the rings by gently sliding a rolled up piece of filter paper into the vessel lumen. The rings were then mounted in a water-jacketed tissue bath, maintained at 37 °C, between a moveable and a fixed stainless steel wire, with the moveable end attached to an FT03 Grass transducer coupled to a Model 7D Grass Polygraph for recording isometric force responses. The bath was filled with 20 mL of oxygenated (95% oxygen/5% carbon dioxide) Krebs solution of the following composition (nM):(130) NaCl, (15) $NaHCO_3$, (15) KCl, (1.2) NaH_2PO_4, (1.2) $MgSO_4$, (2.5) $CaCl_2$, and (11.4) glucose. The preparations were equilibrated for 1 h before approximately 1 g of passive tension was placed on the rings. For the agonist assay, the rings were exposed to increasing concentrations of the test compound, at 30-min intervals, during which time the tissue was washed three times with 20 mL of fresh Krebs solution. For the measurement of antagonistic activity, paired rings from the same rabbits were used; one was exposed to increasing concentrations of AII (at 30-min intervals) and a second ring was exposed to increasing concentrations of AII in the presence of the test compound, which was added 5 min prior to the addition of AII. The concentration-response curves for AII in the presence of the antagonist were evaluated in terms of the percent of the maximal contraction of the control ring exposed only to AII. pD_2 values for AII were calculated from the AII concentration response curves while pA_2s were determined according to the method of Schild.[23]

The in vivo antagonist activity of the peptides was evaluated in ganglion-blocked, anesthetized rats. Male Sprague-Dawley rats (240-400 g) were anesthetized with Inactin (100 mg/kg ip) and instrumented with two catheters (PE-50), one in a single femoral vein and one in a single femoral artery to administer drugs and determine arterial pressure (MAP), respectively. Autonomic neurotransmission was interrupted by treatment with mecamylamine (3 mg/kg iv) and atropine (400 mg/kg ip). When MAP stabilized, AII (30 ng/kg iv bolus) was administered four times at 10-min intervals to achieve a reproducible pressor response. The test peptide was then infused iv for 20 min before rechallenging with AII. Infusion of the antagonist was discontinued, and AII was again administered at 5-10-min intervals during the hour which followed.

The determination of angiotensin II stimulated aldosterone release was performed on isolated glomerulosa cells from Sprague-Dawley rats prepared as reported previously.[24] Incubation tubes contained 1-mL cell suspension ($0.5-2 \times 10^5$ cells) and various concentrations of peptides. All incubations were done in triplicate. The tubes were gassed with 95% O_2/5% CO_2, capped, gently mixed, and placed in a shaking water bath at 37 °C. After incubating for 2 h, the tubes were centrifuged at 100 × g for 15 min at 4 °C. The cell-free media were decanted and stored at -80 °C for aldosterone determination by direct radioimmunoassay (Diagnostic Products Corp.). The aldosterone concentration was determined from a standard curve. Intra- and interassay coefficients of variation were 3.2% and 5.3%, respectively.

The ability of the peptides to alter the drinking response to intracerebroventricular (icv) injection of angiotensin II was studied in conscious Sprague-Dawley rats. Each rat had a guide cannula implanted in the lateral cerebral ventricle under pentobarbital sodium or chloral hydrate anesthesia. Rats were allowed 3-4 days of recovery. All compounds were given icv. The test peptides (500 or 2500 pmol) were given immediately prior to AII (100 pmol). Angiotensin II induced drinking was verified in each rat the day before testing of the experimental compounds. Each experimental compound was tested in a separate group of rats.

Acknowledgment. We acknowledge J. F. Zobel for amino acid analysis and P. Toren and E. W. Kolodziej for mass spectroscopy. We also with to thank E. H. Blaine and R. E. Manning for support during this work.

(23) Schild, O. H. *Br. J. Pharmacol. Chemother.* 2, 189-206.

(24) Douglas, J.; Aguilera, G.; Kondo, T.; Catt, K. *Endocrinol.* **1978**, *102*, 685-96.

N-(3-[^{18}F]Fluoropropyl)-*N*-nordiprenorphine: Synthesis and Characterization of a New Agent for Imaging Opioid Receptors with Positron Emission Tomography

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A series of *N*-fluoroalkyl (**1-5**) and *N*-alkyl (**6-8**) analogues of the high-affinity opioid receptor antagonist diprenorphine (**9**) has been synthesized and evaluated with in vitro binding assays. Three of the *N*-fluoroalkyl compounds were prepared with the positron-emitting radionuclide ^{18}F (**1a**, **2a**, **5a**), and their biodistribution was determined in rats. Compounds **2a** and **5a** were made by using a two-step labeling procedure, [^{18}F]fluoride displacement of an iodoalkyl triflate followed by *N*-alkylation, that required 2 h and proceeded in 4-6% overall radiochemical yield at the end of synthesis. The effective specific activity of compounds **2a** and **5a**, determined by competitive receptor binding assay, was 840-1820 Ci/mmol. Compound **1a** was made by the same two-step procedure, with the bromoalkyl triflate, in 0.3-0.6% radiochemical yield at an effective specific activity of 106-264 Ci/mmol. Specificity of binding in vivo was measured as the percent injected dose/gram of striatal tissue divided by the percent injected dose/gram of cerebellar tissue. The best striatum to cerebellum ratio (3.32 ± 0.74 at 30 min) was achieved with *N*-(3-[^{18}F]-fluoropropyl)-*N*-nordiprenorphine (**2a**, [^{18}F]FPND). The high specific binding demonstrated by this compound indicates that it may be useful for in vivo imaging of opioid receptors with positron emission tomography.

In recent years, positron emission tomography (PET) has emerged as an important technique for studying receptors in living animals and humans.[1] In particular, our current research has focused on the opioid receptor system.[2] Several positron-emitting receptor ligands have been developed and used for imaging opioid receptors in living humans. These include the μ type specific ($\mu \gg \delta > \kappa$) ligand [^{11}C]carfentanil,[3] the universal non type specific

(1) Huang, S. C.; Barrio, J. R.; Phelps, M. E. *J. Cereb. Blood Flow Metab.* **1986**, *6*, 515. Seeman, M. V.; Seeman, P. *Can. J. Psychiatry* **1988**, *33*, 299. Wagner, H. N., Jr.; Burns, D.; Dannals, R. F.; Wong, D. F.; Langstrom, H.; Duelfer, T.; Frost, J. J.; Ravert, H. T.; Links, J. M.; Rosenbloom, S. B.; Lukas, S. E.; Kramer, A. V.; Kuhar, M. *Science* **1983**, *221*, 1264. Farde, L.; Hall, H.; Ehrin, E.; Sedvall, G. *Science* **1986**, *231*, 258.

(2) Chesis, P. L.; Griffeth, L. K.; Mathias, C. J.; Welch, M. J. *J. Nucl. Med.* **1990**, *31*, 192.

(3) Frost, J. J.; Douglass, K. H.; Mayberg, H. S.; Dannals, R. F.; Links, J. M.; Wilson, A. A.; Ravert, H. T.; Crozier, W. C.; Wagner, H. N., Jr. *J. Cereb. Blood Flow Metab.* **1989**, *9*, 398. Frost, J. J.; Wagner, H. N, Jr.; Dannals, R. F.; Ravert, H. T.; Links, J. M.; Wilson, A. A.; Burns, D. D.; Wong, D. F.; McPherson, R. W.; Rosenbaum, A. E.; Kuhar, M. J.; Snyder, S. H. *J. Comput. Assist. Tomogr.* **1985**, *9*, 231.

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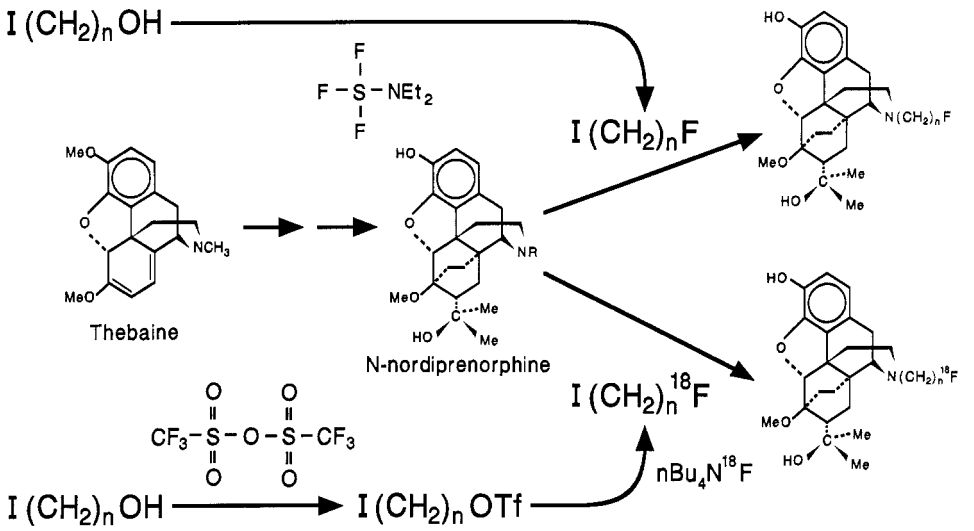
Scheme I



($\mu = \delta = \kappa$) ligand [^{11}C]diprenorphine,[4] and the non type specific ($\mu > \kappa > \delta$) ligand [^{18}F]cyclofoxy.[5]

The opioid receptor system is comprised of at least three types (μ, δ, and κ).[6] Furthermore, there is evidence that neither the μ or κ types are homogeneous and that each can be further subdivided into two subtypes.[7] In addition to their well-established role in the modulation of pain,[8] opioid receptors have been implicated in numerous other normal and pathophysiologic processes including water homeostasis,[9] epilepsy,[10] shock,[11] and neurodegeneration.[12] Each of these functions may be mediated through either a single receptor type or through multiple receptor types involved to varying degrees. PET studies show great promise for helping to further elucidate the complex relationships between physiology and opioid receptor type.

