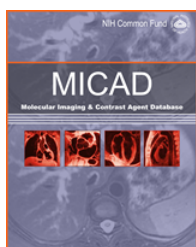




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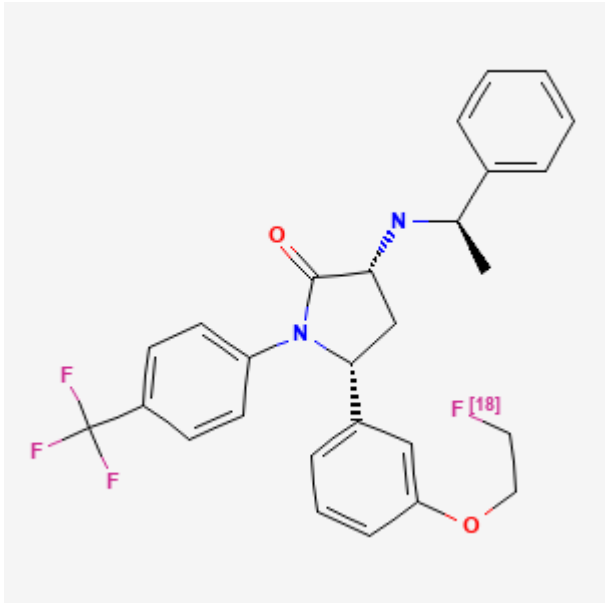


## (3*R*,5*R*)-5-(3-(2-[<sup>18</sup>F]Fluoroethoxy)phenyl)-3-((*R*)-1-phenyl-ethylamino)-1-(4-trifluoromethyl-phenyl)-pyrrolidin-2-one

[<sup>18</sup>F]FEPEP

Kam Leung, PhD<sup>1</sup> and Sean Donohue, PhD<sup>2</sup>

Created: August 6, 2010; Updated: October 7, 2010.

<b>Chemical name:</b>	(3 <i>R</i> ,5 <i>R</i> )-5-(3-(2-[ <sup>18</sup> F]Fluoroethoxy)-3-(( <i>R</i> )-1-phenyl-ethylamino)-1-(4-trifluoromethyl-phenyl)-pyrrolidin-2-one	
<b>Abbreviated name:</b>	[ <sup>18</sup> F]FEPEP	
<b>Synonym:</b>		
<b>Agent category:</b>	Compound	
<b>Target:</b>	Cannabinoid CB1 receptors	
<b>Target category:</b>	Receptor	
<b>Method of detection:</b>	Positron emission tomography (PET)	
<b>Source of signal:</b>	<sup>18</sup> F	
<b>Activation:</b>	No	Click on the above structure for additional information in <a href="#">PubChem</a> .
<b>Studies:</b>	<ul style="list-style-type: none"><li><i>In vitro</i></li><li>Rodents</li><li>Non-human primates</li></ul>	

## Background

[PubMed]

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There are two subtypes of cannabinoid receptors in mammalian tissues: CB1 and CB2 (1, 2). CB1 receptors are expressed abundantly in neuronal terminals in the central nervous system (CNS) and in some peripheral tissues to inhibit neurotransmitter release. CB1 receptors are found predominately in the striatum, hippocampus, substantia nigra, globus pallidus, and cerebellum. CB2 receptors are present mainly on immune cells to modulate cytokine release. Both receptor subtypes are coupled through  $G_{i/o}$  proteins to inhibit adenylate cyclase and to modulate potassium and calcium channels. CB1 receptors have been demonstrated to be involved in analgesia, regulation of food intake, and control of movement in normal subjects (3). Alteration of CB1 receptor function has been implicated in a number of human diseases such as depression, schizophrenia, and obesity (4-6).

