Journal of Labelled Compounds and Radiopharmaceuticals
J. Labelled Cpd. Radiopharm. **42**, 43-54 (1999)

SYNTHESIS OF N1′-([^{18}F]FLUOROETHYL)NALTRINDOLE ([^{18}F]FEtNTI): A RADIOLIGAND FOR POSITRON EMISSION TOMOGRAPHIC STUDIES OF DELTA OPIOID RECEPTORS

William B. Mathews[1], Chris M. Kinter[2], James Palma[2], Robert V. Daniels[2], Hayden T. Ravert[1], Robert F. Dannals[1,3], and John R. Lever*[3,1]

Departments of Radiology[1] and Environmental Health Sciences[3] The Johns Hopkins University, Baltimore, MD 21205 USA, The United States Naval Academy[2], Annapolis, MD 21402 USA

Summary

N1′-([^{18}F]fluoroethyl)naltrindole ([^{18}F]FEtNTI), a novel analog of the delta opioid receptor antagonist naltrindole (NTI), has been prepared for evaluation as a radioligand for use in positron emission tomography. The precursor for radiolabeling was obtained in four steps from naltrexone hydrochloride with an overall yield of 47%. Nucleophilic displacement of a tosylate leaving group by [^{18}F]fluoride, followed by hydrogenolysis (H_2, 10% Pd/C) of a benzyl protecting group on the phenolic moiety, gave [^{18}F]FEtNTI. The average (n = 5) time for radiosynthesis, HPLC purification, and formulation was 77 min from end of bombardment. [^{18}F]FEtNTI of high radiochemical purity was obtained with an average specific activity of 846 mCi/μmol at end of synthesis, and an average radiochemical yield of 10% (not corrected for decay).

Key Words: naltrindole, fluorine-18, delta opioid receptor, positron emission tomography

Introduction

We have developed N1′-([^{11}C]methyl)naltrindole ([^{11}C]MeNTI) as a radioligand for selective localization of delta (δ) opioid receptors by positron

**Correspondence:* John R. Lever, The Johns Hopkins University School of Hygiene and Public Health, Room 2001, 615 North Wolfe Street, Baltimore MD 21205-2179, USA

CCC 0362–4803/99/010043–12$17.50

Received 2 June 1998
Accepted 3 August 1998

emission tomography (PET) (1-5). Compartmental modeling allows quantification of δ opioid receptors in human brain with [^{11}C]MeNTI (5) although binding does not achieve equilibrium (4) over the 90 min time frame of a typical PET imaging protocol that involves carbon-11 (20.4 min half-life). In order to monitor the pharmacokinetics of radioligand binding to δ opioid receptors over a longer interval with improved signal intensity and counting statistics, we also are investigating NTI analogs that are radiolabeled with fluorine-18 (110 min half-life). Here we describe the preparation of N1′-([^{18}F]fluoroethyl)naltrindole ([^{18}F]FEtNTI, Figure 1).

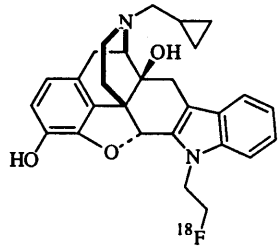
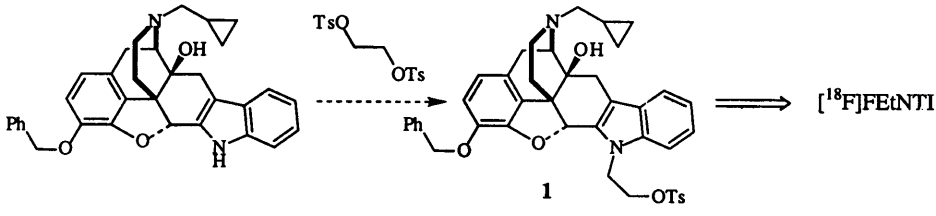


Figure 1. Structure of [^{18}F]FEtNTI

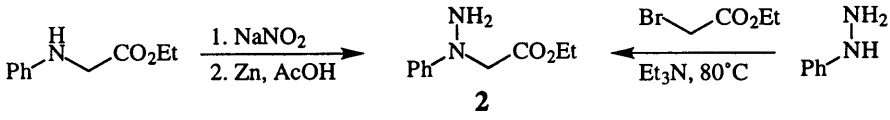
Results and Discussion

A straightforward approach to the production of [^{18}F]FEtNTI would be nucleophilic displacement of a primary leaving group, such as the tosylate of **1**, by [^{18}F]fluoride and subsequent removal of the benzyl protecting group (Scheme 1). We anticipated that **1**, in turn, would be accessible from 3-(O-benzyl)naltrindole, an intermediate used in the synthesis of [^{11}C]MeNTI (2). However, alkylation of the indole nitrogen with ethylene glycol ditosylate proved problematic due to long reaction times and low yields. Similar difficulties were met with other bifunctional reagents, including the *p*-toluenesulfonate ester of 2-bromoethanol, that might lead to related precursors.

