PROBES FOR NARCOTIC RECEPTOR MEDIATED PHENOMENA 11.[1] SYNTHESIS OF 17-METHYL AND 17-CYCLOPROPYLMETHYL-3,14-DIHYDROXY-4,5α-EPOXY-6β-FLUOROMORPHINANS (FOXY AND CYCLOFOXY) AS MODELS OF OPIOID LIGANDS SUITABLE FOR POSITRON EMISSION TRANSAXIAL TOMOGRAPHY

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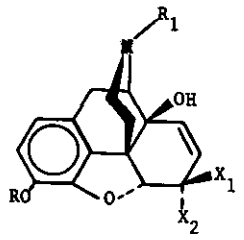
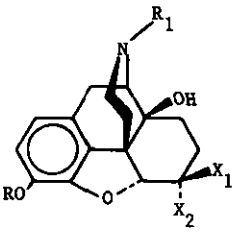
Abstract - Fluorinated derivatives 3,14-dihydroxy-4,5α-epoxy-6β-fluoro-17-methylmorphinan ("fluorooxymorphone"; FOXY, 10) and 17-cyclopropylmethyl-3,14-dihydroxy-4,5α-epoxy-6β-fluoromorphinan (CYCLOFOXY, 18) were prepared based upon the structures of the potent opioid agonist oxymorphone 4 and the antagonist naltrexone 11 respectively. Fluorine was introduced in the final stages of synthesis by a facile nucleophilic displacement with fluoride ion of the 6α-triflate functions in 8 and 16. The synthetic procedures are suitable for the production of the corresponding positron emitting ^{18}F-labeled analogs ^{18}F-FOXY and ^{18}F-CYCLOFOXY, which may be useful for *in vivo* studies of the opioid receptor system using positron emission transaxial tomography. In addition, the tritiation of FOXY (10) to high specific activity is described.

In an effort to understand the structure and function of the opioid receptor system, we have engaged in the synthesis of a variety of opioid ligands designed as pharmacological probes of this system.[1-3] One shortcoming of these lines of investigation is that they are not suitable for

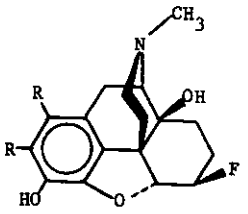


	R	R_1	X_1	X_2
1	Me	Me	=O	
2	Me	Me	H	OH



	R	R_1	X_1	X_2
3	Me	Me	H	OH
4	H	Me	=O	
5	H	Me	H	OH
6	H	Me	OH	H
7	Ac	Me	H	OH
8	Ac	Me	H	OTf
9	Ac	Me	F	H
10	H	Me	F	H
11	H	CPM	=O	
12	H	CPM	H	OH
13	H	CPM	OH	H
14	Ac	CPM	H	OH
15	Ac	CPM	OH	H
16	Ac	CPM	H	OTf
17	Ac	CPM	F	H
18	H	CPM	F	H

CPM = Cyclopropylmethyl



19 R = Br
20 R = ^{3}H

in vivo visualization of opioid receptors in the living human brain.[4] With the development of positron emission transaxial tomography (PETT), in vivo investigation of the opioid receptor system in humans is possible if an appropriate positron emitting opioid ligand is used. To be useful, such a ligand must have high binding affinity and specificity for the opioid receptor system and must be synthetically accessible by introduction of the positron emitting isotope in a rapid, high yield reaction immediately prior to use. Use of ^{18}F, a positron emitting isotope with a half life of 110 min, has proven to be successful for PETT scanning in other systems.[5] We have therefore undertaken the synthesis of fluorine-labeled opioids to be used as models for eventual ^{18}F-incorporation, and have previously reported on the synthesis and biological activity of fluorophen, a fluorine containing derivative of the potent opioid phenazocine.[6] Herein we wish to report the synthesis of two new fluorinated opioids 10 and 18 by routes which involve facile introduction of fluorine in the final stages in a manner suitable for incorporation of ^{18}F. Also included in this report is the tritiation of 10 to high specific activity.

Morphinan 10 ("fluorooxymorphone", FOXY), whose structure is based on the potent opioid agonist oxymorphone (4), was obtained in a clean, rapid (20 min) reaction of triflate 8 with KF/18-crown-6 in refluxing acetonitrile. The choice of triflate (trifluoromethanesulfonate) as the leaving group in this nucleophilic displacement is based upon its proven value in similar reactions[7] and the observation that methyl triflates are $10^{4.3}$ times more reactive to solvolysis than tosylates.[8] In the reaction of 8 with fluoride the 3-OAc group was retained, giving 9, which upon treatment with aqueous NH_3 yielded the title compound FOXY (10). However, for experiments utilizing ^{18}F where shorter reaction times are critical, the 3-OAc derivative 9 can be taken directly for in vivo studies, eliminating the hydrolysis step. By analogy to other 3-OAc 4,5-epoxymorphinans such as heroin, the presence of the 3-OAc group in 9 should facilitate uptake in the brain where rapid enzymatic deacetylation would yield the free ^{18}F-FOXY (10).

