mixture of oripavine **7a,** N-ethylnororipavine **7b,** or N-propylnororipavine 7**c** (0.27 mmol), $MeSO_3H$ (2.5 mL) and fluoroethanol or fluoropropanol (0.5 mL) was stirred for 30 min at 0 ^{o}C. The mixture was warmed to rt slowly and then warmed up to 95 ^{o}C stirring for 30 min at this temperature. After cooling to room temperature, the mixture was poured into ice water and basified to pH = 9-10 with ammonium hydroxide. The mixture was extracted with CH_2Cl_2 (50 mL x 3). The combined organic layer was washed with brine, dried with Na_2SO_4, and evaporated in vacuo. The residue was purified on silica gel column eluting with CH_3OH: CH_2Cl_2 = 1:50 obtaining **8a-f** in 6-47% yield as a white solid. The free base was converted to HCl salt with 1N HCl in ether.

(*R*)-(–)-2-(3-fluoropropanoxy)-N-*n*-propylnorapomorphine (8a).

6% isolated yield. M.p. (HCl salt) 180-182 ^{o}C. Anal. calcd. for $C_{22}H_{26}NFO_3$•HCl: C, 64.78; H, 6.67; N, 3.42. Found: C, 64.54; H, 6.67; N, 3.02. ^{1}H NMR (base, 300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 2.4 Hz, 1H), 6.56 (d, *J* = 7.6 Hz, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 6.47 (d, *J* = 7.6 Hz, 1H), 5.6 (br, 2H), 4.72 (t, *J* = 6.0 Hz, 1H), 4.55 (t, *J* = 6.0 Hz, 1H), 4.10-4.01 (m, 2H), 3.40 (m, 1H), 3.24-3.04 (m 2H), 2.90-2.81 (m, 2H), 2.70-2.50 (m, 4H), 2.22-1.98 (m, 2H), 1.70-1.61 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (base,

75 MHz, $CDCl_3$) δ 157.2, 143.8, 143.0, 133.5, 133.1, 127.8, 120.2, 118.8, 114.0, 112.8, 112.4, 80.5 (d, *J* = 163.1 Hz), 63.3 (d, *J* = 5.4 Hz), 59.4, 54.9, 48.4, 33.87, 30.3 (d, *J* = 20.1 Hz), 27.9, 18.4, 11.9.

(*R*)-(–)-2-Fluoroethyoxy- N-*n*-propylnorapomorphine (8b).

47% isolated yield. M.p. (HCl salt) 203-205 ^{o}C (decomposed). Anal. calcd. for $C_{21}H_{24}NFO_3$•HCl•1.25H_2O: C, 60.64; H, 6.61; N, 3.36. Found: C, 60.52; H, 6.47; N, 3.15.^{1}H NMR (base, 300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 2.4 Hz, 1H), 7.64 (br, s, 2H), 6.51 (d, *J* = 2.4 Hz, 1H), 6.49 (s, 2H), 4.78 (t, *J* = 4.2 Hz, 1H), 4.62 (t, *J* = 4.2 Hz, 1H), 4.18 (m, 1H), 4.11 (m, 1H), 3.39 (m, 1H), 3.19-3.07 (m 2H), 2.96-2.83 (m, 2H), 2.68-2.48 (m, 4H), 1.63-1.55 (m, 2H), 0.93 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (base, 75 MHz, $CDCl_3$) δ 156.7, 144.0, 143.2, 133.5, 127.8, 126.5, 120.2, 118.8, 114.0, 112.7, 81.9 (d, *J* = 169.1 Hz), 67.0 (d, *J* = 20.3 Hz), 59.3, 55.5, 48.6, 33.8, 28.3, 18.2, 12.0.

(*R*)-(–)-N-ethyl-2-(3-Fluoropropanoxy)-norapomorphine (8c).