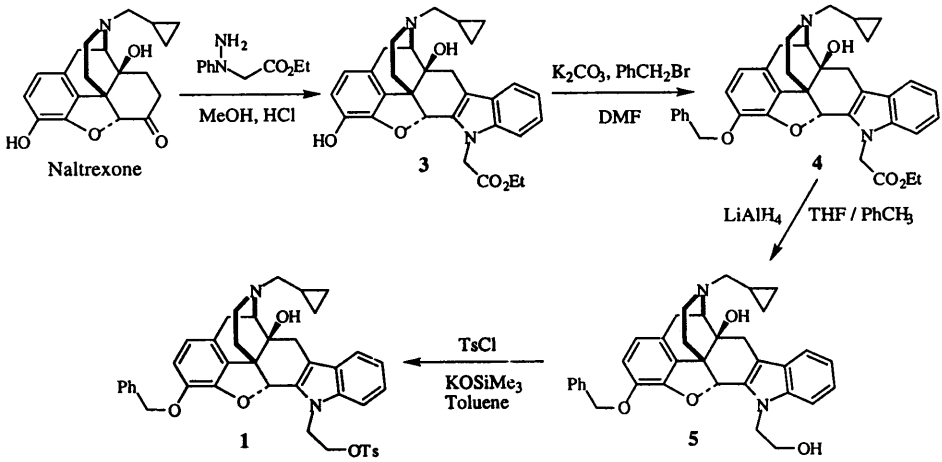


Scheme 1. Initial route to [^{18}F]FEtNTI.

As a consequence, development of an alternate route to precursor **1** was required. The multi-step method by which the precursor ultimately was prepared is shown in Scheme 2. The ethyl 1-phenylhydrazinoacetic acid **2** was prepared by the procedure reported by Brandt and colleagues (6). However, the two-step process of reducing the N-nitrosoamine obtained from the nitrosation of ethyl anilinoacetate was capricious in our hands, and generally gave very low yields of **2**. A more reliable method for making the carboethoxyphenylhydrazine **2** was found to be the direct alkylation of phenylhydrazine with ethyl bromoacetate.

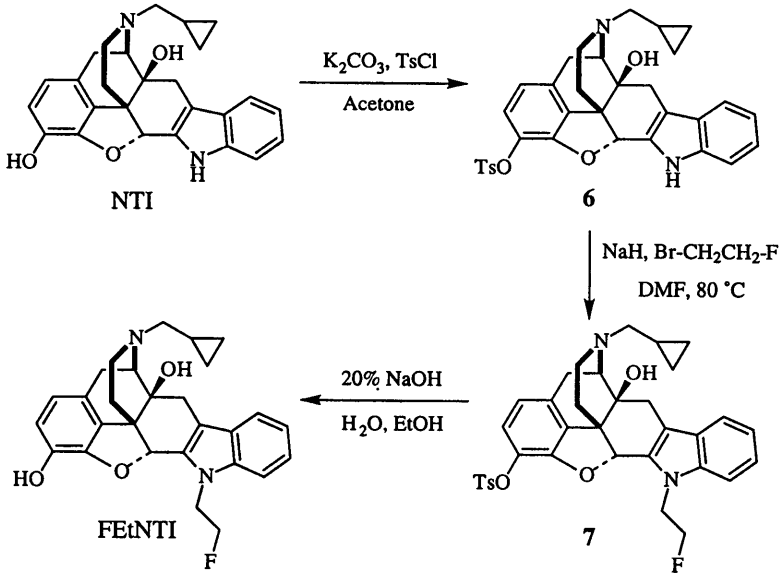


Using the general procedure of Portoghese (7), Fischer indole cyclization of naltrexone hydrochloride with **2** in glacial acetic acid gave N1′-substituted naltrindole **3** in 64% yield. Protection of the phenol as the benzyl ether was accomplished in 96% yield by treatment of **3** with potassium carbonate and benzyl bromide in DMF. Reduction of ester **4** with lithium aluminum hydride in toluene afforded primary alcohol **5** in 89% yield. Conversion to the target tosylate **1** was achieved in 86% yield by treatment of **5** with *p*-toluenesulfonyl chloride and potassium trimethylsilanolate. Thus, the precursor for radiolabeling was obtained from naltrexone in 4 steps, with an overall yield of 47%.