Triflate 8 was prepared by reaction of 6α-OH compound 7 with a molar excess of trifluoromethanesulfonic anhydride in pyridine/$CHCl_3$. The excess anhydride did not acylate the 14-OH group under these conditions. The 3-acetyl-14-hydroxy-dihydromorphine 7 was obtained as a crystalline solid, mp 125-126°C (previously reported as a gum[9]) by treatment of the corresponding 3-OH compound 5 with acetic anhydride in aqueous $NaHCO_3$.[9] The 3-OH compound 5 could be obtained directly from 14-hydroxydihydromorphinone (4) by reduction with $NaBH_4$. However in contrast to previous reports,[10] substantial formation of epimeric 6β-OH product 6 was observed, necessitating tedious purification by silica gel chromatography to obtain the pure 6α-OH epimer 5. Alternately, pure 6α-OH compound 2 could be obtained by $NaBH_4$ reduction[11] of the didehydro compound 1[12] which followed by hydrogenation[11] to 3 and O-demethylation (BBr_3 in $CHCl_3$)[13] yielded 5.

FOXY (10) has been shown to have a high affinity for opioid mu-receptors and exhibits one of the lowest levels of nonspecific binding for any mu-opioid ligand presently available.[14] However, it has previously been reported that even agonist with very high in vivo receptor affinities accumulate poorly at receptor sites.[15] Although two exceptions have been claimed,[16] the usual failure to detect binding of opioid agonists in vivo may be due in part to their reduced affinity in the sodium-rich cellular environment. Antagonists, in contrast, have been shown to provide much better ligands for in vivo binding studies.[15] In the epoxymorphinan series, N-cyclopropylmethyl compounds are generally narcotic antagonists. It was therefore of interest to prepare the corresponding N-cyclopropylmethyl derivative (CYCLOFOXY, 18) as a ligand possibly superior to FOXY for in vivo receptor imaging. Using a reaction sequence analogous to that described above for the synthesis of FOXY, the potent, prototype narcotic antagonist naltrexone (11) was reduced with $NaBH_4$ in THF to yield predominantly the 6α-OH epimer 12.[17]

(The observed NMR coupling constants for 12 were $J_{5\beta\text{-}6\beta}$ = 4.4 Hz; lit[17] $J_{5\beta\text{-}6\beta}$ = 4.0 Hz for 12 and $J_{5\beta\text{-}6\alpha}$ = 6.0 Hz for the 6β-OH epimer 13.) A small amount of epimeric 13 also formed which could be removed chromatographically at this point, or preferably carried to the next step where acetylation of the crude mixture with acetic anhydride in aqueous $NaHCO_3$ gave a more easily separable mixture of 3-OAc-6α-OH and 6β-OH compounds 14 and 15,[17] respectively. Reaction of pure 14 with excess trifluoromethanesulfonic anhydride in pyridine/$CHCl_3$ gave the 6β-OTf 16. As in the synthesis of FOXY, facile nucleophilic displacement of the triflate group with KF/18-crown-6 in refluxing acetonitrile gave the 3-OAc compound 17, which provided CYCLOFOXY (18) upon heating with aqueous NH_3 in MeOH. Vicinal NMR coupling constants between the 5β-H and 6-F of FOXY (J = 18 Hz) and CYCLOFOXY (J = 21 Hz) were consistent with the 6β-F configuration.[18]

It was of interest to have both FOXY and CYCLOFOXY labeled with tritium in high specific activity for receptor binding and autoradiographic studies. In a procedure similar to that previously used to tritiate other opioid ligands,[19] FOXY was brominated (Br_2 in AcOH) to yield the dibromo derivative 19. Palladium on carbon catalyzed exchange of tritium for bromine gave ^{3}H-FOXY (20) with a specific activity of 16 Ci/mmol. Work is in progress to prepare ^{3}H-CYCLOFOXY in a similar manner.