36% isolated yield. M.p. (HCl salt). 174-176 ^{o}C (decomposed). Anal. calcd. for $C_{21}H_{24}NFO_3$•HCl•H_2O: C, 61.24; H, 6.61; N, 3.40. Found: C, 61.52; H, 6.40; N, 3.38. ^{1}H NMR (base, 300 MHz, CDCl3) δ 7.80 (d, *J* = 2.6 Hz, 1H), 6.62 – 6.46 (m, 3H), 4.72 (t, *J* = 5.8 Hz, 1H), 4.56 (t, *J* = 5.8 Hz, 1H), 4.09-4.06 (m, 2H), 3.49 – 3.46 (m, 1H), 3.25 – 2.85 (m, 4H), 2.79 – 2.61 (m, 2H), 2.52 (t, *J* = 13.6 Hz, 2H), 2.27 – 2.01 (m, 2H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (base, 75 MHz, CDCl3) δ 157.91, 157.08, 143.43, 142.77, 133.80, 133.28, 128.54, 126.71, 120.49, 118.91, 113.81, 112.60, 80.9 (d, J = 163.5 Hz), 63.38 (d, *J* = 5.3 Hz), 58.80, 55.19, 47.58 (d, *J* = 40.0Hz), 34.00, 30.52, 30.26, 28.60, 10.11. ^{19}F NMR (base, 282 MHz, $CDCl_3$) δ 7.69 (tt, *J* = 25.9, 47.2 Hz).

(*R*)-(–)-N-ethyl-2-fluoroethoxynorapomorphine (8d).

32% isolated yield. M.p. (HCl salt) 163-165 °C. Anal. calcd. for $C_{20}H_{22}NFO_3$•HCl•0.75H_2O: C, 61.07; H, 6.28; N, 3.56. Found: C, 60.94; H, 6.18; N, 3.63.^{1}H NMR (HCl salt, 300 MHz, CD_3OD) δ 8.08 (dd, *J* = 2.6, 6.3 Hz, 1H), 6.85 – 6.62 (m, 3H), 4.82 (ddd, *J* = 1.2, 2.3, 4.1 Hz, 1H), 4.66 (dd, *J* = 3.2, 4.7 Hz, 1H), 4.28 – 4.20 (m, 3H), 3.91 – 3.74 (m, 2H), 3.45 – 3.25 (m, 5H), 3.20 – 3.05 (m, 1H), 2.75 (t, *J* = 13.7 Hz, 1H), 1.45 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (HCl salt, 75 MHz, CD_3OD) δ 159.45, 158.33, 145.02, 143.47, 134.43, 130.97, 124.45, 124.43, 121.01, 118.84, 114.83, 114.20, 114.11, 111.61, 82.01 (d, *J* = 168.0 Hz), 67.41, 60.48, 60.42, 54.59, 31.54 (d, *J* = 5.5 Hz), 26.18, 7.91. ^{19}F NMR (HCl salt, 282 MHz, CD_3OD) δ 4.29 (tt, *J* = 28.9, 47.9 Hz).

(*R*)-(–)-2-(3-Fluoropropanoxy)- apomorphine (8e).

3.6 mmol scale; 28% isolated yield. M.p. (HCl salt) 170-175ºC (decomposed). Anal. calcd. for $C_{20}H_{22}FNO_3$•HCl•1/3H_2O: C, 61.77; H, 6.22; N, 3.60. Found: C, 61.95; H, 6.08; N, 3.57. NMR: ^{1}H NMR (HCl salt, 300 MHz, CD_3OD) δ 8.08 (d, *J* = 2.5 Hz, 1H), 6.82 – 6.60 (m, 3H), 4.71 (t, *J* = 5.8 Hz, 1H), 4.55 (t, *J* = 5.8 Hz, 1H), 4.13 (t, *J* = 6.2 Hz, 2H), 3.79 – 3.70 (m, 1H), 3.52 – 3.35 (m, 2H), 3.31 (s, 3H), 3.20 – 3.01 (m, 5H), 2.76 (t, *J* = 13.6 Hz, 1H), 2.21 (p, *J* = 6.0 Hz, 1H), 2.12 (p, *J* = 6.1 Hz, 1H). ^{13}C NMR (HCl salt, 75 MHz, CD_3OD) δ 158.78, 145.11, 143.65, 134.27, 130.49, 124.33, 119.54, 118.81, 114.75, 114.07, 111.93, 111.28, 81.55, 79.38, 63.67, 63.60, 62.84 (dd, J = 6.9, 14.5 Hz), 31.77, 30.45, 30.19. ^{19}F NMR (HCl salt, 282 MHz, CD_3OD) δ 5.57 (tt, *J* = 25.6, 47.3 Hz).

(*R*)-(–)-2-(2-Fluoroethoxy)apomorphine (8f).