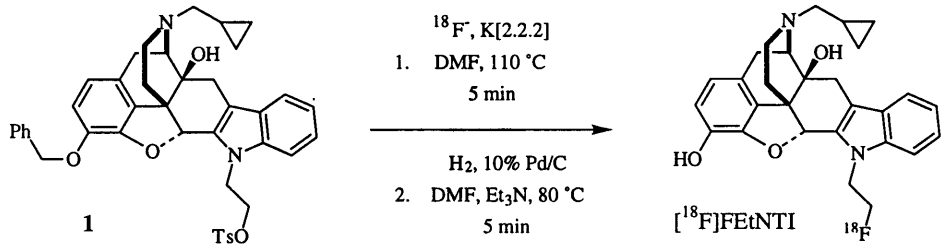
Scheme 2. Synthesis of precursor **1**.

The non-radioactive FEtNTI for use as a characterized, standard sample was prepared as shown in Scheme 3. In this case, we chose to protect the phenolic moiety of NTI as the *p*–toluenesulfonate ester in order to direct alkylation with 1-bromo-2-fluoroethane to the indole nitrogen. The use of a tosyl protecting group had precedent from our previous synthesis of a radioiodinated NTI analogue having a N1′–methyl group (8). Treatment of NTI with potassium carbonate and *p*-toluenesulfonyl chloride in acetone gave ester **6** in 86% yield. Alkylation of **6** using sodium hydride and 1-bromo-2-fluoroethane in DMF for 24 h at 80 °C afforded the N1′–fluoroethyl intermediate **7** in 58% yield. Deprotection was accomplished with aqueous sodium hydroxide in ethanol over 2 h at 80 °C to give FEtNTI in 76% yield. The overall yield for the three step process was 38%.



Scheme 3. Synthesis of FEtNTI.

The radiosynthesis of [^{18}F]FEtNTI is outlined in Scheme 4. Radiolabeling was achieved by treating an acetonitrile solution of precursor **1** at 120 °C for 5 min with potassium [^{18}F]fluoride in the presence Kryptofix® [2.2.2]. The benzyl protecting group was then removed by hydrogenolysis (H_2, 10% Pd/C) at 80 °C for 5 min, and the catalyst was eliminated from the crude reaction mixture by filtration.



Scheme 4. Radiosynthesis of [18F]FEtNTI

The product was isolated by semi-preparative reverse-phase HPLC (Figure 2). The major radioactive component exhibited a retention profile that matched that of the standard sample of FEtNTI, and was assigned as [18F]FEtNTI. This material was collected, evaporated to dryness under reduced pressure, and then dissolved in sterile 0.9% saline. The average (n = 5) time for radiosynthesis, HPLC purification, and formulation was 77 minutes from end of bombardment. The chromatographic conditions were selected to ensure adequate separation of [18F]FEtNTI from a more lipophilic, nonradioactive byproduct. This material is likely to be N1′–ethylnaltrindole (EtNTI) from hydrogenation of both the benzyl and tosyl groups of residual precursor **1**. In fact, the retention time matches that of a characterized sample of EtNTI available from other studies (9), and a mixture containing FEtNTI and EtNTI showed the same HPLC pattern as the UV absorbance trace of Figure 2.

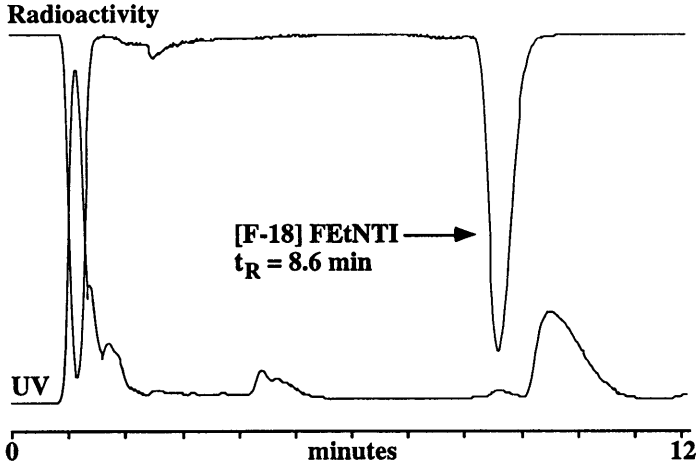


Figure 2. HPLC chromatograms for [18F]FEtNTI isolation.

Chemical purity, radiochemical purity, and specific radioactivity were determined by analytical HPLC methods requiring an additional 5 min. Specific radioactivity was calculated by relating the area of the UV absorbance peak of carrier FEtNTI in an aliquot of [^{18}F]FEtNTI of known radioactivity to the peak area of a standard sample of FEtNTI. [^{18}F]FEtNTI of >99% radiochemical purity was obtained at end-of-synthesis with an average specific activity of 846 mCi/μmol. The average radiochemical yield, not corrected for decay, was 10%.

