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NLM Citation: Leung K. 1-(2-Chlorophenyl)-*N*-[^{11}C]methyl-*N*-(1-methylpropyl)-3-isoquinoline carboxamide. 2006 Jan 6 [Updated 2012 Feb 22]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.
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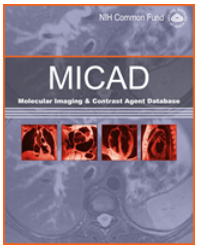

1-(2-Chlorophenyl)-*N*-[^{11}C]methyl-*N*-(1-methylpropyl)-3-isoquinoline carboxamide

[^{11}C]PK11195

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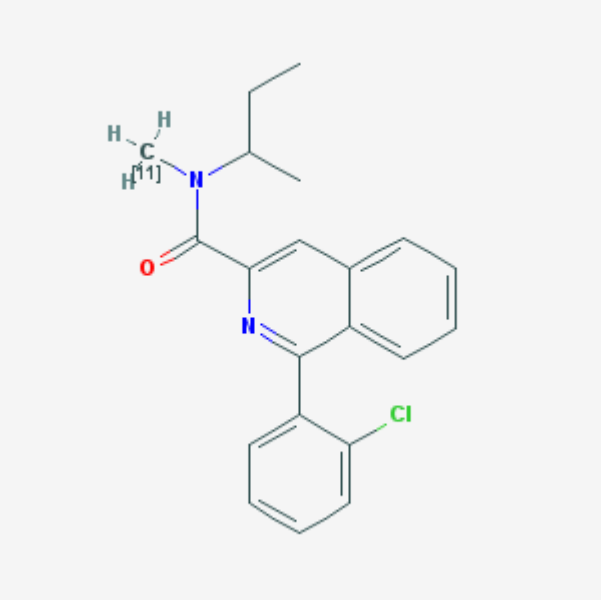
Created: January 6, 2006; Updated: February 22, 2012.

Chemical name:	1-(2-Chlorophenyl)-*N*-[^{11}C]methyl-*N*-(1-methylpropyl)-3-isoquinoline carboxamide
Abbreviated name:	
Synonym:	[^{11}C]PK11195
Agent category:	Compound
Target:	Peripheral-type benzodiazepine receptor
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Non-Human Primates • Humans



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Background

[PubMed]

Benzodiazepines, such as diazepam, are potent psychoactive drugs used for their sedative and anxiolytic properties (1, 2). There are two types of benzodiazepine receptors, which have been identified as the central and peripheral benzodiazepine receptors. The central benzodiazepine receptor (CBR) is found exclusively in the central nervous system on the membranes of neurons and is coupled to the γ-aminobutyric acid receptor/

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chloride channel (3). In contrast, the peripheral benzodiazepine receptor (PBR) is a mitochondrial protein found in brain and peripheral tissues (adrenal gland, heart, lung, kidney, and testis) (4, 5). The brain has lower levels of PBR than do the peripheral tissues. Both glial cells and macrophages contain high levels of PBR (6-8). Increased PBR expression after brain injury or neuroinflammation is associated with microglial activation, such as occurs with the neuronal damage accompanying several neurodegenerative diseases, including Alzheimer's disease, Wernicke's encephalopathy, multiple sclerosis, and epilepsy.

PBR has been studied *in vivo* by positron emission tomography (PET) using 1-(2-chlorophenyl)-*N*-[^{11}C]methyl-*N*-(1-methylpropyl)-3-isoquinoline carboxamide ([11C]PK11195), an isoquinoline carboxamide with specific PBR antagonistic activity (9). [^{11}C]PK11195 is being developed as a PET agent for the non-invasive study of microglia and macrophage activation in the brain, lung, and heart.

Related Resource Links:

- Chapters in MICAD (PBR)
- Gene information in NCBI (PBR)
- Articles in OMIM (PBR)
- Clinical trials (PBR)
- Drug information in FDA (PBR)

Synthesis

[PubMed]

In the report by Hashimoto et al. (10), [^{11}C]PK11195 was synthesized by alkylation of the desmethyl precursor with [^{11}C]methyl iodide, with subsequent separation by high-performance liquid chromatography. Radiochemical purity was greater than 99%, and total synthesis time was 23 min. The specific activity was 51.8 GBq/μmol (1.4 Ci/μmol) at the end of bombardment. No yield was reported.

Shah et al. (11) described the fully remotely controlled synthesis of [^{11}C]S-PK11195 from *S*-desmethyl-PK11195 and [^{11}C]R-PK11195 from *R*-desmethyl-PK11195 with [^{11}C]methyl iodide. The ^{11}C-labeled enantiomers were prepared with a reproducible radiochemical yield of 80% (decay-corrected) based on [^{11}C]methyl iodide. Total synthesis time was 45 min. Radiochemical purity was >99% with specific activities varying between 20 and 96 GBq/μmol (0.54 and 2.6 Ci/μmol) at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro autoradiographic studies of [^{3}H]PK11195 binding produced K_d values of 20.4 ± 1.3, 14.3 ± 2.1, and 3.9 ± 0.4 nM for human high-grade glioma, low-grade glioma, and cortex, respectively (12). The PBR B_{max} values were 12.4 ± 0.7, 4.0 ± 2.0, and 0.79 ± 0.09 pmol/mg protein for human high-grade glioma, low-grade glioma, and cortex, respectively. The high-grade glioma showed a B_{max} 14.5 times higher than that in the cortex. There was also a significant difference between the K_d measured in the tumors and that in normal cortex. Le Fur et al. (9) reported that PBR binding sites in rat myocardial membranes were specific and saturable with a K_d of 1.4 nM and a B_{max} of 2.25 pmol/mg protein.