29% isolated yield. M.p. (HCl salt) 236-238ºC (decomposed). Anal. calcd. for $C_{19}H_{20}FNO_3$•HCl: C, 62.38; H, 5.79; N, 3.77. Found: C, 62.12; H, 5.86; N, 3.77. ^{1}H NMR (base, 300 MHz, CD_3OD) δ 8.10 (d, *J* = 2.6 Hz, 1H), 6.77 – 6.66 (m, 3H), 4.84 – 4.79 (m, 1H), 4.69 – 4.62 (m, 1H), 4.33 – 4.26 (m, 1H), 4.22 – 4.17 (m, 1H), 3.82 (s, 1H), 3.77 (dd, *J* = 4.3, 11.0 Hz, 1H), 3.56 – 3.39 (m, 2H), 3.31 (s, 3H),

3.15 (s, 2H), 3.09 (d, *J* = 3.4 Hz, 1H), 2.76 (t, *J* = 13.3 Hz, 1H). ^{13}C NMR (base, 75 MHz, CD_3OD) δ 159.64, 158.54, 145.13, 143.69, 134.36, 124.31, 118.80, 114.80, 114.10, 114.03, 111.96, 111.29, 83.06, 80.82, 67.56, 67.29, 63.06 – 62.73 (m), 54.57, 31.75. ^{19}F NMR (base, 282 MHz, CD_3OD) δ 4.27 (tt, *J* = 28.8, 47.8 Hz).

(*R*)-(–)-N-*n*-propyl-2-(2-fluoropropanoxy)-10-trifluoromethylsulfonyloxy-11-hydroxynoraporphine (10a).

To a 6 dram vial under nitrogen atmosphere were added: N-*n*-propyl-3-(trifluoromethylsulfonyloxy)nororipavine **9c** (396 mg, 0.866 mmol) and 3-fluoropropanol (300 μL). The vial was cooled to 0 ºC and methanesulfonic acid (3 mL) was added. After brief stirring, the reaction was heated to 95 ºC and stirred for 2 hours. After cooling, the acid solution was diluted with cold water (100 mL) and brought to pH 8-9 by dropwise addition of concentrated ammonium hydroxide solution. The aqueous phase was extracted with ethyl acetate (2x50 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, concentrated, and purified by flash column chromatography using 1:40 methanol:dichloromethane as eluent. The resulting fractions were collected and concentrated to about 10 mL, and white crystals precipitated. The crystals were filtered, washed with ether/hexanes, and dried to afford 114 mg of **10a** as fine pale green needles, 26% yield. M.p. (free base) 158-160 ºC (decomposed). ^{1}H NMR (300 MHz, DMSO) δ 7.28 – 7.11 (m, 2H), 6.95 (t, *J* = 9.7 Hz, 1H), 6.71 (dd, *J* = 2.3, 14.0 Hz, 1H), 4.67 (q, *J* = 5.8 Hz, 1H), 4.51 (q, *J* = 5.8 Hz, 1H), 4.05 (t, *J* = 6.0 Hz, 3H), 3.15 (dd, *J* = 12.0, 23.5 Hz, 1H), 2.86 (dd, *J* = 10.7, 16.4 Hz, 4H), 2.68 (d, *J* = 16.7 Hz, 1H), 2.48 (dt, *J* = 1.8, 3.6 Hz, 2H), 2.40 - 2.00 (m, 2H), 1.65 – 1.35 (m, 2H), 0.89 (dd, *J* = 6.5, 8.1 Hz, 3H). ^{13}C NMR (75 MHz, DMSO) δ 157.12, 157.02, 149.46, 135.90, 135.39, 130.76, 129.35, 129.31, 129.27, 129.18, 128.52, 126.20, (118.91, q, *J* = 329 Hz), 113.04, 81.50 (d, *J* = 172.7 Hz), 63.99, 59.48

(d, *J* = 10.5 Hz), 56.25, 48.96, 34.43, 30.47 (d, *J* = 19.8 Hz), 20.03, 12.60. ^{19}F NMR (282 MHz, DMSO) δ 8.99 (dd, *J* = 6.4, 19.4 Hz), -74.63.

(*R*)-(–)-N-*n*-propyl-2-(2-fluoroethoxy)-10-(trifluoromethylsulfonyl)oxy-11-hydroxynoraporphine (10b).