Conclusion

We have developed synthetic procedures that provide [^{18}F]FEtNTI in good radiochemical yield with a high degree of radiochemical purity. The specific radioactivity of the ligand is moderate, but sufficient for radiopharmacological and PET studies. Preliminary findings indicate that FEtNTI shows high apparent affinity (Ki = 93 pM) for δ opioid receptors *in vitro* in rat brain homogenates, and that [^{18}F]FEtNTI shows specific binding to δ opioid receptors *in vivo* in mouse brain (10). Thus, [^{18}F]FEtNTI warrants further investigation as a radioligand for PET studies of δ opioid receptors. Recently, an abstract concerning the synthesis of N1′-(*p*-[^{18}F]fluorobenzyl)naltrindole was reported (11). This radiofluorinated NTI derivative would be expected to be substantially more lipophilic than [^{18}F]FEtNTI, and an eventual comparison of the *in vivo* pharmacokinetics of these two radiotracers might provide insight into structure activity relationships for this class of ligands for δ opioid receptors.

Experimental

DMF was distilled under reduced pressure from barium oxide and stored under argon over 3Å molecular sieves. *p*-Toluenesulfonyl chloride was recrystallized from $CHCl_3$ and petroleum ether to give white needles with mp 67 - 68 °C (literature (12) mp 67 - 69 °C). NTI was prepared from naltrexone (Mallinckrodt, Inc.) as previously described (7). Other chemicals and solvents were the best reagent grade available, and were used as received. Short-path column chromatography was conducted with E. Merck 7729 (< 230 mesh) silica gel under nitrogen pressure. Analytical TLC was conducted on Macherey-Nagel silica gel 60 UV-254 plates (250 μm). Uncorrected melting points were determined with a Thomas-Hoover capillary apparatus. High resolution mass spectroscopy (HRMS) by fast atom bombardment (FAB) or electron impact (EI) was done at the University of Minnesota Mass Spectroscopy Facility. Elemental analyses were determined by Atlantic Microlab, Inc. (Norcross, GA). ^{1}H NMR spectra were obtained at 300 MHz, and chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane. [^{18}F] was produced with a biomedical cyclotron (Instrument AB Scanditronix MC-16F) using the ^{18}O(p,n)^{18}F reaction. Radioactivity was measured using a Capintec CRC-12R dose calibrator.

Ethyl 1-phenylhydrazinoacetic acid. Ethyl bromoacetate (4.9 mL, 7.4 g, 44 mmol) was added dropwise over 15 min to a solution of phenylhydrazine (4.4 mL, 4.8 g, 44 mmol) in triethylamine (6.2 mL, 4.5 g , 44 mmol) at room temperature. The viscous solution was then warmed to 90 °C. After 5 h, the mixture was cooled and diluted with Et_2O (50 mL) and saturated NaCl (50 mL). The layers were separated and the aqueous layer was washed with Et_2O (1 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a thick orange oil. The oil was dissolved in Et_2O (75 mL) and treated with HCl (g) to give a red solid that was washed with cold Et_2O. Recrystallization from EtOH gave a white solid (1.69 g, 7.35 mmol, 16.5%) that was identical spectroscopically to that obtained by the literature procedure (6). ^{1}H NMR (DMSO): 7.30 (m, 2H), 7.0 (m, 3H), 4.61 (s, 2H), 4.08 (q, J = 7.0 Hz, 2H), 1.13 (t, J = 7.0 Hz, 3H). HREIMS: Calcd. for $C_{10}H_{14}N_2O_2$: 194.1055 ([M + H]$^+$); Found 194.1049.

