N-[2-(3-cyanophenyl)-3-(4-(2-[^{18}F]fluorethoxy)phenyl)-1-methylpropyl]-2-(5-methyl-2-pyridyloxy)-2-methylproponamide

[^{18}F]MK-9470

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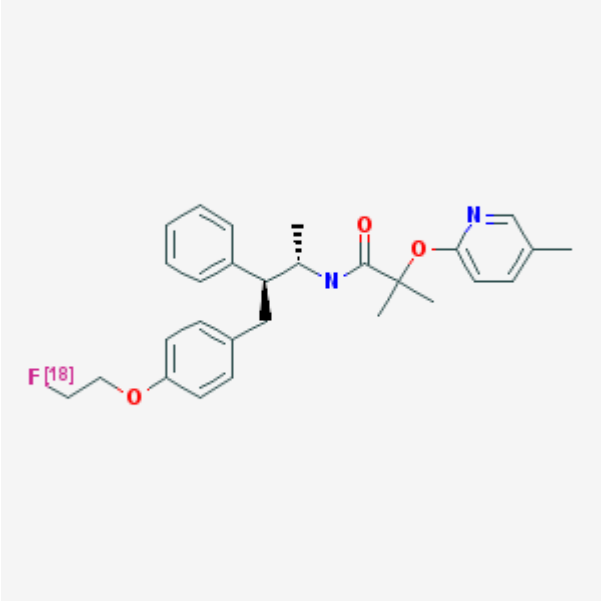
Chemical name:	*N*-[2-(3-cyanophenyl)-3-(4-(2-[^{18}F]fluorethoxy)phenyl)-1-methylpropyl]-2-(5-methyl-2-pyridyloxy)-2-methylproponamide
Abbreviated name:	[^{18}F]MK-9470
Synonym:	
Agent Category:	Compound
Target:	Cannabinoid CB1 receptor
Target Category:	Receptor-ligand binding
Method of detection:	Positron emission tomography (PET)
Source of Signal/ Contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Non-human primates • Humans



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Background

[PubMed]

Psychoactive cannabinoids derived from the marijuana plant (*Cannabis sativa*) have two known types of G-protein–coupled receptors that are linked to adenylate cyclase activity. The cannabinoid-1 receptor (CB1R) is distributed primarily in different parts of the human brain (1, 2), and the cannabinoid-2 receptor (CB2R) has been detected primarily in cells of the peripheral immune system (3). The CB1R is of particular interest because its endogenous lipid ligands are involved in the regulation of energy metabolism and body weight, and in drug and substance addiction in animals and humans (4-6). The motivation to feed oneself was reported to be regulated by CB1R ligands in rats, and CB1R knockout mice were shown to be lean and resistant to dietary obesity (7, 8). Consequently, SR-141716A, a reverse agonist (i.e., it binds to the same site on the receptor as agonist, but mediates an opposite effect), is now available in the European Union for the treatment of obesity (9).

Investigators have been interested in the *in vivo* imaging of CB1R and have developed ligands that can be used in conjunction with single-photon emission computed tomography (SPECT) and positron emission tomography (PET). The agents developed so far to study the CB1R show high, non-specific binding (a characteristic of lipophilic compounds), have a low penetration of the brain (a characteristic of highly polar or lipophilic compounds), display a low affinity for the receptor, and produce unsatisfactory images (9-11). Although compounds labeled with radioactive carbon (^{11}C) produced satisfactory results with PET, these compounds have a short half-life (20.4 min) (9, 12). In an effort to develop a PET ligand for CB1R with a longer half-life, *N*-[2-(3-cyanophenyl)-3-(4-(2-[^{18}F]fluoroethoxy)phenyl)-1-methylpropyl]-2-(5-methyl-2-pyridyloxy)-2-methylpropanamide ([^{18}F]MK-9470), a compound labeled with radioactive fluoride (^{18}F), was developed and evaluated in baboons and humans (9, 13, 14).

Synthesis

[PubMed]

A phenol precursor of [^{18}F]MK-9470 was used to produce the radiochemical as described by Burns et al. (9). Briefly, Kryptofix222 was added to an aqueous solution of ^{18}F, and the solution was dried under argon at 115°C. After cooling, a mixture of bromoethyltriflate in