Under nitrogen atmosphere, a mixture of N-*n*-propyl-3-(trifluoromethylsulfonyloxy)nororipavine **9c** (457 mg), $MeSO_3H$ (5.0 mL) and 2-fluoroethanol (1.0 mL) was stirred for 30 min at 0 ºC. The mixture was warmed to rt slowly and then warmed up to 95 ºC stirring for 30 min at this temperature. After cooling to room temperature, the mixture was poured into ice water and brought to pH = 9-10 with ammonium hydroxide. The mixture was extracted with CH_2Cl_2 (50 mL x 3). The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography using CH_3OH: CH_2Cl_2 (1:50) as eluent to afford **10b** (67 mg) in 27% yield as a pale white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 1.8 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.77 (d, *J* = 1.8 Hz, 1H), 4.84 (t, *J* = 4.2 Hz, 1H), 4.68 (t, *J* = 4.2 Hz, 1H), 4.28 (m, 1H), 4.19 (m, 1H), 3.35 (m, 1H), 3.23-3.06 (m 2H), 2.88 (m, 1H), 2.73 (m, 1H), 2.58-2.45 (m, 2H), 1.85 (m, 2H), 1.61 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H).

(*R*)-(–)-N-ethyl-2-(2-fluoropropanoxy)-10-(trifluoromethylsulfonyloxy)-11-hydroxynoraporphine (10c).

To a 6 dram vial under nitrogen atmosphere were added: N-ethyl-3-(trifluoromethylsulfonyloxy)nororipavine **9b** (140 mg, 0.316 mmol) and 3-fluoropropanol (70 μL) until no lumps remained. The resulting suspension was stirred for 5 minutes and then methanesulfonic acid (625 μL) and stirred art 95 ºC for 1 hour. After cooling, the acidic solution was transferred to water (10 mL) and treated with concentrated ammonium hydroxide solution until pH 8-9 was reached. The

resulting aqueous solution was extracted with ethyl acetate (3x5 mL), filtered through sodium sulfate, concentrated, and purified by column chromatography using 1:50 MeOH:DCM as eluent to afford 118.4 mg of a crude solid (77%; ~10% inseparable impurity present by NMR). The impure product **10c** was carried to the next step. ^{1}H NMR (300 MHz, CDCl3) δ 7.75 (s, 1H), 7.09 (d, 1H, *J* = 8.01 Hz), 6.82 (d, 1H, *J* = 7.87 Hz), 6.61 (s, 1H), 4.72 (s, 1H), 4.56 (s, 1H), 4.10-4.09 m, 2H), 3.41-3.31 (m, 1H), 3.09-3.05 (m, 4H), 2.75-2.46 (m, 4H), 2.21-2.08 (m, 2H), 1.79-1.50 (m, 1H), 1.26-1.0147 (m, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 157.71, 156.94, 137.52, 134.06, 134.02, 126.80, 126.77, 124.89, 123.100 (q, *J* = 315.4 Hz), 119.96, 115.75, 113.14, 112.56, 80.67 (d, *J* = 164.1 Hz), 63.40 (d, *J* = 4.9 Hz), 58.09, 55.10, 47.59 (d, *J* = 19.3 Hz), 34.35, 29.54, 28.58, 10.11. ^{19}F NMR (282 MHz, CDCl3) 7.22 (tt, *J* = 48.54, 24.89 Hz).

(*R*)-(–)-N-ethyl-2-(2-fluoroethoxy)-10-(trifluoromethyl)sulfonyloxy)-11-hydroxynoraporphine (10d).

To a 6 dram vial under nitrogen atmosphere were added: N-ethyl-3-(trifluoromethylsulfonyloxy)nororipavine **9b** (119 mg, 0.268 mmol) and fluoroethanol (60 µL). The vial was cooled to 0 ºC and methanesulfonic acid (0.53 mL) was added. After brief stirring, the reaction was heated to 95 ºC and stirred for 30 minutes. After cooling, the acid solution was diluted with cold water (50 mL) and brought to pH 8-9 by dropwise addition of concentrated ammonium hydroxide solution. The aqueous phase was extracted with ethyl acetate (2×50 mL) and with dichloromethane (1×40 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, concentrated, and purified by flash column chromatography using 1:15 methanol:dichloromethane as eluent. The resulting fractions were collected and concentrated to about 10 mL, and white crystals precipitated. After storing it in the freezer overnight, the crystals were filtered and dried to afford 58 mg of (*R*)-(–)-N-ethyl-2-(2-fluoroethoxy)-10-(trifluoromethyl)sulfonyloxy)-11-hydroxynoraporphine