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-1´-(2´´-carboethoxyethyl)-6,7-2´,3´-indolomorphinan (3). Ethyl 1-phenylhydrazinoacetic acid (0.34 g, 1.5 mmol) was added to naltrexone hydrochloride (0.38 g, 1.0 mmol) in glacial acetic acid (5 mL) at room temperature. The heterogeneous reaction mixture became a homogeneous yellow solution upon warming at 105 °C for 20 min. Heating was continued for 5.5 h, at which time the reaction was judged complete by TLC (9:1:0.5 $CHCl_3$/MeOH/NH_4OH). The mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The dark residue was dissolved in MeOH (50 mL), diluted with water (50 mL), and the pH was adjusted to 9 with NaOH pellets. The mixture was extracted with CH_2Cl_2 (2 x 50 mL) and the combined extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give 0.51 g of a dark solid. Purification by short-path column chromatography (50 g silica gel; 49:49:2 EtOAc/Hexanes/Et_3N) gave 0.32 g (0.64 mmol, 64%) of **3** as an off-white solid: mp 124 - 129 °C. ^{1}H NMR ($CDCl_3$): 7.43 (d, J = 8.1 Hz, 1H), 7.18 (m, 2H), 7.05 (m, 1H), 6.58 (d, J = 8.1 Hz, 1H), 6.51 (d, J = 8.1 Hz, 1H), 5.70 (s, 1H), 4.95 (s, 2H), 4.25 (m, 2H), 3.38 (d, J = 6.3 Hz, 1H), 3.12 (d, J = 18.6 Hz, 1H), 2.91 (d, J = 15.6 Hz, 1H), 2.8 (m, 2H), 2.62 (d, J = 16.2 Hz, 1H), 2.50 - 2.30 (m, 4H), 1.83 (br d, J = 11.4 Hz, 1H), 1.3 (m, 3H), 0.80 (m, 1H), 0.57 (br d, J = 7.5 Hz, 2H), 0.17 (br d, J = 5.1 Hz, 2H). HRFABMS: Calcd. for $C_{30}H_{33}N_2O_5$: 501.2389 ([M + H]$^+$); Found 501.2371.

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-benzyloxy-14-hydroxy-1´-(2´´-carboethoxyethyl)-6,7-2´,3´-indolomorphinan (4). A solution of **3** (0.32 g, 0.64 mmol) in DMF (3.8 mL) containing anhydrous potassium carbonate (0.29 g, 2.1 mmol; 3.3 eq.) and benzyl bromide (99 μL, 0.83 mmol; 1.3 eq.) was heated at 95 °C for 4 h. After 4 h, the reaction was not

complete by TLC (49:49:2 EtOAc/Hexanes/Et_3N), so an additional aliquot of benzyl bromide (20 μL) was added and heating was continued. After an additional 2 h, the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (25 mL) and washed with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2 x 35 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Short-path column chromatography (35 g silica; 35:65:2 EtOAc/Hexanes/Et_3N) gave 0.36 g (0.61 mmol, 96%) of **4** as an off-white solid: mp 76 - 79 °C. ^1H NMR ($CDCl_3$): 7.45 (d, J = 7.5 Hz, 1H), 7.32 (m, 2H), 7.26 (m, 3H), 7.19 (br d, J = 4.5 Hz, 2H), 7.05 (m, 1H), 6.67 (d, J = 8.1 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 5.74 (s, 1H), 5.09 - 4.88 (m, 4H), 4.07 (q, J = 7.2 Hz, 2H), 3.38 (d, J = 6.0 Hz, 1H), 3.13 (d, J = 18.6 Hz, 1H), 3.0 - 2.6 (m, 4H), 2.5 - 2.2 (m, 4H), 1.83 (br d, J = 13.8 Hz, 1H), 1.15 (t, J = 7.2 Hz, 3H), 0.80 (m, 1H), 0.57 (br d, J = 8.1 Hz, 2H), 0.16 (br d, J = 5.1 Hz, 2H). HRFABMS: Calcd. for $C_{37}H_{39}N_2O_5$: 591.2859 ([M + H]$^+$); Found 591.2855.

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-benzyloxy-14-hydroxy-1′-(2′′-hydroxyethyl)-6,7-2′,3′-indolomorphinan (5). A THF solution of $LiAlH_4$ (0.61 mL, 0.61 mmol; 1.0 M) was added by syringe to a solution of **4** (0.36 g, 0.61 mmol) in anhydrous toluene (8.0 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C, quenched by slow addition of EtOAc (10 mL), and then allowed to warm to room temperature. The mixture was poured into saturated sodium potassium tartrate solution (20 mL), and the layers were separated. The aqueous layer was washed with EtOAc (2 x 25 mL). The organic layers were combined, washed with brine (20 mL), dried ($MgSO_4$), filtered, and then concentrated under reduced pressure. Short-path column chromatography (25 g silica; 49:49:2 EtOAc/Hexanes/Et_3N) gave 0.30 g (0.54 mmol, 89%) of **5** as a white solid: mp 168 - 172 °C. ^1H NMR ($CDCl_3$): 7.45 (d, J = 7.8 Hz, 1H), 7.4 - 7.1 (several m, 9H), 7.06 (t, J = 7.2 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H), 6.56 (d, J = 8.1 Hz, 1H), 5.86 (s, 1H), 5.06 (d, J = 11.7 Hz, 1H), 5.01 (d, J = 11.7 Hz, 1H), 4.5 (dt, J = 15.0, 5.4 Hz, 1H), 4.3 (dt, J 15.0, 5.4 Hz, 1H), 3.96 (t, J = 5.4 Hz, 2H), 3.38 (d, J = 6.3 Hz, 1H), 3.14 (d J = 15.6 Hz, 1H), 2.90 (m, 1H), 2.79 (m, 1H), 2.66 (d, J = 15.6 Hz, 1H), 2.5 - 2.2 (several m, 4 H), 1.83 (br d, J = 12.6 Hz, 1H), 0.9 (m, 1H), 0.58 (br d, J = 7.8 Hz, 2H), 0.17 (br d, J = 4.8 Hz, 2H). HRFABMS: Calcd. for $C_{35}H_{37}N_2O_4$: 549.2753 ([M + H]$^+$); Found 549.2789.