In a fashion analogous to in vitro techniques (e.g. autoradiography), successful visualization of receptors with PET requires a ligand that possesses both high affinity and low nonspecific binding.[13] With PET, however, specificity of binding is achieved only when blood flow or metabolism clears nonspecifically bound ligand from the region of interest more rapidly than receptor-bound ligand. With many receptor-binding radiopharmaceuticals, 1 h or more from the time of injection is required to achieve the optimal level of specific binding.[14] Of the commonly used positron-emitting isotopes, ^{18}F thus offers the considerable advantage of a relatively long half-life (110 min) that permits imaging when receptor specific binding is highest. The nearly 2 h half-life is also advantageous for quantitative receptor modeling, which requires accurate measurement of the arterial input function.[15]

One of the goals of our current research has been to develop an ^{18}F-labeled radiopharmaceutical suitable for imaging opioid receptors with PET that retains the universal, non type specific binding of diprenorphine.[16] In this paper, we describe the synthesis and characterization of a series of *N*-alkyl and *N*-fluoroalkyl diprenorphine analogues. We also report a versatile two-step procedure for preparing the corresponding ^{18}F-labeled amines in good radiochemical yield.[17] One of these new compounds, **2a** ([^{18}F]FPND), displays both the high receptor binding affinity and low nonspecific binding in vivo necessary for imaging with PET.

(4) Jones, A. K. P.; Luthra, S. K.; Maziere, B.; Pike, V. W.; Loc'h, C.; Crouzel, C.; Syrota, A.; Jones, T. *J. Neurosci. Methods* **1988**, *23*, 121. Frost, J. J.; Sadzot, B.; Price, J.; Mayberg, H. S.; Douglass, K. H.; Dannals, R. F.; Lever, J.; Links, J. M.; Wilson, A. A.; Ravert, H.; Wagner, H. N., Jr. *J. Nucl. Med.* **1989**, *30*, 740.

(5) Cohen, R. M.; Carson, R. E.; Channing, M.; Nordahl, T.; Gross, M.; Hauck-Newman, A.; Simpson, N.; Finn, R. D.; Pert, C.; Rice, K.; Blasberg, R.; Larson, S. M. *J. Nucl. Med.* **1988**, *29*, 796. Pert, C. B.; Danks, J. A.; Channing, M. A.; Eckelman, W. C.; Larson, S. M.; Bennett, J. M.; Burke, R. T., Jr.; Rice, K. C. *FEBS Lett.* **1984**, *177*, 281.

(6) James, I. F.; Goldstein, A. *Mol. Pharmacol.* **1984**, *25*, 337. Ward, S. J.; Portoghese, P. S.; Takemori, A. E. *Eur. J. Pharmacol.* **1982**, *85*, 163.

(7) Pasternak, G. W. *Biochem. Pharmacol.* **1986**, *35*, 361. De Costa, B. R.; Rothman, R. B.; Bykov, V.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **1989**, *32*, 281.

(8) Ward, S. J.; Takemori, A. E. *J. Pharmacol. Exp. Ther.* **1983**, *224*, 525. Millan, M. J.; Morris, M. J.; Colpaert, F. C.; Herz, A. *Brain Res.* **1987**, *416*, 349.

(9) Peters, G. R.; Ward, N. J.; Antal, E. G.; Lai, P. Y.; DeMarr, E. W. *J. Pharmacol. Exp. Ther.* **1987**, *240*, 128. Hall, E. D.; Wolf, D. L.; Althaus, J. S.; VonVoightlander, P. F. *Brain Res.* **1987**, *435*, 174.

(10) Frost, J. J.; Mayberg, H. S.; Fisher, R. S.; Douglas, K. H.; Dannals, R. F.; Links, J. M.; Wilson, A. A.; Ravert, H. T.; Rosenbaum, A. E.; Snyder, S. H.; Wagner, H. N., Jr. *Ann. Neurol.* **1988**, *23*, 231. Frost, J. J.; Mayberg, H. S.; Meltzer, C. C.; Sadzot, B.; Goldman, S.; Fisher, R. S.; Dannals, R. F.; Lever, J. R.; Loats, H.; Ravert, H. T.; Wilson, A. A.; Wagner, H. N., Jr. *J. Nucl. Med.* **1989**, *30*, 750. VonVoightlander, P. F.; Hall, E. D.; Camacho Ochoa, M.; Lewis, R. A.; Triezenberg, H. J. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 542.

(11) D'Amato, R.; Holaday, J. W. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 2898.

(12) Hiller, J. M.; Itzhak, Y.; Simon, E. J. *Brain Res.* **1987**, *406*, 17.

(13) Kilbourn, M. R.; Zalutsky, M. R. *J. Nucl. Med.* **1985**, *26*, 655.

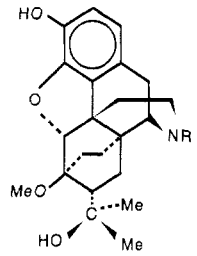
(14) Pomper, M. G.; Katzenellenbogen, J. A.; Welch, M. J.; Brodack, J. W.; Mathias, C. J. *J. Med. Chem.* **1988**, *31*, 1360. Welch, M. J.; Katzenellenbogen, J. A.; Mathias, C. J.; Brodack, J. W.; Carlson, K. E.; Chi, D. Y.; Dence, C. S.; Kilbourn, M. R.; Perlmutter, J. S.; Raichle, M. E. *Appl. Radiat. Isot. Nucl. Med. Biol. Part B* **1988**, *15*, 83. Kung, H. F.; Pan, S.; Kung, M. P.; Billings, J.; Kasliwal, R.; Reilley, J.; Alavi, A. *J. Nucl. Med.* **1989**, *30*, 88.

(15) Perlmutter, J. S.; Kilbourn, M. R.; Welch, M. J.; Raichle, M. E. *J. Neurosci.* **1989**, *9*, 2344. Perlmutter, J. S.; Larson, K. B.; Raichle, M. E.; Markham, J.; Mintun, M. A.; Kilbourn, M. R.; Welch, M. J. *J. Cereb. Blood Flow Metab.* **1986**, *6*, 154. Logan, J.; Wolf, A. P.; Shiue, C. Y.; Fowler, J. S. *J. Neurochem.* **1987**, *48*, 73.

(16) Wood, M. S.; Traynor, J. R. *J. Neurochem.* **1989**, *53*, 173.

(17) Chi, D. Y.; Kilbourn, M. R.; Katzenellenbogen, J. A.; Welch, M. J. *J. Org. Chem.* **1987**, *52*, 658.

Table I. Structure and in Vitro Opioid Receptor Binding Affinity of Diprenorphine Analogues



compd	R	mp, °C	formula	log P(f)[a]	K_i,[b] nM
1	CH_2CH_2F	196–197	$C_{24}H_{32}NO_4F$	−1.28	20.2 ± 3.0
2	$CH_2CH_2CH_2F$	185–186	$C_{25}H_{34}NO_4F$	−0.75	2.4 ± 0.1
3	$CH_2CH_2CH_2CH_2F$	158–159	$C_{26}H_{36}NO_4F$	−0.22	10.7 ± 2.6
4	(*R*)-$CH_2CH(CH_3)CH_2F$	219–221	$C_{26}H_{36}NO_4F$·HCl	−0.34	18.9 ± 3.3
5	(*S*)-$CH_2CH(CH_3)CH_2F$	227–228	$C_{26}H_{36}NO_4F$·HCl	−0.34	10.8 ± 2.5
6	CH_2CH_3	209–210	$C_{24}H_{33}NO_4$	−0.60	8.5 ± 2.2
7	$CH_2CH_2CH_3$	192–193	$C_{25}H_{35}NO_4$	−0.07	2.7 ± 0.4
8	$CH_2CH_2CH_2CH_3$	153–155	$C_{26}H_{37}NO_4$	+0.46	5.9 ± 2.4
9	$CH_2CH(CH_2)_2$	189–190	$C_{26}H_{35}NO_4$	0.00	0.22 ± 0.01

[a] Calculated octanol–H_2O partition coefficients for the free base amines relative to diprenorphine. [b] K_i values were determined from the IC_{50} measured at 25 °C in 50 mM Tris HCl (pH = 7.4) using the Cheng–Prusoff equation. All values represent the mean ± standard deviation for three separate determinations using a single whole brain receptor preparation.

Results and Discussion

Chemistry. The general synthetic outline for this work is shown in Scheme I. The secondary amine precursor *N*-nordiprenorphine was made from the natural product thebaine, in a multistep synthesis previously described.[18] The fluoroalkyl iodides (**10–12**) used to make some of the unlabeled diprenorphine analogues were produced from their respective alcohols by reaction with (diethylamido)sulfur trifluoride (DAST) in an inert solvent. This reaction, first described by Middleton, is rapid and proceeds in high yield.[19] These same alcohols were also converted into reactive triflates (**13–15**) by treatment with trifluoromethanesulfonic anhydride and 2,6-dimethylpyridine in CH_2Cl_2. The resulting iodoalkyl triflates are relatively stable and can be stored for many months at −20 °C without significant decomposition. These triflates were used as precursors in making the ^{18}F-labeled diprenorphine analogues. Diprenorphine **9** and the *N*-(fluoroalkyl)-*N*-nordiprenorphine compounds **1–5** produced for this study are shown in Table I. Several unfluorinated analogues (**6–8**) were also synthesized to permit evaluation of the effect of fluorine substitution on binding affinity. Compounds **1–8** were isolated as their free bases. Flash column chromatography afforded compounds **1–3** and **6–8** as crystalline, white solids. Flash chromatography of compounds **4** and **5** produced colorless oils which were then converted to their respective HCl salts.

Receptor Binding Assays. The binding of [^{3}H]diprenorphine to rat brain membranes was evaluated with both kinetic and saturation binding studies in 50 mM Tris buffer (pH = 7.4 at 25 °C). Scatchard transformation of the saturation binding data was used to obtain values for the dissociation constant (K_D) and receptor binding capacity (B_{max}). For these experiments, the receptor concentration was chosen such that total binding represented approximately 10% of the ligand added to the assay at a ligand concentration equal to K_D. Nonspecific binding was defined as that which occurred in the presence of either 1.0 μM diprenorphine or 10 μM naloxone. Over the ligand concentration range from 0.1 to 10 times K_D, specific binding accounted for greater than 90% of total binding. Specific binding as a function of receptor concentration was also measured and found to be linear over the range from 0.2 to 5.0 times the protein concentration generally used.