10d as fine white needles, 44% yield. M.p. (free base) 171-173 ºC (decomposed). ^{1}H NMR (300 MHz, DMSO) δ 7.21 (dd, *J* = 5.3, 13.4 Hz, 2H), 6.96 (t, *J* = 10.0 Hz, 1H), 6.81 – 6.65 (m, 1H), 4.89 – 4.72 (m, 1H), 4.64 (t, *J* = 3.8 Hz, 1H), 4.34 – 4.05 (m, 2H), 3.17 – 2.83 (m, 5H), 2.72 (d, *J* = 16.0 Hz, 2H), 2.44 – 2.08 (m, 2H), 1.06 (t, *J* = 5.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO) δ -43.99 – -47.06 (m), -74.12, -74.52. The product contains an inseparable trace of the 2-methoxy analog (reflected in a ^{19}F shift corresponding to the 2-MeO byproduct).

(*R*)-(–)-2-(2-fluoroethoxy)-10-(trifluoromethylsulfonyloxy)-11-hydroxyaporphine (10e).

To a 25 mL round bottomed flask was added oripavine-3-triflate **9a** (1.0 g, 2.33 mmol). The flask was flushed with nitrogen and put on ice. Next, 2-fluoroethanol (1.0 mL) was added, followed by methanesulfonic acid (5.5 mL). The mixture was stirred briefly at 0 ºC, then heated at 90-95 ºC while stirring for 40 minutes. After cooling, the mixture was transferred dropwise to ice water (100 mL) while stirring. The aqueous mixture was basified with ammonium hydroxide solution, then extracted with dichloromethane (2x30 mL). The organic extracts were combined, washed with brine, concentrated, and purified over silica gel using 1:20 methanol:dichloromethane eluent (which was not adequate for purification). The resulting solid was then recrystallized from methanol and then the mother liquor was concentrated and the title compound was recrystallized again from DCM/ether to afford 579 mg of **10g** as fine grey-green needles (54% yield) (It was found to contain about 11% by mol of 2-methoxy analog as an inseparable impurity). ^{1}H NMR (300 MHz, DMSO) δ 7.70 (s, 1H), 7.25 (d, *J* = 8.2 Hz, 2H), 6.98 (s, 1H), 6.77 (d, *J* = 15.4 Hz, 1H), 4.74 (d, *J* = 47.9 Hz, 2H), 4.22 (d, *J* = 27.5 Hz, 2H), 3.76 (s, 0.3H), 3.27 – 3.11 (m, 2H), 2.96 (s, 3H), 2.75-2.71 (m, 1H), 2.45 (s, 3H), 2.42 – 2.13 (m, 1H). ^{19}F NMR (282 MHz, DMSO) δ 7.72 –7.20 (m), -74.16, -74.53.

(*R*)-(–)- N-*n*-propyl-2-(2-fluoropropanoxy)-11-hydroxynoraporphine (11a).