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-benzyloxy-14-hydroxy-1′-[2′′-(*p*-tolylsulfonyl)oxyethyl]-6,7-2′,3′-indolo morphinan (1). Potassium trimethylsilanolate (377 mg, 2.94 mmol; 5.4 eq.) was added to a solution of **5** (0.30 g, 0.54 mmol) and *p*-toluenesulfonyl chloride (0.21 g, 1.1 mmol; 2 eq.) in toluene (3.5 mL) at 0 °C. After 1 h, the mixture was warmed to room temperature, diluted with CH_2Cl_2 (25 mL), and poured into

saturated NaCl (25 mL). The layers were separated, and the aqueous phase was washed with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Short-path column chromatography (30 g silica gel; 40:60:2 EtOAc/Hexanes/Et_3N) gave 0.33 g (0.47 mmol, 86%) of **1** as a white solid: mp 112 - 116 °C. ^{1}H NMR ($CDCl_3$): 7.40 (d, J = 8.1 Hz, 2H), 7.33 (m, 3H), 7.26 (m, 3H), 7.09 (d, J = 3.9 Hz, 2H), 7.00 (m, 1H), 6.76 (d, J = 8.1 Hz, 2H), 6.70 (d, J = 8.1 Hz, 1H), 6.60 (d, J = 8.1 Hz, 1H), 5.75 (s, 1H), 5.08 (d, J = 12.3 Hz, 1H), %.03 (d, J = 12.3 Hz, 1H), 4.70 - 4.25 (several m, 4H), 3.40 (d, J = 6.0 Hz, 1H), 3.16 (d, J = 18.6 Hz, 1H), 2.89 - 2.75 (m, 3H), 2.57 (d, J = 15.6 Hz, 1H), 2.53 - 2.38 (m, 3H), 2.3 (m, 1H), 2.18 (s, 3H), 1.82 (d, J = 11.7 Hz, 1H), 0.9 (m, 1H), 0.58 (br d, J = 8.1 Hz, 2H), 0.17 (br d, J = 4.8 Hz, 2H). HRFABMS: Calcd. for $C_{42}H_{43}N_2O_6S$: 703.2842 ([M + H]$^+$); Found 703.2859. Anal. Calcd. for $C_{42}H_{42}N_2O_6S \cdot 1.5\ H_2O$: C, 69.12; H, 6.21; N, 3.84; S, 4.39. Found: C, 69.35; H, 5.94; N, 3.77; S, 4.32.

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-(*p*-tosyloxy)-14-hydroxy-6,7-2′,3′-indolomorphinan (6). A solution of NTI (1.02 g, 2.46 mmol) in acetone (8.6 mL) was added to anhydrous potassium carbonate 2.45 g (17.7 mmol) and the suspension was treated with *p*-toluenesulfonyl chloride (516 mg, 2.71 mmol; 1.1 eq). The mixture was brought to reflux for 3 h, cooled to room temperature, and then stirred overnight. The reaction was quenched by addition of water (10 mL), and the solution was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The product was purified by flash chromatography (EtOAc containing 0.1% Et_3N) to give 1.10 g (79%) of **6** as a tan solid: mp 143 - 146 °C. ^{1}H NMR ($CDCl_3$): 8.07 (br s, H), 7.60 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 8.3 Hz, 1H), 7.3 - 7.0 (m, 4H), 6.73 (d, J = 8.3 Hz, 1H), 6.54 (d, J = 8.3 Hz, 1H), 5.58 (s, 1H), 3.38 (d, J = 6.2 Hz, 1H), 3.12 (d, J = 18.9 Hz, 1H), 2.9 - 2.0 (series m, H), 1.58 (br m, H), 0.88 (m, 1H), 0.55 (d, J = 7.9 Hz, 2H), 0.15 (d, J = 4.7 Hz, 2H). HRFABMS: Calcd. for $C_{33}H_{33}N_2O_5S$: 569.2110 ([M + H]$^+$); Found 569.2120. Anal. Calcd. for $C_{33}H_{32}N_2O_5S \cdot 1.0\ H_2O$: C, 67.56; H, 5.84; N, 4.77; S, 5.46. Found: C, 67.30; H, 5.60; N, 4.66; S, 5.31.