EXPERIMENTAL

Melting points were determined on a Fischer-Johns apparatus and are corrected. NMR spectra were recorded using a Varian 220 MHz spectrometer with $Si(CH_3)_4$ as the internal reference. Infrared spectra were recorded on a Beckman 4230 spectrometer. Silica gel GF plates for thin layer chromatography were purchased from Analtech, Inc., Newark, Delaware. Chemical ionization mass spectra (CIMS) were obtained on a Finnigan 1015D spectrometer with a Model 6000 data collection system and electron ionization mass spectra (EIMS) were obtained on a Hitachi-Perkin Elmer RMU-6E spectrometer (70 eV). Column chromatography was performed using 230-400 mesh EM silica gel. Mass spectra and elemental analysis were obtained from the Section on Analytical Services and Instrumentation, NIADDK.

4,5α-Epoxy-17-methyl-3,6α,14-trihydroxymorphinan (14-hydroxydihydromorphine, 5):

A solution of 1.0 g (3.2 mmol) of 6α,14-dihydroxy-4,5α-epoxy-3-methoxy-17-methylmorphinan[11] (14-hydroxydihydrocodeine, 2) in $CHCl_3$ (30 mL) was stirred at 20°C with BBr_3 (1.8 mL, 6 eq) for 30 min. The resulting white suspension was cautiously treated with MeOH until no further reaction occurred, then evaporated to a foam and partitioned between aqueous Na_2CO_3 (10 mL) and $CHCl_3$ (3 x 30 mL). Evaporation of $CHCl_3$ and crystallization from MeOH/ether gave 5 as white crystals (650 mg, 67%), mp 250-252°C (lit.[10] 250°C).

3-Acetoxy-4,5α-epoxy-14-hydroxy-17-methyl-6α-trifluoromethanesulfonyloxymorphinan (8):
A solution of 2.0 g (5.8 mmol) of 3-acetoxy-6α,14-dihydroxy-4,5α-epoxy-17-methylmorphinan 7 (mp 125.0-126.5°C, previously reported as gum[9]) in $CHCl_3$ (30 mL) with pyridine (4 mL) was stirred at 20°C while two additions of 970 µL (1.63 g, 5.8 mmol) of trifluoromethanesulfonic anhydride were made. After 20 min, TLC ($CHCl_3$:MeOH:NH_4OH;90:10:1) indicated a single product spot (Rf = 0.57) with no starting material (Rf = 0.43). The mixture was partitioned between aqueous $NaHCO_3$ (50 mL) and $CHCl_3$ (2 x 30 mL), dried (Na_2SO_4) and evaporated to a red oil. Silica gel flash chromatography (CH_2Cl_2:MeOH 10:1) provided 8 as a yellow oil homogeneous on TLC (2.0 g, 72%); CIMS (NH_3) m/e 378 (M+1); NMR ($CDCl_3$):δ1.43-1.77 (m, 4H), 1.93-2.10 (m, 1H), 2.16-2.32 (m, 3H), 2.29 (s, 3H), 2.35 (s, 3H), 2.43 (d, 1H, J = 7 Hz) 2.59 (dd, 1H, J = 6 Hz and 18 Hz), 2.80 (d, 1H, J = 6 Hz), 3.18 (d, 1H, J = 18 Hz), 4.74 (d, 1H, J = 4 Hz), 5.41 (quintet, 1H, J = 4 Hz), 6.67 (d, 1H, J = 8 Hz), 6.86 (d, 1H, J = 8 Hz).

3,14-Dihydroxy-4,5α-epoxy-6β-fluoro-17-methylmorphinan hydrochloride (FOXY.HCl, 10.HCl):
A solution of triflate 8 (1.0 g, 2.1 mmol) in acetonitrile (30 mL) was stirred at reflux with KF (880 mg, 15.2 mmol) and 18-crown-6 ether (1.1 g, 4.2 mmol). The reaction was complete at 20 min by TLC. It was evaporated and purified by silica gel flash chromatography (CH_2Cl_2:MeOH: NH_4OH 100:5:1) yielding the 3-OAc derivative of FOXY 9 as a syrup. This was dissolved in MeOH (10 mL) and stirred at 80°C for 30 min with concentrated NH_4OH (500 µL). The solvent was evaporated to yield crude product as a crystalline solid which was acidified with methanolic HCl and crystallized from 2-propanol/isopropyl ether, yielding 10.HCl as a white crystalline solid (440 mg, 62%): mp 196-200°C; CIMS (NH_3) m/e 306 (M+1); NMR ($CDCl_3$):δ1.20-1.50 (m, 3H), 1.57-1.70 (m, 1H), 1.75-1.95 (m, 1H), 2.05-2.30 (m, 3H), 2.36 (s, 3H), 2.53 (dd, 1H, J = 6 Hz and 18 Hz), 2.78 (d, 1H, J = 6 Hz), 2.66 (d, 1H, J = 18 Hz), 4.34 (doublet of quintets, 1H, J = 6 Hz and 49 Hz), 4.61 (dd, 1H, J = 6 Hz and 21 Hz), 6.57 (d, 1H, J = 8 Hz), 6.70 (d, 1H, J = 8 Hz). Anal. Calcd. for $C_{17}H_{20}O_3F.HCl.2.5\ H_2O$: C, 52.78; H, 6.77; N, 3.62. Found: C, 52.79; H, 6.42; N, 3.31.