To a 6 dram vial under nitrogen atmosphere were added: (*R*)-(–)-2-fluoropropanoxy-11-hydroxy-10-trifluoromethanesulfonyloxyaporphine **10a** (70 mg, 0.197 mmol), palladium on carbon (17 mg), magnesium turnings (14 mg), and ammonium acetate (74 mg). The vial was then capped and evacuated and flushed with nitrogen (3 cycles) and anhydrous methanol was added (6 mL). The resulting suspension was then stirred at room temperature for 1 day. After the reaction was judged complete by TLC, the reaction was quenched by adding triethylamine (0.5 mL), filtered through a pad of Celite, and washed with two portions of methanol. The methanol solution was then concentrated and loaded onto silica gel and purified twice by column chromatography using 1:10 methanol:dichloromethane to afford 15.2 mg of **11a** as a brown foam (0.0428 mmol, 22% yield). M.p. (HCl salt) 150-153 ºC (decomposed). Anal. calcd for ($C_{22}H_{26}FNO_2$•3/4H_2O): C, 71.91; H, 7.50; N, 3.80. Found: C, 71.30; H, 7.43; N, 3.80. ^{1}H NMR (base, 300 MHz, CDCl3) δ 7.63 (d, *J* = 2.4 Hz, 1H), 7.05 (t, *J* = 7.7 Hz, 1H), 6.84 (d, *J* = 7.3 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 6.60 (s, 1H), 4.72 (t, *J* = 5.8 Hz, 1H), 4.56 (t, *J* = 5.8 Hz, 1H), 4.09 (t, *J* = 6.1 Hz, 2H), 3.80 (s, 1H), 3.32 (d, *J* = 13.1 Hz, 1H), 3.12 (m, 3H), 2.90 (s, 1H), 2.71 (d, *J* = 15.9 Hz, 1H), 2.48 (m, 3H), 2.14 (ddd, *J* = 5.9, 11.8, 23.7 Hz, 2H), 1.63 (dd, *J* = 9.2, 15.8, 2H), 0.96 (t, *J* = 7.3, 3H). ^{13}C NMR (base, 75 MHz, CDCl3) δ 157.06, 152.83, 138.68, 134.87, 132.70, 128.17, 128.11, 121.26, 120.55, 115.58, 112.68, 111.94, 80.85 (d, *J* = 164.1 Hz), 63.48 (d, *J* = 5.3 Hz), 59.23, 56.45, 55.24, 49.04, 35.31, 30.45 (d, *J* = 19.9 Hz), 29.50, 19.32, 12.10. ^{19}F NMR (base, 282 MHz, CDCl3) δ 7.65 (tt, *J* = 25.9, 47.1 Hz).

(*R*)-(–)-N-*n*-propyl-2-(2-fluoroethoxy)-11-hydroxynoraporphine (11b).

To a 6 dram vial containing (*R*)-(–)-N-*n*-propyl-2-(2-fluoroethoxy)-11-hydroxy-10-(trifluromethylsulfonyloxy)aporphine **10b** (110 mg) were added: Pd/c (19 mg), a magnesium turning (16 mg), and ammonium acetate (84 mg). The vial was flushed with nitrogen and then anhydrous methanol (7 mL) was added. The resulting mixture was then allowed to stir at RT for 3 days. The

suspension was filtered through a pad of Celite and washed with two portions of methanol. The filtrate was concentrated and suspended in dichloromethane (~20 mL). The organic layer was washed with a mixture of 28% ammonium hydroxide/water/brine (2:3:2 mL). The aqueous phase was extracted again with ethyl acetate (5 mL) and dichloromethane (5 mL) and the combined organic extracts were filtered through sodium sulfate. The combined organic phase was then concentrated and purified by column chromatography using 1:30 (MeOH:DCM) as eluent to afford crude product (56 mg). The residue was purified a second time using 10:5:2 hexanes:ethyl acetate:triethylamine as eluent to afford 22.7 mg of (*R*)-(–)-N-*n*-propyl-2-(2-fluoroethoxy)-11-hydroxyoxynoraporphine **11b** in 30% isolated yield. The free base was then dissolved in dichloromethane and treated with 1N ethereal HCl to obtain the HCl salt. The solvent was removed under vacuum and the solid was dissolved in minimum MeOH and precipitated by dropwise addition to ~10 mL ether, to afford 21.5 mg of the hydrochloride salt. M.p. (HCl salt) 167-170 ºC. Anal. calcd for $C_{21}H_{24}FNO_2 \cdot H_2O$: (free base): C, 70.17; H, 7.29; N, 3.90. Found: C, 70.12; H, 7.10; N, 3.61.^{1}H NMR (free base, 300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.3 Hz, 1H), 7.02 (dd, *J* = 10.8, 4.7 Hz, 1H), 6.81 (d, *J* = 7.1 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.60 (d, *J* = 2.2 Hz, 1H), 4.85 – 4.55 (m, 2H), 4.29 – 4.02 (m, 2H), 3.36 (d, *J* = 11.8 Hz, 1H), 3.14 (ddd, *J* = 17.7, 14.1, 4.3 Hz, 3H), 2.93 (td, *J* = 12.7, 6.1 Hz, 1H), 2.77 – 2.37 (m, 4H), 1.75 – 1.47 (m, 2H), 0.95 (dd, *J* = 8.2, 6.5 Hz, 3H). ^{13}C NMR (base, 75 MHz, $CDCl_3$) δ 156.66, 153.12, 138.44, 134.52, 132.92, 128.13, 128.09, 121.15, 120.35, 115.66, 112.94, 112.02, 82.03 (d, *J* = 170.2 Hz), 67.06 (d, *J* = 20.4 Hz), 59.12, 56.28, 48.92, 35.01, 29.19, 18.97, 12.07. ^{19}F NMR (base, 282 MHz, $CDCl_3$) δ 6.02 (tt, *J* = 47.5, 28.1 Hz).