[^{3}H]Diprenorphine binding to rat whole brain membranes was characterized by high affinity (K_D = 0.047 ± 0.013 nM) and saturability (B_{max} = 209 ± 21 fmol/mg of protein) as determined by Scatchard analysis of saturation binding data (n = 6). With rat striatal membranes a higher receptor binding capacity was observed (B_{max} = 284 ± 43 fmol/mg of protein), but no change in receptor affinity (K_D = 0.046 ± 0.009 nM) (n = 6) was seen. In all cases the Scatchard plots were linear with Hill coefficients equal to 1.00 ± 0.03. These data are consistent with the known lack of opioid receptor type specificity for diprenorphine.[20] The K_D for [^{3}H]diprenorphine binding to rat whole brain membranes was also determined independently by kinetic analysis. The ratio of the dissociation rate constant measured at 25 °C (k_{-1} = 0.032 ± 0.002 min^{-1}) and the association rate constant at 25 °C (k_1 = 0.50 ± 0.04 min^{-1} nM^{-1}) yields a K_D equal to 0.061 ± 0.002 (n = 2).

Opioid receptor binding affinity (K_i) of compounds **1–9** was determined by competition with [^{3}H]diprenorphine (concentration ≈ 1 K_D) for binding to a rat whole brain membrane preparation. Binding affinity for these analogues was reduced from 1 to 2 orders of magnitude relative to diprenorphine (Table I). Of the compounds evaluated, **2** and its unfluorinated counterpart **7** had the highest receptor binding affinity. The 10–100-fold increase in K_i for the analogues, compared with diprenorphine, is not explained by the presence of a fluorine atom on the alkyl side chain as evidenced by the similar binding affinity of compounds **2** and **7**. For the other analogue pairs (**1** and **6**, **3** and **8**), the binding affinity was decreased about 2-fold by the presence of the fluorine atom on the side chain. The observed K_i values for compounds **1–9** confirm the previous observation that receptor interaction with the *N*-cyclopropylmethyl group is important for maintaining very high opioid receptor binding affinity.[21]

(18) Bentley, K. W.; Hardy, D. G. *J. Am. Chem. Soc.* **1967**, *89*, 3281.
(19) Middleton, W. J. *J. Org. Chem.* **1974**, *40*, 574.
(20) Chang, K. J.; Hazum, E.; Cuatrecasas, P. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 4141. Sadee, W.; Perry, D. C.; Rosenbaum, J. S.; Herz, A. *Eur. J. Pharmacol.* **1982**, *81*, 431.

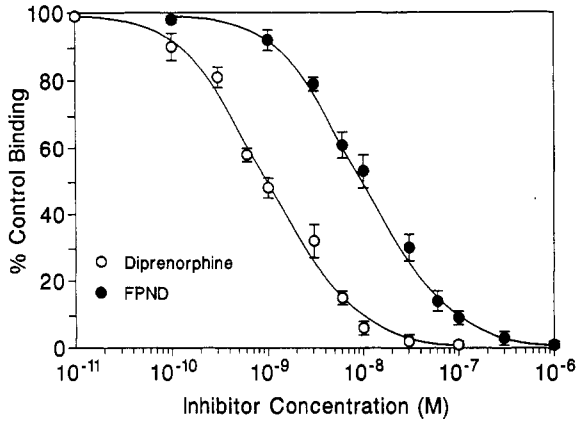


Figure 1. [^{3}H]Diprenorphine competition binding curves for **2** (FPND) and **9** (diprenorphine). Data are expressed as the percentage of control [^{3}H]diprenorphine binding at 25 °C with rat whole brain membranes. Data represent the means ± standard deviation for three separate determinations using a single whole brain receptor preparation.

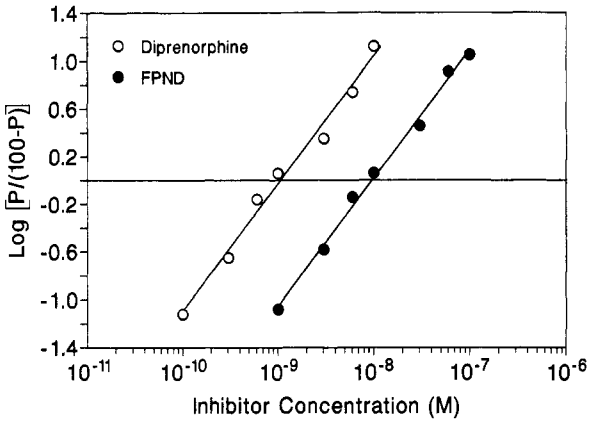


Figure 2. Modified Hill plot using [^{3}H]diprenorphine competition binding data for **2** (FPND) and **9** (diprenorphine) from a single representative experiment. The IC_{50} occurs when log $[P/(100 - P)] = 0$, where P is the percentage inhibition of [^{3}H]diprenorphine receptor specific binding.

All competition binding curves were smooth and symmetrical. Data for **2** (FPND) and **9** (diprenorphine) are shown (Figure 1). The concentration of competitor that reduced specific binding of the radioligand 50% (IC_{50}) was determined by linear regression from a plot of log[L] against $\log[P/(100 - P)]$, where [L] is the concentration of competing ligand and P is the percentage inhibition of [^{3}H]diprenorphine binding. An example of this modified Hill plot using competition binding data for **2** and **9** from a single experiment is shown (Figure 2). All of these plots had slopes equal to 1.00 ± 0.05, consistent with the expected lack of receptor type specificity for the new compounds. Measured IC_{50} values were converted to K_i values with the Cheng–Prusoff equation, which is valid when radioligand depletion in the absence of competitor is small.[22]

The opioid receptor binding of **2a** ([^{18}F]FPND) was evaluated in vitro by direct saturation binding studies using rat striatal membranes. These studies were done at

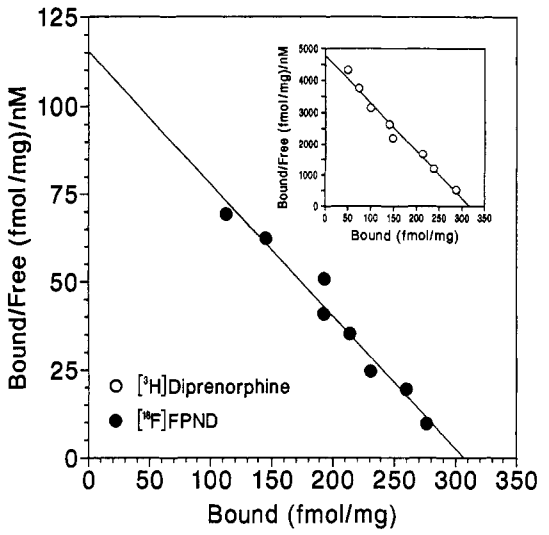


Figure 3. Scatchard analysis of **2a** ([^{18}F]FPND) and [^{3}H]diprenorphine saturation binding at 25 °C from single representative experiments using rat striatal membranes. The ordinate is expressed as the ratio of bound ligand in units of fmol/mg of protein and free ligand in units of nM.

the same receptor concentration as the [^{3}H]diprenorphine binding experiments such that total binding represented <1% of the ^{18}F-labeled ligand added to the assay at a ligand concentration equal to K_D. As with the previously described studies, nonspecific binding was defined as that which was not blocked by the addition of either 1.0 μM diprenorphine or 10 μM naloxone. With **2a**, specific binding accounted for 60–40% of total binding over the ligand concentration range from 0.1 to 10 times K_D. As before, specific binding as a function of receptor concentration was measured and found to be linear over the range from 0.2 to 5.0 times the routinely used protein concentration. A representative Scatchard plot for the binding of **2a** to rat striatal membranes is shown (Figure 3). For comparison a Scatchard plot of [^{3}H]diprenorphine binding to rat striatal membranes is also shown (Figure 3, inset). Scatchard analysis of binding data for **2a** in 50 mM Tris buffer (pH = 7.4 at 25 °C) yielded K_D equal to 2.62 ± 0.81 nM and B_{max} equal to 294 ± 46 fmol/mg of protein (n = 4). In all cases the Scatchard plots were linear with Hill coefficients equal to 1.00 ± 0.03. These data suggest that **2a** and [^{3}H]diprenorphine both bind to the same total opioid receptor population differing only in their affinity for this family of receptors.

A number of opioid structure–activity studies based on pharmacological end points have been published.[23] The ability of the N-cyclopropylmethyl and N-allyl groups to confer antagonist activity to selected morphinans is well-documented in a variety of assays.[24] Pharmacology does not play a major role, however, in the evaluation of new ^{18}F-labeled receptor imaging agents. Assuming a typical effective specific activity of 1000 Ci/mmol, a 10 mCi dose of a compound with molecular weight equal to 500 has a mass of only 5 μg; far below the pharmacologically active dose even for the extremely potent oripavine class of opiates. Instead, it is the fundamental properties of receptor binding affinity and lipophilicity that are more

(21) Takemori, A. E.; Larson, D. L.; Portoghese, P. S. *Eur. J. Pharmacol.* **1981**, *70*, 445. Loew, G. H.; Berkowitz, D. S. *J. Med. Chem.* **1975**, *18*, 656.

(22) Cheng, Y. C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099. Goldstein, A.; Barrett, R. W. *Mol. Pharmacol.* **1987**, *31*, 603.

(23) Portoghese, P. S.; Alreja, B. D.; Larson, D. L. *J. Med. Chem.* **1981**, *24*, 782. Feinberg, A. P.; Creese, I.; Snyder, S. H. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 4215.

(24) Portoghese, P. S.; Nagase, H.; Lipkowski, A. W.; Larson, D. L.; Takemori, A. E. *J. Med. Chem.* **1988**, *31*, 836. Kobylecki, R. J.; Carling, R. W.; Lord, J. A. H.; Smith, C. F. C.; Lane, A. C. *J. Med. Chem.* **1982**, *25*, 116.

relevant in predicting the utility of new compounds for receptor imaging with PET. Calculated octanol–water partition coefficients for compounds **1–8** relative to **9** (diprenorphine) are listed in Table I. The lipophilicity range is approximately 2 log units (−1.28 to +0.46) for this group of compounds with log P(f) for diprenorphine defined as 0.00.

