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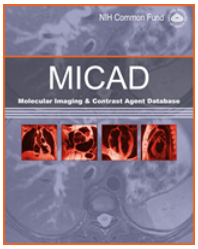

(3*R*,5*R*)-5-(3-[^{18}F]Fluoromethoxy-phenyl)-3-((*R*)-1-phenyl-ethylamino)-1-(4-trifluoromethyl-phenyl)-pyrrolidin-2-one

[^{18}F]FMPEP

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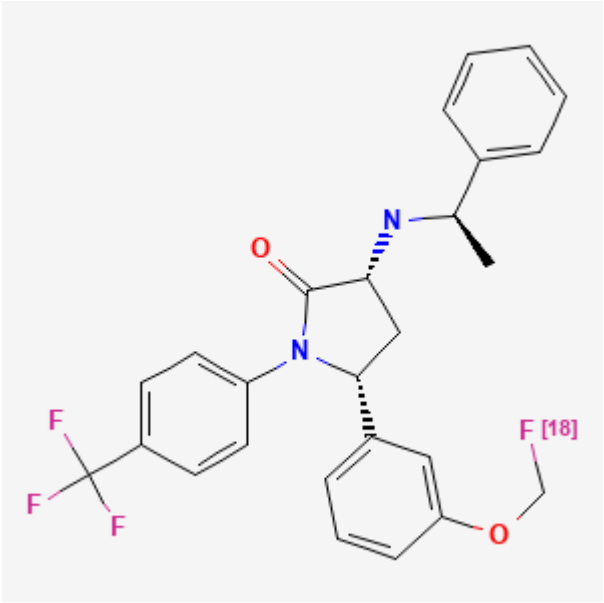
Chemical name:	(3*R*,5*R*)-5-(3-[^{18}F]Fluoromethoxy-phenyl)-3-((*R*)-1-phenyl-ethylamino)-1-(4-trifluoromethyl-phenyl)-pyrrolidin-2-one
Abbreviated name:	[^{18}F]FMPEP
Synonym:	
Agent category:	Compound
Target:	Cannabinoid CB1 receptors
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates



Click on the above structure for additional information in PubChem.

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). Alternation of CB1 receptor function has been implicated in a number of human diseases such as depression, schizophrenia, and obesity (4-6).

Δ9-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-[^{18}F]Fluoromethoxy-phenyl)-3-((*R*)-1-phenyl-ethylamino)-1-(4-trifluoromethyl-phenyl)-pyrrolidin-2-one ([^{18}F]FMPEP) 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. (11) reported the synthesis of [^{18}F]FMPEP by reaction of the *O*-desmethyl precursor with [^{18}F]fluoromethyl bromide for 10 min at 110°C. An average radiochemical yield was 5.92 ± 1.34% (n = 3) with a total synthesis time of ~120 min. Specific activities were >57 GBq/μmol (1.54 Ci/μmol,) at the end of synthesis with a radiochemical purity of >95%. cLog $D_{7.4}$ of FMPEP was calculated to be 5.7.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Donohue et al. (11) reported that FMPEP inhibited functional [γ-^{35}S]GTP binding at the human recombinant CB1 receptor with high potency (K_b=0.187 ± 0.018 nM) compared to rimonabant (K_b = 0.698 ±0.200 nM). FMPEP was significantly less potent at the human recombinant CB2 receptor (K_b = 669 ± 137 nM for FMPEP and K_b > 1,977 nM for rimonabant at CB2).

Animal Studies

Rodents

[PubMed]

Donohue et al. (11) performed *ex vivo* biodistribution studies in rats (n = 3) at 0.25, 0.5, 1, 2, 4, and 8 h after injection of FMPEP (0.03 mg/kg, i.v.) using mass spectroscopy for determination of concentration in the frontal cerebral cortex. Peak concentration (30 ng/g tissue or ~0.40% ID/g) was achieved with 15-60 min after injection. The level was reduced to 8 ng/g (~0.11% ID/g) at 8 h. Pretreatment with rimonabant (3 mg/kg, i.v.; 15 min before FMPEP injection) reduced the level by ~90% 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 [^{18}F]FMPEP. Brain radioactivity increased to high levels (5.0-6.5 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 63.5 and 37.1 mL/cm^3 for the striatum and pons, respectively. Pretreatment with rimonabant (3.0 mg/kg, i.v.) 30 min before the tracer injection reduced the radioactivity by 94% in the striatum and ~78% in the pons. SUV in the mandible increased from 1.4 at 10 min to 3.1 at 180 min.

Human Studies

[PubMed]

No publication is currently available.

NIH Support

Intramural research program

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