(*R*)-(–)-N-*n*-ethyl-2-(2-fluoropropanoxy)-11-hydroxynoraporphine (11c).[1]

To a 6 dram vial under nitrogen atmosphere was added: (*R*)-(–)-N-ethyl-2-fluoropropanoxy-11-hydroxy-10-(trifluoromethylsulfonyloxy)aporphine **10c** (118 mg, 0.242 mmol), $Pd(OAc)_2$ (16 mg,

10%), and dppp (11 mg, 10%). The vial was capped and evacuated and flushed with nitrogen 3 times. Next, anhydrous DMF (1.5 mL) was added, followed by triethylhydrosilane (100 mL). After brief stirring at RT, the mixture was heated at 60 ºC for 4 hours. The reaction mixture was quenched by removing DMF under reduced pressure, dissolving the residue in dichloromethane (50 mL), and washing with 28% ammonium hydroxide solution (15 mL). The residue was purified 3 times by column chromatography using 1:30 to 1:10 MeOH to DCM gradient to afford 24 mg of the **11c** (27% yield). The title product was converted to the HCl salt by treatment with excess ethereal HCl. M.p. (HCl salt) 156-158 ºC (decomposed). Anal. Calcd. for $C_{21}H_{24}FNO_2$•1/2 H_2O: C, 71.98; H, 7.19; N, 4.00. Found: C, 71.99; H, 7.19; N, 3.89. ^{1}H NMR (free base, 300 MHz, CDCl3) δ 7.67 (s, 1H), 7.02 (t, 1H, *J* = 7.69 Hz), 6.80 (d, 1H, *J* = 7.25 Hz), 6.71 (d. 1H, *J* = 8.00 Hz), 6.58 (s, 1H), 4.71 (t, 1H, *J* = 5.76 Hz), 4.55 (t, 1H, *J* = 5.73 Hz), 4.08 (t, 2H, *J* = 6.00 Hz), 3.37 (d, 1H, *J* = 14.05 Hz), 3.19-3.05 (m, 4H), 2.75-2.49 (m, 4H), 2.139 (dt, 2H, *J* = 25.82, 5.89 Hz), 1.17 (t, 3H, *J* = 7.02 Hz). ^{13}C NMR (base, 75 MHz, CDCl3) δ 157.71, 156.94, 139.13, 137.52, 134.06, 134.02, 126.80, 126.77, 124.89, 119.96, 119.63, 115.75, 113.14, 112.56, 112.01, 80.67 (d, *J* = 164.1 Hz), 63.40 (d, *J* = 4.9 Hz), 58.09, 55.10, 47.59 (d, *J* = 19.3 Hz), 34.35, 29.54, 28.58, 10.11. ^{19}F NMR (base, 282 MHz, CDCl3) δ 7.67 (tt, *J* = 48.24, 24.64 Hz).

(R)-(–)-2-N-ethyl-(2-fluoroethoxy)-11-hydroxynoraporphine (11d)

A 6 dram vial which contained (*R*)-(–)-N-ethyl-2-fluoroethoxy-11-hydroxy-10-(trifluoromethylsulfonyloxy)noraporphine **10d** (140 mg, 0.286 mmol) was equipped with a spin vane and evacuated and flushed with dry nitrogen (3 cycles). Next, 10% palladium on carbon (45 mg), magnesium turning (21 mg), and ammonium acetate (88 mg) were loaded to the vial and the vial was evacuated and flushed with dry nitrogen (3 cycles). Next, anhydrous methanol (8 mL) was added and the contents were stirred overnight at RT. The next day, the reaction was quenched by adding a few drops of ammonium hydroxide solution, then filtered through a pad of silica gel and washed with two