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-(*p*-tosyloxy)-14-hydroxy-1′-(2-fluoroethyl)-6,7-2′,3′-indolomorphinan (7). Powdered NaH (5 mg) was added to a solution of **6** (50 mg, 0.088 mmol) and 1-bromo-2-fluoroethane (14.5 mg, 0.114 mmol) in DMF (0.3 mL) at room temperature. The mixture was warmed to 80 °C, maintained at that temperature for 24 h, and then allowed to cool. The mixture was poured into saturated $NaHCO_3$ (5 mL), and the aqueous layer was washed with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced

pressure. Column chromatography (7 g silica gel; 25:75:2 EtOAc/Hexanes/Et_3N) gave 31.3 mg (0.0510 mmol, 58%) of **7**. ^1H NMR ($CDCl_3$): 7.65 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 8.3 Hz, H), 7.22 - 7.13 (m, H), 7.04 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 6.55 (d, J = 8.3 Hz, 1H), 5.64 (s, 1H), 4.83 (m, H), 4.65 (m, H), 4.25 (series m, H), 3.36 (d, J = 6.2 Hz, 1H), 3.04 (d, J = 18.9 Hz, 1H), 2.6 - 2.0 (series m, H), 1.63 (br d, J = 13.0 Hz, 1H), 0.88 (m, 1H), 0.57 (br d, J = 7.9 Hz, 2H), 0.15 (br d, J = 4.7 Hz, 2H). HRFABMS: Calcd. for $C_{35}H_{36}N_2O_5FS$: 615.2329 ($[M + H]^+$); Found 615.2363.

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-1′-(2′′-fluoroethyl)-6,7-2′,3′-indolomorphinan (FEtNTI). A solution of **7** (18.9 mg, 30.8 μmol) in EtOH (0.8 mL) was treated with 20% aqueous KOH (0.2 mL) at 80 °C. After 2 h, the mixture was allowed to cool to room temperature, and poured into saturated $NaHCO_3$ (5 mL). The aqueous layer was washed with CH_2Cl_2 (2 x 5 mL) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by column chromatography (5 g silica gel; 25:75:2 EtOAc/Hexanes/Et_3N) gave 10.8 mg (23.5 μmol, 76%) of FEtNTI as a white solid: mp 215 - 218 °C (dec.). ^1H NMR ($CDCl_3$): 7.44 (d, J = 7.8 Hz, 1H), 7.30 - 7.15 (m, H), 7.05 (t, J = 7.2 Hz, 1H), 6.45 (d, J = 8.1 Hz, 1H), 6.39 (d, J = 8.2 Hz, 1H), 5.73 (s, 1H), 4.80 - 4.50 (m, 2H), 4.50 - 4.20 (m, 2H), 3.37 (d, J = 6.3 Hz, 1H), 3.10 (d, J = 18.5 Hz, 1H), 2.92 (d, J = 15.7 Hz, 1H), 2.85 - 2.25 (series m, H), 1.79 (br d, J = 12.5 Hz, 1H), 0.88 (m, 1H), 0.57 (d, J = 7.5 Hz, 2H), 0.16 (d, J = 4.8 Hz, 2H). HRFABMS: Calcd. for $C_{28}H_{30}N_2O_3F$: 461.2240 ($[M + H]^+$); Found 461.2211. Anal. Calcd. for $C_{28}H_{29}N_2O_3F \cdot 0.25\ H_2O$: C, 72.32; H, 6.39; N, 6.02. Found: C, 72.34; H, 6.92; N, 5.42.

Radiosynthesis of [^{18}F]FEtNTI. Potassium [^{18}F]fluoride was prepared using the Hamacher method (13). In brief, [^{18}O]H_2O (2.0 mL, 97.9% isotopic abundance) was bombarded with 16 MeV protons and transferred under helium pressure to a hot cell through Teflon tubing (1/16" i.d.). The aqueous solution of [^{18}F]fluoride was concentrated by passage through a column (2.5 x 50 mm) of DOWEX 1-X8 resin (17.5 mg). The [^{18}F]fluoride was eluted from the resin with water (0.3 mL) containing 2.3 mg of potassium carbonate. This solution was transferred to a 5 mL crimp-top vial containing 2.3 mg of potassium carbonate and 13 mg of Kryptofix® [2.2.2]. The potassium [^{18}F]fluoride was dried by azeotropic removal of water at 120 °C using five 0.2 mL portions of acetonitrile followed by heating of the residue at 120 °C for three min. Precursor **1** (1.0 - 1.5 mg) in acetonitrile (0.3 mL) was added to the vial containing [^{18}F]fluoride, and the mixture was heated at 120 °C for 5 min. During this time, 10% Pd/C (6 - 8 mg) was activated with hydrogen gas, and then taken up as a slurry in dry DMF (0.2 mL) containing triethylamine (25 μL). The catalyst