Radiosynthesis. Three of the *N*-fluoroalkyl compounds (**1**, **2**, and **5**) were selected for ^{18}F-labeling and in vivo evaluation. The corresponding ^{18}F-labeled compounds are designated **1a**, **2a**, and **5a**. [^{18}F]Fluoride was prepared from [^{18}O]H_2O by the [^{18}O(p,n)^{18}F] reaction as previously described.[25] The ^{18}F radioactivity (300–400 mCi) was placed in a Vacutainer containing *n*-Bu_4NOH and dried under a stream of N_2 at 110 °C. The *n*-$Bu_4N^{18}F$ complex was resolubilized in THF (80–90% yield) and transferred to a borosilicate tube containing the triflate. After 2 min at room temperature, the triflate displacement reaction was terminated by passage over a Pasteur pipet 1-cm silica column. The purified [^{18}F]fluoroalkyl iodide (50–60% yield) was eluted into a Pierce Reacti-vial previously charged with *N*-nordiprenorphine in DMF and then heated for 30 min at 130 °C. Reverse-phase HPLC purification afforded 15–25 mCi of **2a** and **5a** in 4–6% radiochemical yield at the end of synthesis (EOS). Effective specific activities for these compounds determined by competitive receptor binding assay ranged from 840 to 1820 Ci/mmol (6.8 ± 1.3 μg of **2** or **5**/preparation, n = 12). Compound **1a** was made in similar fashion except 1-bromo-2-[^{18}F]-fluoroethane was used as the alkylating agent.[26] Reverse-phase HPLC purification of **1a** afforded 1–2 mCi in 0.3–0.6% radiochemical yield (EOS) at an effective specific activity of 106 to 264 Ci/mmol (4.2 ± 1.1 μg of **1**/preparation, n = 4) as determined by competitive receptor binding assay.

Determination of the effective specific activity of the final ^{18}F-labeled product by [^3H]diprenorphine competitive receptor binding assay requires knowledge of the activity and radiochemical purity of the original ^{18}F-labeled ligand. It does not, however, require knowledge of the chemical purity of the ^{18}F-labeled ligand. By definition, the value determined by the assay is the mass of chemically pure [^{19}F]ligand that would inhibit [^3H]diprenorphine receptor specific binding equivalently as the corresponding [^{18}F]-ligand preparation being tested. This calculated mass can then be compared with the true mass observed by physical methods such as UV absorption. These values will differ widely if the [^{18}F]ligand preparation contains either a small mass of a chemically impurity with significantly higher receptor affinity than the primary compound or a large mass of an impurity with a significantly lower receptor affinity than the primary compound.

An important feature of the [^{18}F]fluoride triflate displacement reaction is the large molar excess of the triflate relative to *n*-$Bu_4N^{18}F$. Most of the excess triflate is hydrolyzed by *n*-Bu_4NOH, but a small amount remains unreacted. Both the residual triflate and the hydroxyalkyl iodide pass through the silica column, which removes only unreacted [^{18}F]fluoride. This is demonstrated by the representative HPLC trace for the purification of compound **2a** (Figure 4A). The masses of the cold peaks observed during this purification step are proportional to the amount of triflate used in the displacement reaction.

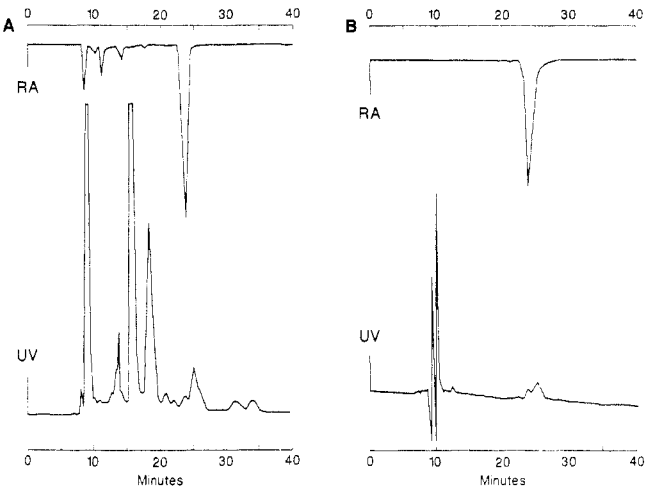


Figure 4. (A) HPLC trace showing the purification of **2a** ([^{18}F]FPND). An Alltech Econosil CN column (25 cm × 10 mm) was eluted with 1% aqueous NH_4OAc/CH_3CN (75:25, v:v) at 2.0 mL/min. Radioactivity (RA) was measured with a flow through NaI(Tl) detector. UV detection was at 254 nm (0.05 absorbance units full scale). The major UV absorbing peaks, in order of elution, are 3-iodo-1-propanol (9 min), unreacted *N*-nordiprenorphine (16 min), *N*-(3-hydroxypropyl)-*N*-nordiprenorphine (19 min), and *N*-(3-iodopropyl)-*N*-nordiprenorphine (25.5 min). (B) HPLC trace of purified compound **2a** in normal saline/EtOH (90:10, v:v) used for animal biodistribution studies is shown. Conditions are the same as in A except for UV detection (0.01 absorbance units full scale).

The final ^{18}F-labeled product as isolated by this method is chemically contaminated by the leading edge of the iodoalkylated compound (Figure 4B).

Compounds **1–9** were all found to have the same extinction coefficient for UV absorption at 254 nm within experimental error. Based on the assumption that the iodoalkylated compound shares this extinction coefficient, we determined the true mass of **2** (t_R = 24.0 min) to be 5.9 ± 1.8 μg/preparation, while the mass of the *N*-iodoalkyl side product (t_R = 25.5 min) was 5.1 ± 1.6 μg/preparation (n = 10). In all cases the specific activity of the final product calculated from the true mass of **2** agreed within ±50% of the effective specific activity determined by competitive receptor binding. A consideration of the masses determined by the two methods suggests that the *N*-iodoalkyl side product has an approximately 5-fold lower opioid receptor affinity than does **2**. We thus conclude that this small contaminant mass does not play an important role in the biodistribution of **2a**.

Biodistribution Studies. Purified compounds **1a**, **2a**, and **5a** were prepared for injection in normal saline/EtOH (90:10, v:v), and 10–20-μCi aliquots were injected (iv, femoral vein) into mature female Sprague–Dawley rats (~180 g). Specificity of binding in vivo was measured as the ratio of activity localized in the striatum (percent injected dose/gram) to that localized in the cerebellum (percent injected dose/gram). In rats the striatum has been shown to be a region of high opioid receptor density, while the cerebellum is essentially devoid of opioid receptors.[27] Data for striatal and cerebellar binding at 30 and 60 min are shown in Table II. Striatal uptake for the three compounds varied in parallel with the binding affinities measured in vitro (see Table I). Compound **2a** exhibited the highest specific binding in vivo while **1a**

(25) Kilbourn, M. R.; Jerabek, P. A.; Welch, M. J. *Appl. Radiat. Isot. Int. J. Radiat. Appl. Instrum. Part A.* **1985**, *36*, 327.

(26) 2-Iodo-1-[[(trifluoromethyl)sulfonyl]oxy]ethane is unstable to storage at −20 °C and is rapidly decomposed on contact with silica gel or neutral alumina.

(27) Leysen, J. E.; Gommeren, W.; Niemegeers, C. J. E. *Eur. J. Pharmacol.* **1983**, 209. Rothman, R. B.; McLean, S. *Biol. Psychiatry* **1988**, *23*, 435.

Table II. In Vivo Binding Specificity of Selected ^{18}F-Labeled Diprenorphine Analogues in Rats[a]

	1a $CH_2CH_2{}^{18}F$		2a $CH_2CH_2CH_2{}^{18}F$		5a (S)-$CH_2CH(CH_3)CH_2{}^{18}F$	
tissue	30 min (6)[b]	60 min (6)	30 min (6)	60 min (10)	30 min (3)	60 min (4)
striatum[c]	0.103 ± 0.039	0.041 ± 0.019	0.342 ± 0.041	0.090 ± 0.036	0.198 ± 0.031	0.068 ± 0.003
cerebellum	0.087 ± 0.026	0.037 ± 0.013	0.100 ± 0.029	0.033 ± 0.016	0.176 ± 0.045	0.062 ± 0.015
striatum/cer	1.21 ± 0.40	1.06 ± 0.39	3.32 ± 0.74	2.84 ± 0.92	1.15 ± 0.14	1.13 ± 0.26

[a] Female Sprague–Dawley rats (~180 g) were injected with 10–20 μCi of the ^{18}F-labeled compound and sacrificed at the indicated times. [b] The number of animals in each group is in parentheses. [c] Striatum and cerebellum activity is shown in units of %ID/g of tissue. All values are means ± standard deviation.

showed the lowest specific binding.

It is important to consider whether this difference in specific binding is attributable to the higher specific activity of **2a** compared with that of **1a**. The opioid receptor binding capacity of rat brains measured in vitro is approximately 200 fmol/mg of protein as previously mentioned. For a rat with a total brain weight equal to 1.3 g this is equivalent to 20 pmol/brain. Now consider an ^{18}F-labeled ligand with the relatively low effective specific activity of 100 Ci/mmol. For this ligand, a typical 20 μCi dose is associated with a mass of 200 pmol. The maximal total brain uptake for each of the ^{18}F-labeled ligands **1a**, **2a**, and **5a** occurs at 1–2 min postinjection in the rat and represents approximately 2% of the injected dose. At 30 min postinjection this value drops to approximately 0.4% of the injected dose. From these data we can see that the maximum possible receptor occupancy is only 20% at 2 min and 4% at 30 min. Moreover, the actual receptor occupancy is much lower than this since most of the radioactivity taken up initially by the brain is nonspecifically bound within the extravascular compartment. This indicates that the low specific binding seen with **1a** at 30 min is not explained by its lower effective specific activity compared with that of **2a** and **5a**.