volumes of methanol. The filtrate was concentrated and purified by flash column chromatography using 1:30 to 1:20 methanol:dichloromethane gradient to afford 55 mg of **11d** as a slightly green foam as product, yield 57%. The free base was converted to HCl salt by treatment with ethereal HCl. M.p. (HCl salt) 168 ºC. ^{1}H NMR (base, 300 MHz, CDCl3) δ 7.73 (d, *J* = 2.5 Hz, 1H), 7.02 (t, *J* = 7.7 Hz, 1H), 6.79 (d, *J* = 7.3 Hz, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 6.60 (d, *J* = 2.3 Hz, 1H), 4.77 (m, 1H), 4.62 (m, 1H), 4.20 (m, 1H), 4.11 (m, 1H), 3.38 (m, 1H), 3.12 (m, 4H), 2.59 (m, 4H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (base, 75 MHz, CDCl3) δ 156.62, 153.31, 138.41, 134.46, 132.98, 128.10, 128.07, 121.18, 120.20, 115.67, 113.03, 112.01, 82.03 (d, *J* = 169.5 Hz), 67.04 (d, *J* = 20.2 Hz), 58.54, 48.06, 47.85, 34.92, 29.19, 10.46. Anal. Calcd. for $C_{20}H_{22}FNO_2$ •HCl•0.6H_2O, C, 64.11; H, 6.51; N, 3.74. Found: C, 64.02, H, 6.54; N, 3.76.

(*R*)-(–)-2-(2-fluoroethoxy)-11-hydroxyaporphine (11e).

To a 100 mL round bottomed flask were sequentially added: (*R*)-(–)-2-(2-fluoroethoxy)-11-hydroxy-3-(trifluoromethylsulfonyloxy)aporphine **10e** (300 mg), palladium on carbon (10%, 57 mg), magnesium turnings (50 mg), and ammonium acetate (252 mg). The flask was flushed with dry nitrogen and anhydrous methanol (20 mL) was added. The mixture was allowed to stir for 24 hours, until judged complete by TLC. The contents were filtered through a plug of Celite, which was washed with methanol (2x20 mL), and concentrated. The residue was dissolved in dichloromethane and methanol and adsorbed onto silica gel, and the solvents were removed under reduced pressure. The product was purified from the silica gel by column chromatography using 1:15 methanol: dichloromethane as eluent to afford 119 mg of (*R*)-(–)-2-fluoroethoxy-11-hydroxyaporphine **11e** as a glassy green film in 58% isolated yield. The free base was then dissolved in methanol and treated with ethereal hydrogen chloride to afford 111 mg of the corresponding hydrochloride salt as a pale tan solid. M.p. (HCl salt): 184-188 ºC (decomposed). Anal. calcd. for $C_{19}H_{19}NO_2F$•HCl•2/3H_2O: C, 63.07; H, 6.22; N, 3.87. Found: C, 63.12;

H, 6.15; N, 3.89. ^{1}H NMR (base, 300 MHz, CD3OD) δ 7.80 (d, *J* = 2.6 Hz, 1H), 6.94 – 6.81 (m, 1H), 6.66 (d, *J* = 7.9 Hz, 1H), 6.60 (d, *J* = 7.3 Hz, 1H), 6.43 (d, *J* = 2.5 Hz, 1H), 4.69 – 4.57 (m, 1H), 4.51 – 4.42 (m, 1H), 4.10 – 4.01 (m, 1H), 4.00 – 3.88 (m, 1H), 3.28 – 3.14 (m, 1H), 3.01 – 2.79 (m, 4H), 2.51 (dd, *J* = 3.5, 16.5 Hz, 1H), 2.33 (s, 3H), 2.39 – 2.24 (m, 1H). ^{13}C NMR (base, 75 MHz, CD3OD) δ 157.10, 154.69, 137.67, 133.54, 133.23, 128.10, 126.68, 120.73, 119.58, 115.26, 113.69, 111.97, 82.07 (d, *J* = 168.9 Hz), 67.28 (d, *J* = 19.9 Hz), 62.06, 52.90, 42.68, 34.86, 28.68. ^{19}F NMR (base, 282 MHz, CD3OD) δ 4.67 (tt, *J* = 29.0, 47.9 Hz).

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1. Hupp, C. D.; Neumeyer, J. L. Rapid Access to Morphinones: Removal of 4,5-Ether Bridge with Pd-catalyzed triflate reduction. *Tetrahedron Lett.* **2010**, *51*, 2359-2361.