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1,2-dichlorobenzene was added to the mixture, and the solution was heated to 115°C. This was followed by a flow of argon to distill the [^{18}F]fluoroethylbromide produced through a short ascarite column into a mixture of *N*-[2-(3-cyanophenyl)-3-(4-hydroxyphenyl)-1-methylpropyl]-2-(5-methyl-2-pyridyloxy)-2-methylpropanamide in dimethylformamide containing cesium carbonate (Cs_2CO_3) at room temperature. The mixture was subsequently transferred to a V-vial containing Cs_2CO_3 preheated to 100°C, and the solution was heated at this temperature for 5 min, diluted with water, and purified with reverse-phase high-performance liquid chromatography using a Waters RP C_{18} XTerra column. The appropriate fraction was concentrated and transferred under vacuum to another vial to obtain [^{18}F]MK-9470. The radiochemical yield of the reaction was reported to be 3.1% with a purity of >98% and a specific activity of 116 TBq/mmol (1,359 Ci/mmol). For use in humans, the collected fractions were sterile-filtered and diluted to 6.0% ethanol in sodium acetate buffer (pH 5.5). These preparations were reported to be >95% pure and always had a specific activity >10 GBq/μmol (0.27 Ci/μmol). The stability of [^{18}F]MK-9470 was not reported (9).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro binding studies were performed as described by Patel et al. (15). The 50% inhibitory concentration of [^{18}F]MK-9470 for humans was reported to be 0.7 nM (9).

Animal Studies

Rodents

[PubMed]

No references are currently available.

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

The biodistribution of [^{18}F]MK-9470 was investigated in rhesus monkey brains (9). The animals (n = 4) were given a bolus intravenous (IV) injection of the radiochemical, and imaging was started at the time of injection. PET scans showed that [^{18}F]MK-9470 accumulated primarily in gray matter regions of the monkey brain with significantly lower levels in the white matter. A chase study was also performed. The animals were given a bolus injection of unlabeled MK-9470 120 min after the [^{18}F]MK-9470 injection.

This was followed by a constant infusion of MK-0364, a structural analog of MK-9470, until steady-state plasma levels of ~1 μM were attained, and the scan was continued for 180 min after initial injection. Under these conditions a substantial decrease in binding of [^{18}F]MK-9470 was observed in the gray matter, dropping to levels close to those observed in the white matter. The reversibility of MK-9470-CB1R binding was also investigated. The monkeys were injected with [^{18}F]MK-9470 followed by administration of a bolus injection of unlabeled MK-9470 (9). This was reported to result in rapid washout of the label from the various gray matter regions of the monkey brain, indicating that the receptor binding of [^{18}F]MK-9470 was reversible.

Human Studies

[PubMed]

Burns et al. investigated the *in vivo* uptake of [^{18}F]MK-9470 in the brains of four healthy human volunteers (9). The individuals were given a bolus injection of the radiochemical, and imaging was initiated immediately. The label was observed to accumulate in all the gray matter areas of the brain, and it remained constant for 120–360 min after administration. The maximum uptake was observed in the striatum, frontal cortex, and posterior cingulated regions of the brain. The cerebellum had an intermediate level of uptake, and the lowest uptake was observed in the thalamus and the hippocampus.

Burns et al. also studied the occupancy of CB1R in the human brain (9). A total of nine healthy individuals received an oral dose of either MK-0364 (the doses were 1, 4, and 7.5 mg for 2, 3, and 2 volunteers, respectively) or placebo (n = 2 subjects) once a day for 14 days. Baseline scans were obtained before treatment and ~24 h after the last dose of placebo or MK-0364. The subjects were given a slow, bolus IV injection of [^{18}F]MK-9470, and imaging was performed. The measured CB1R occupancy values for the 1, 4, and 7.5 mg doses of MK-0364 in the brain were reported to be 11 ± 1%, 23 ± 7%, and 41 ± 12%, respectively (9).

The biodistribution and radiation dosimetry of [^{18}F]MK-9470 was studied in healthy human volunteers (14). Eight nonobese individuals were given a bolus injection of [^{18}F]MK-9470 and underwent whole-body PET/computed tomography scans for 6 h after the injection. Brain uptake of the radiopharmaceutical reached a plateau between 90 and 120 min after injection. Between 3.2% and 4.9% of the injected dose was detected in the brain. The radiochemical was reported to be excreted primarily through the hepatobiliary route. On average, the absorbed dose values for the gall bladder, upper large intestine, small intestine, and liver were 159, 98, 87, and 86 μGy/MBq, respectively. The mean effective dose was reported to be 22.8 ± 4.3 μSv/MBq (14).

In another study, the cerebral CB1R distribution and variation with age (volunteer age range, 18.5 to 68.7 years) and gender was investigated under *in vivo* conditions in 50 healthy volunteers (13). The [^{18}F]MK-9470 was administered through a slow IV injection, and the individuals were subjected to PET scans for 120 min. An increased binding of [^{18}F]MK-9470 with age was reported only for women ($P < 0.05$), and this was evident

mainly in the basal ganglia, lateral temporal cortex, and the limbic system, primarily in the hippocampus. The [^{18}F]MK-9470 binding was higher in men compared with women ($P < 0.001$) and was detected mainly in clusters of the limbic system and the cortico-striato-thalmic-cortical circuit.

Supplemental Information

[Disclaimers]

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