(20*R*)-4,5-α-Epoxy-6-(2-[^{18}F])fluoroethoxy)-3-hydroxy-α,17-dimethyl-α-(2-phenyleth-1-yl)-6,14-ethenomorphinan-7-methanol

[^{18}F]FE-PEO

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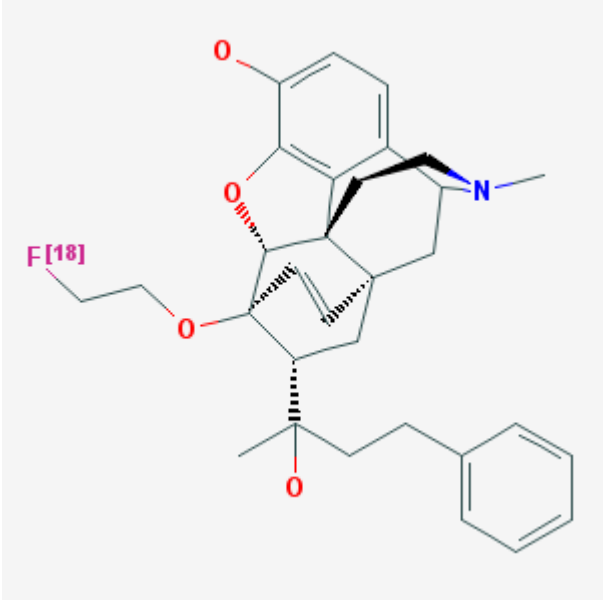
Chemical name:	(20*R*)-4,5-α-Epoxy-6-(2-[^{18}F]fluoroethoxy)-3-hydroxy-α,17-dimethyl-α-(2-phenyleth-1-yl)-6,14-ethenomorphinan-7-methanol
Abbreviated name:	[^{18}F]FE-PEO
Synonym:	
Agent category:	Compound
Target:	Opioid receptors
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal \contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

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Background

[PubMed]

Opioids such as morphine are analgesics that are commonly used in clinical practice. Three opioid receptors (mu, μ; delta, δ; and kappa, κ) that mediate opioid effects have been identified by molecular cloning: δ (enkephalin-preferring), κ (dynorphin-preferring), and μ (morphine- and ß-endorphin–preferring) (1). Each type of opioid receptor consists of subtypes of receptors, as suggested by pharmacological studies (2, 3). These receptors exhibit apparent specificity to both the central and the peripheral nervous systems, and their presence is ubiquitous in these systems. The opioid receptors (G-protein–coupled, resulting in decreased adenylyl cyclase activity) play an important role in the regulation of analgesia, shock, appetite, thermoregulation, and cardiovascular, mental, and endocrine function (2-5). Although μ opioid receptors are the major receptors to mediate the analgesic effects of opioids, δ and κ receptors are also important in antinociception. Opioids have been found to protect cells from ischemic injury in the heart and brain *via* the δ receptors. On the other hand, κ antagonists prevent neurodegeneration.

The μ opioid receptors are localized predominately in the hypothalamus and thalamus, and the δ opioid receptors are localized predominately in the striatum, limbic system, and cerebral cortex (6, 7). The κ opioid receptors (κ_1 and κ_2) are the most abundant brain opioid receptors and are widely distributed in deeper layers of the neocortex (particularly temporal, parietal, and frontal cortices), striatum, amygdala, and thalamus, with lower levels in the hippocampus, occipital cortex, and cerebellum (8-10). The κ opioid receptors have been implicated in several clinical brain disorders, including drug abuse (11), epilepsy (12), Tourette's syndrome (13), and Alzheimer's disease (14).