Nonspecific binding also plays a major role in determining the utility of a radiopharmaceutical for use with PET. Compounds **1a** and **2a** were found to have equivalent cerebellar uptake while the more lipophilic compound **5a** exhibited cerebellar binding twice that of the other two. Of the three compounds, only **2a** demonstrated a striatum-to-cerebellum ratio significantly greater than unity. The ratio observed for this compound (3.32 ± 0.74) at 30 min is comparable with other radiopharmaceuticals that have been successfully employed to image opioid receptors with PET.[3-5]

A more complete evaluation of the biodistribution of compound **2a** is shown in Table III. After administration of **2a**, radioactivity was cleared rapidly from all of the organs examined. TLC analysis revealed that the original unmetabolized compound constitutes less than 25% of the radioactivity present in blood at 30 min. Low accumulation of radioactivity in the bone indicates that metabolism of **2a** in female rats proceeds without significant production of [^{18}F]fluoride. In some experiments, several rats were coinjected with **2a** and the opioid receptor antagonist naloxone (Narcan, 1 mg/kg). Naloxone coinjection depressed the specific binding ratio to unity by reducing binding in the striatum and frontal cortex without significantly affecting cerebellar binding ($p < 0.01$, Student's t test). This indicates that the specific binding observed with **2a** was opioid receptor mediated.

Conclusions

[^{18}F]FPND is a high-affinity, opioid receptor ligand that can be readily prepared at high specific activity in good radiochemical yield. In female Sprague–Dawley rats, this ligand exhibits significant preferential accumulation in brain regions known to have a high density of opioid receptors. This specific binding is entirely blocked by coinjection of the prototypic opioid receptor antagonist naloxone. These data suggest that [^{18}F]FPND may be useful for in vivo imaging of opioid receptors with positron emission tomography.

Experimental Section

General Methods. *N*-Nordiprenorphine was the generous gift of Reckitt and Colman Ltd., Kingston-upon-Hill, England. Diprenorphine and [^3H]diprenorphine were obtained as gifts from the National Institute of Drug Abuse. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Dimethylformamide and acetonitrile (anhydrous, gold standard), tetrabutylammonium hydroxide (n-Bu_4NOH; 1.0 M in H_2O), (diethylamido)sulfur trifluoride (DAST), and trifluoromethanesulfonic anhydride were purchased from the Aldrich Chemical Co., Milwaukee, WI. *N,N*-Diisopropylethylamine (i-Pr_2NEt), diethylene glycol dibutyl ether, 2,6-dimethylpyridine, and methylene chloride were distilled from CaH_2 before use. All other chemicals were reagent grade and used without further purification, unless otherwise specified. Sep-Paks (C_{18}) Waters Associates, Milford, MA, and Vacutainers (BD No. 6434, red top) Becton Dickson, Rutherford, NJ, were obtained commercially.

Flash chromatography was performed as specified by Still, using (230–400 mesh) Kieselgel silica.[28] Melting points were determined on an Electrothermal apparatus and are uncorrected. Kodak (13181 Silica Gel) and Fisher (Redi/Plate Silica Gel G) plates were used for TLC analysis of compounds **1–9**, **1a**, **2a**, and **5a**. The plates were developed with EtOAc and either visualized with I_2 or counted (radio-TLC) with a Berthold Tracemaster 20 automatic TLC-linear analyzer. The HPLC system used included a Waters 6000A pump, a Linear UV-106 detector (254 nm), a NaI(Tl) radioactivity detector with associated electronics, and an Alltech Econosil CN column (10 mm × 25 cm). The column was eluted with 1% aqueous NH_4OAc/CH_3CN (75:25, v:v) at a flow rate of 2.0 mL/min. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian XL300 spectrometer. Chemical shifts are reported in ppm downfield from a tetramethylsilane reference. Fast-atom bombardment mass spectra (FABMS) were recorded with a VG ZAB-SE double-focusing mass spectrometer. Elemental analysis (Galbraith Laboratories, Knoxville, TN) agreed within ±0.4% of the theoretical values.

General Procedure: 3-Hydroxy-4,5α-epoxy-6-methoxy-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethano-17-(3-fluoropropyl)morphinan (2). *N*-Nordiprenorphine (50 mg, 0.13 mmol), 11 (73 mg, 0.39 mmol), and $NaHCO_3$ (13 mg, 0.15 mmol) were refluxed in CH_3CN for 14 h. After removal of the solvent in vacuo, the solid residue was taken up in 50 mL of brine and extracted with Et_2O (3 × 50 mL). The combined Et_2O was dried ($MgSO_4$) and concentrated in vacuo to yield a pale yellow solid. Flash column purification (EtOAc, silica) afforded 48 mg (84%) of the free amine as a crystalline, white solid: mp 185–186 °C; TLC, single uniform spot (Kodak plates, R_f = 0.48); HPLC, single peak (t_R = 24.0 min); ^1H NMR (300 MHz, DMSO-d_6) δ 0.56 (t, 1 H, J_{HH} = 12.6 Hz), 0.87–1.44 (m, 3 H), 1.15 (s, 3 H), 1.26 (s, 3 H), 1.52 (d, 1 H, J_{HH} = 11.7 Hz), 1.65–1.86 (m, 4 H), 1.96 (td, 1 H, J_{HH} = 12.7, 5.5 Hz), 2.15–2.26 (m, 2 H), 2.39–2.50 (m, 3 H), 2.64 (t, 1 H, J_{HH} = 10.6 Hz), 2.72 (d, 1 H, J_{HH} = 6.0 Hz), 2.90 (d, 1 H, J_{HH} = 18.2 Hz), 3.37 (s, 3 H), 4.34 (s, 1 H), 4.41 (s, 1 H), 4.50 (dt, 2 H, J_{HH} = 6.0, J_{HF} = 47.6 Hz), 6.43 (d, 1 H, J_{HH} = 7.8 Hz),

(28) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Table III. Biodistribution of ^{18}F Activity following Injection of *N*-(3-[^{18}F]Fluoropropyl)-*N*-nordiprenorphine (**2a**) into Sprague–Dawley Rats[a]

		unblocked			naloxone[b]	
units	tissue	5 min (15)[c]	30 min (18)	60 min (18)	5 min (5)	30 min (5)
%ID/organ	blood	4.69 ± 1.29	1.46 ± 0.25	0.71 ± 0.24	2.89 ± 1.48	1.17 ± 0.71
	muscle	5.94 ± 1.50	3.40 ± 0.53	0.84 ± 0.26	4.92 ± 2.22	2.97 ± 1.65
	liver	7.84 ± 1.48	2.86 ± 0.97	0.98 ± 0.27	6.59 ± 3.79	2.10 ± 1.36
	kidney	1.16 ± 0.23	0.20 ± 0.02	0.06 ± 0.01	0.81 ± 0.35	0.18 ± 0.10
	bone	4.94 ± 1.40	3.73 ± 1.31	2.89 ± 0.97	3.43 ± 1.70	2.21 ± 1.39
	brain	1.83 ± 0.61	0.37 ± 0.12	0.094 ± 0.050	0.80 ± 0.49	0.10 ± 0.06
%ID/g	striatum	1.46 ± 0.50	0.350 ± 0.083	0.103 ± 0.031	0.54 ± 0.29	0.097 ± 0.023
	frontal cortex	1.36 ± 0.47	0.255 ± 0.092	0.075 ± 0.025	0.46 ± 0.20	0.080 ± 0.034
	cerebellum	0.68 ± 0.23	0.106 ± 0.026	0.036 ± 0.019	0.45 ± 0.31	0.086 ± 0.023
	striatum/cer	2.15 ± 0.24	3.37 ± 0.76	2.95 ± 1.04	1.32 ± 0.25	1.13 ± 0.03
	cortex/cer	1.71 ± 0.21	2.44 ± 0.39	2.37 ± 0.59	1.05 ± 0.22	0.92 ± 0.18

[a] Female Sprague–Dawley rats (~180 g) were injected with 10–20 μCi of compound **2a** and sacrificed at the indicated times. [b] Rats were coinjected with naloxone (Narcan, 1 mg/kg). [c] The number of animals in each group is in parentheses. All values are means ± standard deviation.

6.57 (d, 1 H, J_{HH} = 7.9 Hz), 8.98 (s, 1 H); ^{13}C NMR (^1H decoupled, DMSO-d_6) δ 18.9, 22.7, 27.9, 28.1 (d, J_{CF} = 19.5 Hz), 28.8, 29.0, 31.1, 35.2, 35.3, 43.2, 45.3, 45.6, 50.0 (d, J_{CF} = 5.7 Hz), 51.4, 58.5, 73.1, 78.9, 82.1 (d, J_{CF} = 161 Hz), 93.6, 116.5, 118.8, 126.2, 132.2, 138.2, 145.5; FABMS *m/z* 432 (M^+). Anal. ($C_{25}H_{34}NO_4F$) C, H.

3-Hydroxy-4,5α-epoxy-6-methoxy-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethano-17-(2-fluoroethyl)morphinan (1). The procedure used for **2** was repeated with *N*-nordiprenorphine (50 mg, 0.13 mmol) and **10** (68 mg, 0.39 mmol). Flash column purification (EtOAc, silica) afforded 21 mg (38%) of the free amine as a crystalline, white solid: mp 196–197 °C; TLC, single uniform spot (R_f = 0.46); HPLC, single peak (t_R = 22.5 min); ^1H NMR (300 MHz, DMSO-d_6) δ 0.56 (t, 1 H, J_{HH} = 12.6 Hz), 1.03–1.49 (m, 3 H), 1.14 (s, 3 H), 1.26 (s, 3 H), 1.52 (d, 1 H, J_{HH} = 10.8 Hz), 1.70 (t, 1 H, J_{HH} = 12.2 Hz), 1.84 (t, 1 H, J_{HH} = 9.4 Hz), 1.97 (td, 1 H, J_{HH} = 12.7, 5.4 Hz), 2.21–2.29 (m, 2 H), 2.49–2.75 (m, 4 H), 2.79 (d, 1 H, J_{HH} = 6.5 Hz), 2.92 (d, 1 H, J_{HH} = 18.5 Hz), 3.36 (s, 3 H), 4.34 (s, 1 H), 4.41 (s, 1 H), 4.48 (dt, 2 H, J_{HH} = 5.0, J_{HF} = 47.1 Hz), 6.44 (d, 1 H, J_{HH} = 8.1 Hz), 6.57 (d, 1 H, J_{HH} = 7.9 Hz), 8.98 (s, 1 H); ^{13}C NMR (^1H decoupled, DMSO-d_6) δ 18.9, 23.2, 28.0, 28.8, 29.0, 31.2, 35.1, 35.3, 43.5, 45.3, 45.4, 51.4, 54.8 (d, J_{CF} = 19.8 Hz), 59.4, 73.1, 78.8, 82.4 (d, J_{CF} = 165 Hz), 93.5, 116.5, 118.8, 126.2, 132.2, 138.2, 145.5; FABMS *m/z* 418 (M^+). Anal. ($C_{24}H_{32}NO_4F$) C, H.