3-Acetoxy-17-cyclopropylmethyl-4,5α-epoxy-6α-hydroxymorphinan oxalate(14 oxalate):
Naltrexone.HCl (11.HCl) (20 g, 53 mmol) was dissolved in H_2O (200 mL) by warming then made alkaline by addition of NH_4OH (30 mL) and extracted with $CHCl_3$ (3 x 100 mL). Evaporation of the $CHCl_3$ extract gave naltrexone base as a white solid in quantitative yield. This was dissolved in THF (200 mL) and cooled on ice while $NaBH_4$ (1.0 g, 26 mmol) was added. After 1 h excess hydride was destroyed by stirring for 30 min with dilute HCl (5 mL). Evaporation of the solvent left a foam which was partitioned between dilute NH_4OH (20 mL) and $CHCl_3$ (2 x 150 mL), washed with dilute NH_4OH (100 mL) and evaporated to a white foam containing predominantly 6α-OH isomer 12 with a little 6β-OH isomer 13. The foam was mixed with H_2O (400 mL) containing

$NaHCO_3$ (50 g), then acetic anhydride was added (30 mL) and the mixture stirred at 20°C for 40 min. The resulting clear solution was extracted with $CHCl_3$ (3 x 100 mL), evaporated to a syrup and purified by silica gel flash chrmatography (CH_2Cl_2:MeOH:NH_4OH 100:5:1) to yield pure 6α-OH 14 as a syrup. Crystallization of the oxalate salt (1 mol eq of oxalic acid) from acetone: MeOH gave 14 oxalate as a white salt (9.4 g, 37% yield): mp 184-187°C (gas); NMR ($CDCl_3$):δ4.62 (d, 5_β-H, $J_{5\beta-6\beta}$ = 5.0 Hz; lit.[16] 4.63 (d, 5_{β}-H, $J_{5\beta-6\beta}$ = 5.2 Hz). Anal. Calcd. for $C_{22}H_{27}NO_5.C_2H_2O_4$. 1.5 H_2O: C, 57.36; H, 6.42; H, 2.79. Found: C, 57.45; H, 6.21; N, 2.86.

3-Acetoxy-17-cyclopropylmethyl-4,5α-epoxy-6α-trifluoromethanesulfonyloxymorphinan (16):
Oxalate salt 14 (4.8 g, 10 mmol) was partitioned between aqueous $NaHCO_3$ (50 mL) and $CHCl_3$ (2 x 100 mL). Evaporation of the $CHCl_3$ extracts gave free amine 14 as a colorless syrup in quantitative yield. This was taken up in $CHCl_3$ (30 mL) to which was added pyridine (4 mL) then trifluoromethanesulfonic anhydride (2 x 1.7 mL, 20 mmol total). After 10 min the reaction mixture was diluted with $CHCl_3$ (100 mL), washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and evaporated to a red oil. Silica gel flash chromatography (CH_2Cl_2:MeOH:NH_4OH 100:5:1) gave product 16 as a yellow syrup, (5.0 g, 97%): CIMS (NH_3) m/e 518 (M+1); NMR ($CDCl_3$):δ0.14 (d, 1H, J = 5 Hz), 0.56 (d, 1H, J = 8 Hz), 0.68-0.91 (m, 1H), 1.43-1.77 (m, 4H), 1.93-2.10 (m, 1H), 2.24-2.39 (m, 3H), 2.17 (s, 3h), 2.30 (s, 3H), 2.70-3.02 (m, 2H), 3.04-3.60 (m, 2H), 4.76 (d, 1H, J = 4 Hz), 5.34-5.45 (m, 1H), 6.66 (d, 1H, J = 8 Hz), 6.86 (d, 1H, J = 8 Hz).