Diprenorphine is a highly potent and nonselective opioid receptor antagonist with subnanomolar affinity (7). Diprenorphine has been labeled as [6-*O*-*methyl*-^{11}C]diprenorphine ([^{11}C]DPN) (15, 16). [^{11}C]DPN is being developed as a positron emission tomography (PET) agent for the noninvasive study of opioid receptors in the brain. However, pharmacological studies in humans (17) and rats (18) have demonstrated minimal competition between the high-efficacy agonists and the non-subtype–selective antagonist radioligand [^{11}C]DPN, which limits the use of [^{11}C]DPN PET to monitor *in vivo* occupancy (20R). -4,5-α-Epoxy-17-methyl-3-hydroxy-6-methoxy-α,17-dimethyl-α-(2-phenylethyl)-6,14-ethenomorphinan-7-methanol (PEO) has been found to be a highly potent opioid receptor agonist (19). [6-*O*-*methyl*-^{11}C]PEO

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([11C]PEO) was evaluated for use with PET imaging of opioid receptors in rats, and the agent showed specific accumulation in the striatum, thalamus, and frontal cortex. For 18F-labeling, Riss et al. (20) prepared (20R)-4,5-α-epoxy-6-(2-[18F]fluoroethoxy)-3-hydroxy-α,17-dimethyl-α-(2-phenyleth-1-yl)-6,14-ethenomorphinan-7-methanol ([18F]FE-PEO) for use with PET imaging of opioid receptors in the brain.

Related Resource Links:

- Chapters in MICAD (opioid receptors)
- Gene information in NCBI (opioid receptors)
- Articles in Online Mendelian Inheritance in Man (OMIM) (opioid receptors)
- Clinical trials (opioid receptors)
- Drug information in FDA (opioid receptors)

Synthesis

[PubMed]

Riss et al. (20) performed synthesis of [18F]FE-PEO. The tosyloxyethyl-precursor was subjected to nucleophilic fluorination with K[18F]F/Kryptofix2.2.2 for 10 min at 90°C, with a yield of 28 ± 15% and a specific activity of 52–224 GBq/μmol (1.4–6.1 Ci/μmol) after purification with high-performance liquid chromatography. The radiochemical purity of [18F]FE-PEO was >97%, and the total synthesis time was ~90 min. [18F]FE-PEO was >95% intact in rat blood for 2 h at 37°C.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Riss et al. (20) reported *in vitro* binding assays using membranes of cloned human receptor stably expressed on Chinese hamster ovary (CHO) cells (μ and κ) and on HEK-293 cells (δ). FE-PEO exhibited inhibition constant (K_i) values of 0.4 ± 0.03 nM, 0.4 ± 0.02 nM, and 1.6 ± 0.2 nM for the μ ([3H]DPN), κ ([3H]DPN), and δ ([3H]naltrindole) opioid receptors, respectively. Therefore, PEO binds to μ and κ subtypes of opioid receptors with slightly higher affinity than the δ subtype.

In vitro [18F]FE-PEO autoradiographic imaging studies were performed on rat brain sections (20). [18F]FE-PEO bound heterogeneously to the brain sections (n = 24), with high accumulation of radioactivity in the endopiriform nucleus, accumbens, and cingulate cortex. Moderate radioactivity was found in the striatum. Pretreatment of the brain sections (n = 12) with the μ-opioid receptor–selective agonist DAMGO (1,000 nM) reduced radioactivity in the endopiriform nucleus, cingulate cortex, and striatum by 61%, 59%, and 42%, respectively. Pretreatment of the brain sections (n = 12) with the opioid receptor–nonselective antagonist naloxone (10 μM) reduced radioactivity in the endopiriform nucleus, cingulate cortex, and striatum by 63%, 65%, and 66%, respectively.

Animal Studies

Rodents

[PubMed]

Riss et al. (20) performed dynamic PET imaging studies for 180 min in rats (n = 3) injected with 20 MBq (0.54 mCi) [^{18}F]FE-PEO. High distribution volume (V_T) values were observed in the thalamus, striatum, and frontal cortex, with the lowest V_T value in the cerebellum. Kinetic modeling with the 2-tissue compartment model (2TCM) and Logan plot analysis provided better fits than 1TCM. The V_T values obtained with 2TCM correlated well with those from the Logan analysis (R^2 = 0.957; $P < 0.001$). The Logan V_T values were 5, 6, 8, and 1 for the thalamus, striatum, frontal cortex, and cerebellum, respectively. No blocking or *ex vivo* biodistribution studies were performed.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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