3-Hydroxy-4,5α-epoxy-6-methoxy-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethano-17-(4-fluorobutyl)morphinan (3). The procedure used for **2** was repeated with *N*-nordiprenorphine (50 mg, 0.13 mmol) and 1-bromo-4-fluorobutane (61 mg, 0.39 mmol). Flash column purification (EtOAc, silica) afforded 27 mg (46%) of the free amine as a crystalline, white solid: mp 158–159 °C; TLC, single uniform spot (R_f = 0.50); HPLC, single peak (t_R = 25.7 min); ^1H NMR (300 MHz, DMSO-d_6) δ 0.56 (t, 1 H, J_{HH} = 12.5 Hz), 1.03–1.26 (m, 3 H), 1.14 (s, 3 H), 1.26 (s, 3 H), 1.29–1.54 (m, 3 H), 1.61–1.75 (m, 3 H), 1.83 (t, 1 H, J_{HH} = 9.3 Hz), 1.97 (td, 1 H, J_{HH} = 10.4, 5.4 Hz), 2.15–2.24 (m, 2 H), 2.35–2.51 (m, 3 H), 2.66 (t, 1 H, J_{HH} = 10.5 Hz), 2.73 (d, 1 H, J_{HH} = 5.4 Hz), 2.91 (d, 1 H, J_{HH} = 18.5 Hz), 3.37 (s, 3 H), 4.33 (s, 1 H), 4.41 (s, 1 H), 4.46 (dt, 2 H, J_{HH} = 6.1 Hz, J_{HF} = 47.6 Hz), 6.43 (d, 1 H, J_{HH} = 7.9 Hz), 6.56 (d, 1 H, J_{HH} = 8.0 Hz) 8.98 (s, 1 H); ^{13}C NMR (^1H decoupled, DMSO-d_6) δ 18.9, 22.5, 22.8 (d, J_{CF} = 5.2 Hz), 27.8 (d, J_{CF} = 19.1 Hz), 27.9, 28.8, 29.0, 31.2, 35.2, 35.3, 43.2, 45.3, 45.7, 51.4, 53.6, 58.3, 73.2, 78.9, 83.8 (d, J_{CF} = 161 Hz), 93.6, 116.5, 118.8, 126.3, 132.2, 138.2, 145.5; FABMS *m/z* 446 (M^+). Anal. ($C_{26}H_{36}NO_4F$) C, H.

3-Hydroxy-4,5α-epoxy-6-methoxy-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethano-17(*R*)-(3-fluoro-2-methylpropyl)morphinan (4). The procedure used for **2** was repeated with *N*-nordiprenorphine (100 mg, 0.27 mmol) and (*S*)-1-fluoro-2-methyl-3-iodopropane (164 mg, 0.82 mmol). Flash column purification (EtOAc, silica) afforded 67 mg (52%) of the free amine as a colorless oil: TLC, single spot (R_f = 0.50); HPLC, single peak (t_R = 26.1 min); ^1H NMR (300 MHz, DMSO-d_6) δ 0.56 (t, 1 H, J_{HH} = 12.7 Hz), 0.93 (d, 3 H, J_{HH} = 6.7 Hz), 1.00–1.46 (m, 3 H), 1.15 (s, 3 H), 1.27 (s, 3 H), 1.51 (d, 1 H, J_{HH} = 10.9 Hz), 1.70 (t, 1 H, J_{HH} = 12.0 Hz), 1.84 (t, 1 H, J_{HH} = 9.5 Hz), 1.93–2.01 (m, 2 H), 2.21–2.51 (m, 5 H), 2.67 (t, 1 H, J_{HH} = 10.5 Hz), 2.71 (d, 1 H, J_{HH} = 6.2 Hz), 2.91 (d, 1 H, J_{HH} = 18.1 Hz), 3.38 (s, 3 H), 4.33 (s, 1 H), 4.36 (dm, 2 H, J_{HF} = 43.1 Hz), 4.41 (s, 1 H), 6.43 (d, 1 H, J_{HH} = 8.1 Hz), 6.57 (d, 1 H, J_{HH} = 7.9 Hz), 8.96 (s, 1 H); ^{13}C NMR (^1H decoupled, DMSO-d_6) δ 14.5 (d, J_{CF} = 5.2 Hz), 18.7, 23.0, 27.8, 28.7, 28.9, 31.1, 31.9 (d, J_{CF} = 17.9 Hz), 35.2, 35.4, 43.8, 45.4, 45.6, 51.4, 56.7 (d, J_{CF} = 6.5 Hz), 58.8, 73.1, 78.9, 86.4 (d, J_{CF} = 165 Hz), 93.7, 116.5, 118.7, 126.1, 132.1, 138.2, 145.5; for FABMS, elemental analysis, and receptor binding assays the free base was converted to its HCl salt in an ethanolic HCl solution; mp 219–221 °C; FABMS, *m/z* 446 (M^+). Anal. ($C_{26}H_{36}NO_4F$·HCl) C, H.

3-Hydroxy-4,5α-epoxy-6-methoxy-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethano-17(*S*)-(3-fluoro-2-methylpropyl)morphinan (5). The procedure used for **2** was repeated with *N*-nordiprenorphine (100 mg, 0.27 mmol) and **12** (164 mg, 0.82 mmol). Flash column purification (EtOAc, silica) afforded 42 mg (33%) of the free amine as a colorless oil: TLC, single spot (R_f = 0.50); HPLC, single peak (t_R = 25.7 min); ^1H NMR (300 MHz, DMSO-d_6) δ 0.56 (t, 1 H, J_{HH} = 8.8 Hz), 0.91 (d, 3 H, J_{HH} = 6.5 Hz), 0.99–1.09 (m, 1 H), 1.15 (s, 3 H), 1.18–1.47 (m, 2 H), 1.27 (s, 3 H), 1.52 (d, 1 H, J_{HH} = 12.8 Hz), 1.70 (t, 1 H, J_{HH} = 12.2 Hz), 1.84 (t, 1 H, J_{HH} = 9.6 Hz), 1.92–2.03 (m, 2 H), 2.16–2.37 (m, 4 H), 2.48 (m, 1 H), 2.66 (d, 1 H, J_{HH} = 6.3 Hz) 2.68 (t, 1 H, J_{HH} = 13.6 Hz), 2.89 (d, 1 H, J_{HH} = 18.2 Hz), 3.38 (s, 3 H) 4.33 (s, 1 H), 4.39 (dm, 2 H, J_{HF} = 47.9 Hz), 4.40 (s, 1 H), 6.42 (s, 1 H, J_{HH} = 8.1 Hz), 6.57 (s, 1 H, J_{HH} = 8.0 Hz), 8.94 (s, 1 H); ^{13}C NMR (^1H decoupled, DMSO-d_6) δ 14.4 (d, J_{CF} = 5.0), 18.7, 23.2, 27.8, 28.7, 28.9, 31.1, 32.0 (d, J_{CF} = 18.0 Hz), 35.2, 35.4, 43.5, 45.4, 45.5, 51.4, 57.0 (d, J_{CF} = 6.3 Hz), 59.6, 73.1, 78.9, 86.5 (d, J_{CF} = 165 Hz), 93.6, 116.5, 118.7, 126.2, 132.1, 138.2, 145.5; for FABMS, elemental analysis, and receptor binding assays the free base was converted to its HCl salt; mp 227–228 °C; FABMS *m/z* 446 (M^+). Anal. ($C_{26}H_{36}NO_4F$·HCl) C, H.

3-Hydroxy-4,5α-epoxy-6-methoxy-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethano-17-ethylmorphinan (6). The procedure used for **2** was repeated with *N*-nordiprenorphine (100 mg, 0.27 mmol) and 1-iodoethane (168 mg, 1.08 mmol). Flash column purification (EtOAc, silica) afforded 76 mg (72%) of the free amine as a crystalline, white solid: mp 209–210 °C; TLC, single uniform spot (R_f = 0.48); HPLC, single peak (t_R = 24.5 min); ^1H NMR (300 MHz, $CDCl_3$) δ 0.69–0.77 (m, 1 H), 0.96–1.05 (m, 2 H), 1.02 (t, 3 H, J_{HH} = 7.1 Hz), 1.17 (s, 3 H), 1.35 (s, 3 H), 1.64 (d, 1 H, J_{HH} = 11.1 Hz), 1.72–1.81 (m, 2 H), 1.89 (t, 1 H, J_{HH} = 10.2 Hz), 1.98 (td, 1 H, J_{HH} = 12.2, 5.2), 2.15–2.30 (m, 2 H), 2.40–2.55 (m, 3 H), 2.75–2.84 (m, 2 H), 3.00 (d, 1 H, J_{HH} = 18.5 Hz), 3.51 (s, 3 H), 4.37 (s, 1 H), 5.28 (s, 1 H), 6.36 (br s, 1 H), 6.48 (d, 1 H, J_{HH} = 8.2 Hz), 6.67 (d, 1 H, J_{HH} = 7.9 Hz); ^{13}C NMR (^1H decoupled, $CDCl_3$) δ 13.1, 17.6, 22.6, 24.9, 29.7, 29.9, 32.3, 35.6, 35.9, 43.6, 47.7, 48.7, 52.8, 57.9, 63.9, 74.8, 80.5, 97.1, 116.5, 119.3, 127.8, 132.1, 137.5, 145.5; FABMS *m/z* 400 (M^+). Anal. ($C_{24}H_{33}NO_4$) C, H.