17-Cyclopropylmethyl-3,14-dihydroxy-4,5α-epoxy-6β-fluoromorphinan hydrochloride (CYCLOFOXY.HCl, 18.HCl):
Triflate 16 (3.26 g, 6.3 mmol) in acetonitrile (100 mL) was stirred at reflux with KF (3.9 g, 68 mmol) and 18-crown-6 ether (5.1 g, 19.3 mmol). After 1 h the reaction was removed, evaporated to a gum and purified by silica gel flash chromatography (CH_2Cl_2:NH_4OH 100:1) to yield 3-OAc 17 as a foam (1.0 g). This was dissolved in MeOH (50 mL) and stirred with NH_4OH (1 mL) for 1.5 h. The reaction mixture was then evaporated, acidified with methanolic HCl and crystallized from 2-propanol: isopropyl ether to yield 18.HCl as white crystals (890 mg, 37% yield): mp 206-210°C; EIMS m/e 345 (M^+); NMR ($CDCl_3$):δ0.11 (d, 2H, J = 5 Hz), 0.52 (d, 2H, J = 8 Hz), 0.74-0.92 (m, 1H), 1.23-1.52 (m, 3H), 1.59-1.74 (m, 1H), 1.77-1.93 (m, 1H), 2.05-2.30 (m, 2H), 2.36 (d, 2H, J = 7 Hz), 2.48-2.68 (m, 2H), 3.00 (d, 1H, J = 18 Hz), 3.56 (d, 1H, J = 6 Hz), 4.34 (doublet of quintets, 1H, J = 6 Hz and 48 Hz), 4.61 (dd, 1H, J = 6 Hz and 21 Hz), 6.55 (d, 1H, J = 8 Hz), 6.70 (d, 1H, J = 8 Hz). Anal. Calcd. for $C_{20}H_{25}ClFNO_3$: C, 62.91; H, 6.60; N, 3.67. Found: C, 62.55; H, 6.87; N, 3.28.

3,14-Dihydroxy-4,5α-epoxy-6β-fluoro-17-methylmorphinan-1,2-^{3}H (^{3}H-FOXY, 20):

To a solution of FOXY.HCl, (10.HCl) (240 mg, 0.79 mmol) in AcOH (5 mL) was added 5 drops of 48% aqueous HBr and bromine vapor was passed over the stirred solution. After 1.5 h solvent was evaporated and the residue partitioned between aqueous $NaHCO_3$ (5 mL) and $CHCl_3$ (10 mL). Evaporation of the $CHCl_3$ extract gave a foam which was purified by silica gel flash chromatography (CH_2Cl_2:MeOH:NH_4OH;90:5:0.5) to yield 19 as a syrup. Acidification with methanolic HCl gave 19.HCl as a white amorphous powder (155 mg, 39%): CIMS (NH_3) 460, 461, 463 (isotopic distribution for M+1); NMR ($CDCl_3$, free base):δ1.20-1.50 (m, 3H), 1.57-1.70 (m, 1H), 1.75-1.95 (m, 1H), 2.05-2.30 (m, 3H), 2.37 (s, 3H), 2.34-2.52 (m, 1H), 2.85 (d, 1H, J = 6 Hz), 2.66 (d, 1H, J = 18 Hz), 4.34 (doublet of quintets, 1H, J = 6 Hz and 49 Hz), 4.61 (dd, 1H, J = 6 Hz and 21 Hz).

A solution 19.HCl (10 mg) in MeOH (2 mL) was stirred with 10% Pd-C (15 mg) under an atmosphere of tritium gas (25 Ci). (Tritiation was performed at the New England Nuclear Corp., 549 Albany St., Boston, Mass., 62118.) After 24 h the mixture was filtered, labile tritium removed in vacuo and the residue (311 mCi) taken up in MeOH (2 mL). A 30 mCi aliquot was applied to a 2.5 cm x 9 cm aluminum backed EM silica gel 60 TLC plate (200 μ), and developed ($CHCl_3$:MeOH:NH_4OH: 100:3:3). The plate was cut into 7 x 1 cm bands which were each eluted with MeOH (2 mL) and aliquots subjected to liquid scintillation spectrophotometry. Bands 5 and 6, containing 48% of the total eluted activity, were pooled and rechromatographed in an identical manner, yielding ^{3}H-FOXY 20 (2 mCi). When an aliquot of 20 was cochromatographed with authentic FOXY (10) (TLC, solvent system as above), 97% of the total radioactivity ran with 10 (visualized with I_2) indicating 97% radiochemical purity. The UV spectrum of 20 was identical with authentic 10, and specific activity of 20 was calculated as 16 Ci/mmol based upon its uv absorption at 285 nm.

Note added after acceptance of this manuscript:

The synthesis of [^{18}F]-3-Acetylcyclofoxy has now been accomplished and this material proved highly satisfactory for visualization of opiate receptors in the brain of a living baboon.[20]

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