$\Delta^9$ -Tetrahydrocannabinol (THC) is a major active cannabinoid found in marijuana and activates CB1 receptors (7). THC has a very high lipophilicity (log  $D_{7.4}$  value of 7), which causes imaging studies using radiolabeled THC to be unsuccessful because of slow entry into the brain and high nonspecific binding. However, a high lipophilicity is essential for binding to CB1 receptors, and an optimal lipophilicity (log  $D_{7.4}$  1–4) is required for crossing the blood–brain barrier (BBB). Existing radiolabeled ligands are mainly analogs of the antagonist rimonabant (SR141716A) and the agonist WIN 55,212-2, which also exhibit high nonspecific binding and lipophilicity, limiting their application in imaging (8). Therefore, there is a need to lower the lipophilicity of the CB1 radioligands with little effect on binding affinity and ability to cross the BBB (3R, 5R).

-5-(3-(2-[ $^{18}\text{F}$ ]Fluoroethoxy)phenyl)-3-((R)-1-phenyl-ethylamino)-1-(4-trifluoromethyl-phenyl)-pyrrolidin-2-one ([ $^{18}\text{F}$ ]FEPEP) is being evaluated for use as a CB1 tracer (9, 10).

## Related Resource Links:

- [Chapters in MICAD](#)
- [Gene information in NCBI \(CB1 receptors\)](#)
- [Articles in OMIM](#)
- [Clinical trials \(CB1\)](#)

## Synthesis

[PubMed]

Donohue et al. (9) reported the synthesis of [ $^{18}\text{F}$ ]FEPEP by reaction of the *O*-desmethyl precursor with [ $^{18}\text{F}$ ]-2-fluoroethyl bromide, which itself was prepared from [ $^{18}\text{F}$ ]fluoride ion and bromoethyl tosylate, for 5 min at 110°C. An average radiochemical yield was  $7.92 \pm 2.16\%$  ( $n = 6$ ) with a total synthesis time of ~120 min. Specific activities were  $>86 \text{ GBq}/\mu\text{mol}$  ( $2.32 \text{ Ci}/\mu\text{mol}$ ) at the end of synthesis with a radiochemical purity of  $>95\%$ . cLog  $D_{7.4}$  of FEPEP was calculated to be 5.8.

## In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Donohue et al. (9) reported that FEPEP inhibited functional [ $\gamma$ - $^{35}\text{S}$ ]GTP binding at the human recombinant CB1 receptor with high potency ( $K_b = 0.424 \pm 0.021 \text{ nM}$ ) compared to rimonabant ( $K_b = 0.698 \pm 0.200 \text{ nM}$ ). FEPEP was significantly less potent at the human recombinant CB2 receptor ( $K_b > 8,260 \text{ nM}$  for FEPEP and  $K_b > 1,977 \text{ nM}$  for rimonabant at CB2).

## Animal Studies

### Rodents

[PubMed]

Donohue et al. (9) performed *ex vivo* biodistribution studies in rats ( $n = 3$ ) at 0.25, 0.5, 1, 2, 4, and 8 h after injection of FEPEP (0.03 mg/kg) using mass spectroscopy for determination of concentration in the frontal cerebral cortex. Peak concentration (~22 ng/g tissue or 0.29% ID/g) was achieved with 15-30 min after injection. The level was reduced to 0.7 ng/g (0.01% ID/g) at 8 h. Pretreatment with rimonabant (3.0 mg/kg) (15 min before FEPEP injection) reduced the level by ~70% at 30 min after injection.

## Other Non-Primate Mammals

[PubMed]

No publication is currently available.

## Non-Human Primates

[PubMed]

Terry et al. (10) performed PET imaging in five rhesus monkeys with injection of [<sup>18</sup>F]FEPEP. Brain radioactivity increased to high levels (2.0-3.5 standardized uptake value (SUV) in the striatum) within 20 min after injection. Total distribution volume ( $V_T$ ) values determined using two-tissue compartment model were 21.6 and 25.0 mL/cm<sup>3</sup> for the striatum and pons, respectively. Pretreatment with rimonabant (3.0 mg/kg) 30 min before the tracer injection reduced the radioactivity by 71% in the striatum and ~47% in the pons. SUV in the mandible increased from ~0.4 at <10 min to ~1 at 180 min.

## Human Studies

[PubMed]

No publication is currently available.

## NIH Support

Intramural research program

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