3-Hydroxy-4,5α-epoxy-6-methoxy-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethano-17-propylmorphinan (7). The procedure used for **2** was repeated with *N*-nordiprenorphine (100 mg, 0.27 mmol) and 1-bromopropane (133 mg, 1.08 mmol). Flash column purification (EtOAc, silica) afforded 94 mg (86%) of the

free amine as a crystalline, white solid: mp 192–193 °C; TLC, single uniform spot (R_f = 0.50); HPLC, single peak (t_R = 26.0 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70–0.76 (m, 1 H), 0.89 (t, 3 H, J_{HH} = 7.4 Hz), 0.95–1.14 (m, 2 H), 1.17 (s, 3 H), 1.36 (s, 3 H), 1.39–1.46 (m, 2 H), 1.64 (d, 1 H, J_{HH} = 11.5 Hz), 1.70–1.79 (m, 2 H), 1.89 (t, 1 H, 10.3 Hz), 1.99 (td, 1 H, J_{HH} = 12.2, 5.3 Hz), 2.16–2.36 (m, 4 H), 2.46–2.51 (m, 1 H), 2.72 (d, 1 H, J_{HH} = 6.4 Hz), 2.81 (t, 1 H, J_{HH} = 11.0 Hz), 3.00 (d, 1 H, J_{HH} = 18.3 Hz), 3.51 (s, 3 H), 4.39 (s, 1 H), 5.16 (s, 1 H), 5.52 (br s, 1 H), 6.49 (d, 1 H, J_{HH} = 7.9 Hz), 6.69 (d, 1 H, J_{HH} = 8.0 Hz); ^{13}C NMR (^{1}H decoupled, $CDCl_3$) δ 12.0, 17.6, 20.9, 23.0, 24.9, 29.7, 29.9, 32.3, 35.7, 36.1, 43.8, 47.8, 52.7, 56.8, 58.6, 63.9, 74.6, 80.5, 97.3, 116.3, 119.4, 128.1, 132.2, 137.2, 145.4; FABMS m/z 414 (M^+). Anal. ($C_{25}H_{35}NO_4$) C, H.

3-Hydroxy-4,5α-epoxy-6-methoxy-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethano-17-butylmorphinan (8). The procedure used for **2** was repeated with *N*-nordiprenorphine (100 mg, 0.27 mmol) and 1-bromobutane (108 mg, 0.79 mmol). Flash column purification (EtOAc, silica) afforded 51 mg (45%) of the free amine as a crystalline, white solid: mp 153–155 °C; TLC, single uniform spot (R_f = 0.53); HPLC, single peak (t_R = 28.8 min); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.56 (t, 1 H, J_{HH} = 12.6 Hz), 0.88 (t, 3 H, J_{HH} = 7.1 Hz), 1.01–1.45 (m, 7 H), 1.14 (s, 3 H), 1.26 (s, 3 H), 1.51 (d, 1 H, J_{HH} = 22.1 Hz), 1.70 (t, 1 H, J_{HH} = 12.2 Hz), 1.82 (t, 1 H, 9.3 Hz), 1.95 (td, 1 H, J_{HH} = 12.7, 5.3 Hz), 2.14–2.23 (m, 2 H), 2.30–2.41 (m, 2 H), 2.47 (dt, 1 H, J_{HH} = 6.9, 4.5 Hz), 2.67 (t, 1 H, J_{HH} = 10.0 Hz), 2.72 (d, 1 H, J_{HH} = 6.0 Hz), 2.91 (d, 1 H, J_{HH} = 18.1 Hz), 3.37 (s, 3 H), 4.33 (s, 1 H), 4.41 (s, 1 H), 6.42 (d, 1 H, J_{HH} = 7.9 Hz), 6.56 (d, 1 H, J_{HH} = 7.9 Hz) 8.96 (s, 1 H); ^{13}C NMR (^{1}H decoupled, DMSO-d_6) δ 14.0, 18.8, 20.1, 22.4, 27.8, 28.8, 29.1, 29.4, 31.3, 35.27, 35.31, 43.3, 45.4, 45.8, 51.4, 53.9, 58.4, 73.2, 78.9, 93.7, 116.5, 118.7, 126.3, 132.2, 138.2, 145.5; FABMS m/z 428 (M^+). Anal. ($C_{26}H_{37}NO_4$) C, H.

General Procedure: 3-Hydroxy-4,5α-epoxy-6-methoxy-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethano-17-(3-[^{18}F]fluoropropyl)morphinan (2a). [^{18}F]fluoride was prepared from [^{18}O]H_2O by the [^{18}O(p,n)^{18}F] reaction in a stainless steel cyclotron target with Havar foils. The aqueous [^{18}F]fluoride was placed in a Vacutainer containing *n*-Bu_4NOH (2.5 μmol) and dried under a stream of N_2 at 110 °C by azeotropic distillation using 0.25-mL aliquots of CH_3CN. The *n*-$Bu_4N^{18}F$ complex was then resolubilized in 0.3 mL of THF and transferred to a borosilicate tube containing **14** (1.5 μmol). A thorough study of reaction vessels used for *n*-$Bu_4N^{18}F$ resolubilization showed the Vacutainer to be optimal for this reaction.[29] The [^{18}F]fluoride triflate displacement reaction was terminated after 2 min at room temperature by passage over a Pasteur pipet silica column (1 cm). The column was eluted into a 1.2 mL Pierce Reacti-vial charged with *N*-nordiprenorphine (4.5 mg, 12 μmol) and *i*-Pr_2NEt (4.0 μL, 20 μmol) in 0.5 mL of DMF. After washing the column with DMF to bring the total reaction volume to 1.2 mL, the vial was tightly capped with a Teflon liner and heated for 30 min at 130 °C. Following heating, the reaction mixture was briefly cooled on ince, diluted to 10 mL with H_2O, and run over a C_{18} Sep-Pak (previously activated with 10 mL of MeOH and washed with 10 mL of H_2O). The Sep-Pak was next washed with 2.0 mL of pentane to displace residual H_2O and then eluted with 6.0 mL of CH_2Cl_2. The solvent was removed in vacuo at 40 °C and the ^{18}F radioactivity was taken up in 0.3 mL of CH_3CN for HPLC injection. The product peak was collected and the aqueous solvent was removed by repeating the Sep-Pak procedure. The final product was taken up in normal saline/EtOH (90:10, v:v) and passed through a 2-μm filter prior to animal injection: TLC, single radioactive peak (Fisher plates, R_f = 0.65); HPLC, single radioactive peak (t_R = 24.0 min); chemical purity 30–65%.

3-Hydroxy-4,5α-epoxy-6-methoxy-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethano-17-(2-[^{18}F]fluoroethyl)morphinan (1a). The same procedure used for **2a** was followed with **13** (1.5 μmol): TLC, single radioactive peak (Fisher plates, R_f = 0.62); HPLC, single radioactive peak (t_R = 22.5 min); chemical purity 50–80%.

(29) Brodack, J. W.; Kilbourn, M. R.; Welch, M. J.; Katzenellenbogen, J. A. *Appl. Radiat. Isot. Int. J. Radiat. Appl. Instrum. Part A.* **1986**, *37*, 217.

3-Hydroxy-4,5α-epoxy-6-methoxy-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethano-17(*S*)-(3-[^{18}F]fluoro-2-methylpropyl)morphinan (5a). The same procedure used for **2a** was followed with **15** (1.5 μmol): TLC, single radioactive peak (Fisher plates, R_f = 0.69); HPLC, single radioactive peak (t_R = 25.7 min); chemical purity 35–50%.

General Procedure: 1-Fluoro-3-iodopropane (11). 3-iodo-1-propanol was prepared from 3-bromo-1-propanol and NaI in refluxing acetone by the Finkelstein exchange reaction (83%). DAST (9.01 g, 56 mmol) was cooled to −20 °C and added dropwise to a solution of 3-iodo-1-propanol (10.40 g, 56 mmol) in 20 mL of diethylene glycol dibutyl ether at 0 °C. After stirring for 2 h, the dark brown solution was distilled (0 °C → 40 °C, 0.5 mmHg) into a liquid N_2 cooled flask. Multiple fractions (dark orange in color) were collected as the temperature was raised in stepwise manner. Each fraction was allowed to warm to 0 °C and 1.5 mL of 1.0 N HCl was added. An exothermic reaction with evolution of SO_2 gas was initiated, leaving a cloudy, pale yellow organic phase beneath a colorless aqueous phase. The organic phase was pipetted off and dried (2-cm $MgSO_4$ Pasteur pipet column) to yield 7.76 g (all fractions combined) of a pale yellow liquid (74%) that required no further purification as indicated by NMR: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (d quintet, 2 H, J_{HH} = 6.9 Hz, J_{HF} = 25.9 Hz, CH_2CH_2F), 3.25 (t, 2 H, J_{HH} = 6.9 Hz, CH_2I), 4.48 (dt, 2 H, J_{HH} = 5.3 Hz, J_{HF} = 47.8 Hz, CH_2F); ^{13}C NMR (^{1}H decoupled, $CDCl_3$) δ 1.0 (d, J_{CF} = 5.7 Hz, CH_2I), 33.9 (d, J_{CF} = 20.1 Hz, CH_2CH_2F), 83.0 (d, J_{CF} = 166.9 Hz, CH_2F).

1-Fluoro-2-iodoethane (10). 2-iodo-1-ethanol (82% yield from bromide) (4.15 g, 24.1 mmol) and DAST (3.89 g, 24.1 mmol) were used. The yield was 2.47 g of a pale yellow liquid (59%): ^{1}H NMR (300 MHz, C_6D_6) δ 2.54 (dt, 2 H, J_{HH} = 6.9 Hz, J_{HF} = 18.6 Hz, CH_2I), 3.88 (dt, 2 H, J_{HH}= 6.4 Hz, J_{HF} = 46.9 Hz, CH_2F); ^{13}C NMR (^{1}H decoupled, C_6D_6) δ 1.2 (d, J_{CF} = 22.0 Hz, CH_2I), 82.7 (d, J_{CF} = 173.6 Hz, CH_2F).

