(20*R*)-4,5-α-Epoxy-17-methyl-3-hydroxy-6-[^{11}C]methoxy-α,17-dimethyl-α-(2-phenylethyl)-6,14-ethenomorphinan-7-methanol

[^{11}C]PEO

Kam Leung, PhD[1]

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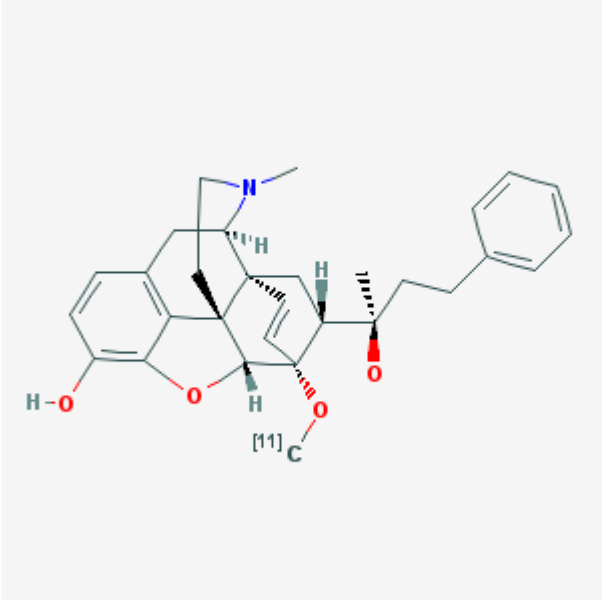
Chemical name:	(20*R*)-4,5-α-Epoxy-17-methyl-3-hydroxy-6-[^{11}C]methoxy-α,17-dimethyl-α-(2-phenylethyl)-6,14-ethenomorphinan-7-methanol	
Abbreviated name:	[^{11}C]PEO, [6-*O*-*methyl*-^{11}C]PEO	
Synonym:	[6-*O*-*methyl*-^{11}C] (20*R*)-Phenylethyl orvinol	
Agent category:	Compound	
Target:	Opioid receptors	
Target category:	Receptor	
Method of detection:	Positron emission tomography (PET)	
Source of signal \contrast:	^{11}C	
Activation:	No	
Studies:	• *In vitro* • Rodents	Click on the above structure for additional information in PubChem.

[1] National Center for Biotechnology Information, NLM, NIH; Email: MICAD@ncbi.nlm.nih.gov.

Corresponding author.

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 receptors consists of subtypes of receptors as suggested by pharmacological studies (2, 3). These receptors exhibit apparent specificity to both the central and peripheral nervous systems, and their presence is ubiquitous in these systems. The opioid receptors (G-protein–coupled, resulting in decrease in 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 non-invasive study of opioid receptors in the brain. However, pharmacological studies in humans (17) and rats (18) 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. (20*R*)-4,5-α-Epoxy-17-methyl-3-hydroxy-6-methoxy-α,17-dimethyl-α-(2-phenylethyl)-6,14-ethenomorphinan-7-methanol (PEO) was found to

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be a highly potent opioid receptor agonist (19). [6-*O-methyl*-^{11}C]PEO ([^{11}C]PEO) has been evaluated for PET imaging of opioid receptors in rats.

Related Resource Links:

- Chapters in MICAD

Synthesis

[PubMed]

Marton et al. (19) performed synthesis of [^{11}C]PEO by [^{11}C]-*O*-methylation of the trityl-protected precursor (2.85 μmol) with [^{11}C]methyl iodide for 5 min at 90°C. Final acidic deprotection of the product was performed in an automatic synthesis module. An average radiochemical yield was 57 ± 16% (n = 16, decay-corrected) with a total synthesis time of ~30 min. Average specific activity was 60 GBq/μmol (1.62 Ci/μmol) at end of synthesis with a radiochemical purity of >99%. The log P of [^{11}C]PEO was 2.36.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Marton et al. (19) reported *in vitro* binding assays using membranes of human cloned receptor stably expressed on Chinese hamster ovary (CHO) cells (μ and κ) and HEK-293 cells (δ). PEO had inhibition constant (K_i) values of 0.18, 0.12, and 5.1 nM for the μ ([^{3}H]DPN), κ ([^{3}H]DPN), and δ ([^{3}H]naltrindole) opioid receptors, respectively. Therefore, PEO binds to μ and κ, subtypes of opioid receptors with higher affinity than the δ subtype. The agonist efficacy of PEO was 105% relative to full effect of DAMGO (μ-agonist) and 113% relative to that of U69593 (κ-agonist).

Animal Studies

Rodents

[PubMed]

Marton et al. performed biodistribution studies in rats injected with 24 MBq (0.65 mCi) [^{11}C]PEO (19), which showed high accumulation of radioactivity in the striatum (0.89% injected dose/gram (ID/g)), thalamus (0.78% ID/g), and frontal cortex (0.76% ID/g) at 60 min after injection. Brain regions to cerebellum ratios increased over time with ratios of 2.95–3.78 at 20 min and of 4.47–5.23 at 60 min. Pretreatment with cyprodime (μ antagonist) decreased the radioactivity levels by 82–86% in the striatum, thalamus, and frontal cortex. Furthermore, pretreatment with naloxone (an opioid receptor antagonist) decreased the radioactivity levels by >95% in the striatum, thalamus, and frontal cortex. The fraction of unchanged [^{11}C]PEO in the brain determined with high-performance liquid chromatography was >92% at 40 min after injection. PET imaging showed high

standardized uptake value (SUV) in the basal ganglia (1.0) and frontal cortex (1.0) and low SUV in the cerebellum (0.2) at 60 min after injection.

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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