slurry was added to the reaction mixture, a balloon reservoir of hydrogen gas was attached to the vessel, and the mixture was heated at 80 °C. After 5 min, the contents of the vessel were taken up in a syringe, and passed through a PTFE filter (13 mm, 0.45 μm) into a small glass vial. The reaction vessel was then rinsed with a mixture of DMF (0.2 mL) and HCl (50 μL, 1.0 M). This wash was passed through the original PTFE filter, and added to the main solution. The combined solution was injected onto a semi-preparative HPLC system that consisted of a Waters 590EF pump, Rheodyne 7126 injector, Waters 440 UV absorbance detector (254 nm) and a flow radioactivity detector. An Econosil C-18 (10 μm, 10 x 250 mm) column (Alltech Applied Sciences) was eluted with 35:65 (*v:v*) acetonitrile:water containing 0.1% trifluoroacetic acid at a flow rate of 10.0 mL/min. The radioactive material corresponding to [^{18}F]FEtNTI (*ca.* 8.6 min retention time) was collected in a rotary evaporator modified for remote addition and removal of solutions. The solvent was evaporated at 80 °C under reduced pressure as it was collected. The residue was dissolved in sterile 0.9% saline (5.0 mL) and transferred to a sterile, pyrogen-free bottle. Analytical HPLC was performed using an Econosil C-18 (10 μm, 4.6 x 250 mm) column and 40:60 (*v:v*) acetonitrile:water containing 0.1% trifluoroacetic acid at a flow rate of 4.0 mL/min. Under these conditions, the retention time for [^{18}F]FEtNTI was approximately 2.3 min. A Hewlett-Packard 3390A integrator and Rainin Dynamax system recorded the HPLC chromatograms.

Acknowledgments

The authors thank Mr. Robert C. Smoot for assistance with cyclotron operation and radiosyntheses. This research was supported by USPHS grants NIDA DA 08816 and NIDA DA 08870, and by a grant from the United States Naval Academy Research Council.

References

1. Lever J.R., Scheffel U., Kinter C.M., Ravert H.T., Dannals R.F., Wagner H.N., Jr., and Frost J.J. - Eur. J. Pharmacol. 216: 459 (1992).

2. Lever J.R., Kinter C.M., Ravert H.T., Musachio J.L., Mathews W.B., and Dannals R.F. - J. Labelled Compds. Radiopharm. 36: 137 (1995).

3. Smith J.S., Zubieta J.K., Price J.C., Madar I., Lever J.R., Kinter C.M., Ravert H.T., Dannals R.F., and Frost J.J. - Soc. Neurosci. Abstr. 20: 1384 (1994).

4. Madar I., Lever J.R., Kinter C.M., Scheffel U., Ravert H.T., Musachio J.L., Mathews W.B., Dannals R.F., and Frost J.J. - Synapse 24: 19 (1996).

5. Madar I., Lesser R.P., Krauss G., Zubieta J.K., Lever J.R., Kinter C.M., Ravert H.T., Musachio J.L., Mathews W.B., Dannals R.F., and Frost J.J. - Ann. Neurol. 41: 358 (1997).

6. Arcari M., Aveta R., Brandt A., Cecchetelli L., Corsi G.B., and Solinas F. - Il Farmaco 47: 405 (1992).

7. Portoghese P.S., Sultana M., and Takemori A.E. - J. Med. Chem. 33: 1714 (1990).

8. Kinter C.M. and Lever J.R. - Nucl. Med. Biol. 22: 599 (1995).

9. Lever J.R. and Johnson S.M. - J. Labelled Compds. Radiopharm. 39: 115 (1997).

10. Mathews W.B., Kinter C.M., Palma J., Daniels R.V., Ravert H.T., Scheffel U., McCallister S.L., Chapman S.A., Finley P.A., Dannals R.F., and Lever J.R. - J. Nucl. Med. 39S: 21P (1998).

11. Akgün E., Sajjad M., Arnett C.D., and Portoghese P.S. - Abstracts of the 214th American Chemical Society National Meeting, Las Vegas, NV, September 1997: MEDI 235.

12. Pelletier S.W. - Chem. Ind. 1034 (1953).

13. Hamacher K., Coenen H.H., and Stöcklin G. - J. Nucl. Med. 27: 235 (1986).