(*R*)-1-Fluoro-2-methyl-3-iodopropane (12). (*R*)-3-iodo-2-methyl-1-propanol (94% yield from bromide) (5.72 g, 28.6 mmol) and DAST (4.60 g, 28.6 mmol) were used. The yield was 3.75 g of a pale yellow liquid (65%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (dd, 3 H, J_{HH} = 6.9 Hz, J_{HF} = 1.0 Hz, CH_3), 1.89 (m, 1 H, CH), 3.22 (d quartet, 2 H, J_{HH} = 6.6, 5.8 Hz, CH_2I), 4.29 (m, 2 H, J_{HF} = 47.6 Hz, CH_2F); ^{13}C NMR (^{1}H decoupled, $CDCl_3$) δ 10.3 (d, J_{CF} = 4.8 Hz, CH_2I), 16.2 (d, J_{CF} = 6.27 Hz, CH_3), 37.8 (d, J_{CF} = 18.1 Hz, CH), 86.5 (d, J_{CF} = 170.7 Hz, CH_2F).

General Procedure: 3-Iodo-1-[[(trifluoromethyl)sulfonyl]oxy]propane (14). Trifluoromethanesulfonic anhydride (10.0 g, 35.5 mmol) was diluted with 25 mL of CH_2Cl_2 and cooled to 0 °C. A solution of 3-iodo-1-propanol (5.54 g, 29.8 mmol), 2,6-dimethylpyridine (4.30 g, 40.2 mmol), and 10 mL of CH_2Cl_2 was added dropwise. After stirring for 30 min, the reaction was quenched by the addition of 50 mL of ice H_2O. The CH_2Cl_2 phase was loaded onto a 3-in. silica column and rapidly eluted with 100 mL of hexane/EtOAc (90:10, v:v). The column eluant was dried ($MgSO_4$), filtered, and concentrated in vacuo to give an orange liquid. Distillation (85 °C, 0.5 mmHg) yielded 3.84 g of a colorless liquid (40%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (quintet, 2 H, J_{HH} = 6.0 Hz, CH_2CH_2I), 3.23 (t, 2 H, J_{HH} = 6.5 Hz, CH_2I), 4.61 (t, 2 H, J_{HH} = 5.9 Hz, CH_2O); ^{13}C NMR (^{1}H decoupled, $CDCl_3$) δ −1.2 (CH_2I), 32.4 (CH_2CH_2I), 76.5 (CH_2O), 118.4 (quartet, J_{CF} = 320 Hz, CF_3).

2-Bromo-1-[[(trifluoromethyl)sulfonyl]oxy]ethane (13). The same procedure used for **14** was employed with trifluoromethanesulfonate anhydride (12.23 g, 43.4 mmol), 2-bromo-1-ethanol (4.96 g, 40.0 mmol), and 2,6-dimethylpyridine (5.02 g, 46.9 mmol). Distillation (50 °C, 0.5 mmHg) yielded 3.91 g of a colorless liquid (38%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.58 (t, 2 H, J_{HH} = 6.4 Hz, CH_2Br), 4.72 (t, 2 H, J_{HH} = 6.3 Hz, CH_2O); ^{13}C NMR (^{1}H decoupled, $CDCl_3$) δ 26.3 (CH_2Br), 74.4 (CH_2O), 118.4 (quartet, J_{CF} = 319 Hz, CF_3).

(*R*)-3-Iodo-2-methyl-1-[[(trifluoromethyl)sulfonyl]oxy]-propane (15). The method employed for **14** was used with trifluoromethanesulfonate anhydride (10.0 g, 35.5 mmol), (*R*)-3-iodo-2-methyl-1-propanol (4.84 g, 24.2 mmol), and 2,6-dimethylpyridine (4.33 g, 40.5 mmol). Distillation (60 °C, 0.5 mmHg) yielded 3.08 g of a colorless liquid (38%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, 3 H, J_{HH} = 6.8 Hz, CH_3), 2.00 (m, 1 H, CH), 3.22 (d quartet, 2 H, J_{HH} = 5.4, 5.3 Hz, CH_2I), 4.42 (d,

quartet, 2 H, J_{HH} = 6.0, 5.4 Hz, CH_2O); ^{13}C NMR (^1H decoupled, $CDCl_3$) δ 8.2 (CH_2I), 16.6 (CH_3), 34.6 (CH), 79.7 (CH_2O), 118.7 (quartet, J_{CF} = 321 Hz, CF_3).

Receptor Binding Assays. Brains from female Sprague–Dawley rats were removed and placed in cold (4 °C) 50 mM Tris HCl buffer (pH = 7.4). Subsequent manipulations were carried out at 4 °C. Whole brains (minus striatum and cerebellum) and striatum were each homogenized in 5 volumes of Tris buffer with a Polytron (60 s, speed = 5) and centrifuged at 20000*g* for 20 min. After discarding the supernatant, the pellets were resuspended in Tris buffer with a glass/glass dounce homogenizer and recentrifuged. The pellets from the second spin were suspended in Tris buffer at a protein concentration of 10 mg/mL and frozen at −20 °C. Protein concentrations were determined by the method of Lowry using BSA as standard.[30]

[^{3}H]Diprenorphine (31.04 Ci/mmol) binding assays were performed in a final volume of 1.0 mL 50 mM Tris HCl (pH = 7.4 at 25 °C). Receptor preparations were routinely used at a final protein concentration of 0.20 mg/mL. Nonspecific binding was determined by the addition of either unlabeled diprenorphine (1.0 μM) or naloxone (10 μM). Assays were terminated after 60 min at 25 °C with a Brandel 48 tube filtration apparatus, using Whatman GF/B glass-fiber sheets presoaked in 0.2% polyethyleneimine (Sigma). Filtration and washing with cold (4 °C) Tris buffer (20 mL/tube) required about 20 s. The filters were then placed in scintillation vials along with 10 mL of a toluene/Triton X-100 (2:1) based scintillation fluid and couunted using a Beckman LS3801 scintillation counter with corrections for background radiation and counter efficiency. All binding assays were conducted with each tube in duplicate.

In vitro saturation binding assays with **2a** ([^{18}F]FPND) were performed in a fashion identical with the [^{3}H]diprenorphine binding assays described in the preceding paragraph. After filtration and washing, the glass-fiber filters were placed in vials and counted in a Beckman 8000 NaI(Tl) well-type scintillation counter. Measured counts were decay corrected to the EOS. Determination of K_D and B_{max} from these data requires knowledge of the specific activity of the ^{18}F-labeled ligand. It was not possible, however, to allocate a large part of the [^{18}F]ligand preparation for accurate measurement of the true mass of **2** by UV absorption. This was because of the need to use nearly the entire preparation to achieve receptor saturation even at the very low receptor density employed. Small aliquots of each **2a** preparation were thus saved for effective specific activity deetermination by competitive receptor binding assay using [^{3}H]diprenorphine. This method is justifiable given the close agreement between the true and effective specific activity for this ^{18}F-labeled ligand as previously discussed.

Partition Coefficients. Octanol–water partition coefficients were calculated for the free base amines relative to diprenorphine by using the molecular fragment approach as developed by Rekker.[31] Relevant log *P*(fragment) values are as follows: CH, +0.24; CH_2, +0.53; CH_3, +0.70; and aliphatic F, −0.51. The log *P* values thus obtained provide a framework for examination of the effect of altering the *N*-methylcyclopropyl group of diprenorphine.

Animal Studies. Biodistribution studies were performed in adult female Sprague–Dawley rats (~180 g) which were allowed food and water ad libitum. Rats were anesthetized with Et_2O, and 10–20 μCi of the ^{18}F-labeled radiopharmaceutical was injected into the surgically exposed femoral vein. After a specified period of time, the animals were reanesthetized and sacrificed by decapitation. Organs, including various brain regions were removed rapidly, added to preweighed vials, counted in a Beckman 8000 NaI(Tl) well-type scintillation counter, and then reweighed. Standards of the ^{18}F-labeled compounds were also prepared and counted in order to permit expression of the data in units of percent injected dose/gram of tissue.

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Registry No. **1**, 125828-19-5; **1a**, 125828-29-7; **2**, 125828-20-8; **29**, 125828-28-6; **3**, 125828-21-9; **4**, 125875-93-6; **4**·HCl, 125828-22-0; **5**, 125828-33-3; **5**·HCl, 125846-19-7; **5a**, 125828-30-0; **6**, 125828-23-1; **7**, 125828-24-2; **8**, 125828-25-3; **9**, 14357-78-9; **10**, 762-51-6; **11**, 462-40-8; **12**, 125828-26-4; (*S*)-**12**, 125828-32-2; **13**, 103935-47-3; **14**, 106114-40-3; **15**, 125828-27-5; $I(CH_2)_2OH$, 624-76-0; $Br(CH_2)_3OH$, 627-18-9; $Br(CH_2)_2OH$, 540-51-2; BrC_4H_9-*n*, 109-65-9; $I(CH_2)_3OH$, 627-32-7; $Br(CH_2)_4F$, 462-72-6; IC_2H_5, 75-03-6; (*R*)-$ICH_2CH(CH_3)CH_2OH$, 125828-34-4; BrC_3H_7-*n*, 106-94-5; (*R*)-$BrCH_2CH(CH_3)CH_2OH$, 93381-28-3; *N*-nordiprenorphine, 125828-31-1.

(30) Lowry, O. H.; Rosebrough, N. J.; Farr, A. L.; Randall, R. J. *J. Biol. Chem.* **1951**, *193*, 265.

(31) Rekker, R. F. *The Hydrophobic Fragmental Constant*; Elsevier/North Holland: New York, 1978. Katzenellenbogen, J. A.; Heiman, D. F.; Carlson, K. E.; Lloyd, J. E. *Receptor-Binding Radiotracers*; Eckelman, W. C., Ed.; CRC Press: Boca Raton, FL, 1982; Vol. 1, pp 93–126.