Animal Studies

Rodents

[PubMed]

Biodistribution studies in normal mice showed high accumulation of radioactivity in the adrenal gland (61% injected dose (ID)/g), followed by the lung (32% ID/g), kidney (20% ID/g), heart (20% ID/g), and liver (6% ID/g) at 5 min after injection of [^{3}H]PK11195 (10). The level of radioactivity was low (2% ID/g) in the brain and blood. The radioactivity decreased rapidly in the heart, lung, and brain from 5 to 20 min, whereas it increased in the spleen, kidney, and adrenal gland. Coadiministration of unlabeled PK11195 decreased the accumulation in the heart and lung in a dose-dependent manner but had no effect in the blood and brain at 5 min post injection. Almost all of the radioactivity in the heart, lung, and brain was intact [^{3}H]PK11195 at 20 min post injection.

Shah et al. (11) investigated the enantiomeric and racemic accumulation of [^{11}C]PK11195 in the brains of normal rats and rats with focal cortical lesions (13). They observed no significant differences in the uptakes of the enantiomers in regions lacking PBR binding sites. However, the *R*-enantiomer was retained to a significantly greater extent than the *S*-enantiomer in olfactory bulbs/tubercles, which contain some PBR binding sites, as well as in 9-day-old focal cortical lesions, which are greatly enriched in PBR binding sites associated with macrophage infiltration (14). The observed differences are consistent with the approximately 2-fold greater affinity of the *R*-enantiomer for PBR binding sites reported *in vitro* (9, 15). Subsequently, most PET studies have used the *R*-enantiomer.

Other Non-Primate Mammals

[PubMed]

Charbonneau et al. (16) obtained PET images of the lung and heart in dogs after injection of [^{11}C]PK11195. The lung had a higher accumulation than the heart at 1 min post injection, but after 5 min, the radioactivity in the myocardium was higher than in the lung. The radioactivity in the heart remained constant, whereas that in the lung was undetectable at 30 min. The B_{max} for the myocardium was estimated to be 6 nmol/cm^{3}. Injection of excess unlabeled PK11195 (568 nmol (0.2 mg)/kg) 30 min after [^{11}C]PK11195 (2.2 nmol/kg) led to a rapid decrease (68%) in the radioactivity in the myocardium. Clonazepam (a CBR agonist, 1 mg/kg) and RO 15-1788 (a CBR antagonist, 1 mg/kg) did not inhibit binding of [^{11}C]PK11195 to PBRs. On the other hand, diazepam (a peripheral and central agonist, 1 mg/kg) was less effective than PK11195.

Jones et al. (6) assessed the use of *R*-[^{11}C]PK11195 PET to monitor macrophage disposition after particulate challenge to the lung. Repeated PET scanning was performed over 4 weeks after injection of *R*-[^{11}C]PK11195 in rabbits treated with 5-ìm particles of either amorphous ($aSiO_2$) or microcrystalline ($xSiO_2$) silica implanted in the right upper pulmonary lobes. Implantation of $aSiO_2$ led to increased macrophages, few neutrophils, and no fibrosis, whereas $xSiO_2$ increased macrophages and neutrophils and caused fibrosis. After both stimuli, radioactivity localized to the challenged area and correlated with macrophage numbers. Radioactivity in challenged/control lung regions peaked at 4 days for $aSiO_2$ (2.88; $n = 2$) and 6 days for $xSiO_2$ (4.62; $n = 2$). The signal remained elevated throughout the study ($aSiO_2$, 2.33 ± 0.77, $n = 14$; $xSiO_2$, 3.99 ± 1.29, $n = 9$), as did macrophage accumulation. Specific binding of *R*-[^{11}C]PK11195 in macrophages was demonstrated by autoradiography in lavage fluid from an inflamed rabbit knee-joint model. These data suggest that PET scanning after [^{11}C]PK11195 provides a noninvasive method for the study of macrophage accumulation in the lung.

Non-Human Primates

[PubMed]

Using PET, Petit-Taboue et al. (17) obtained serial brain scans in 3 baboons after injection of [^{11}C]PK11195 (37 MBq/kg, or 1 mCi/kg) with or without unlabeled PK11195. The accumulation of radioactivity (0.005-0.008% ID/ml) in the brain peaked at 3-5 min, remained almost constant at this level up to 6-8 min, and then slowly decreased for the final 60 min of study. Both co-injection of and pretreatment (8 min after injection of the tracer) with unlabeled PK11195 (1 mg/kg) initially enhanced the accumulation (0.012-0.030% ID/ml) in the brain, but also markedly enhanced the washout rate compared with controls.

Sette et al. (18) studied the time course of changes, as assessed by PET, in brain uptake *in vivo* of ^{11}C-labeled PK11195 and flumazenil (a CBR antagonist) as indirect and direct markers of neuronal loss, respectively, after focal cerebral ischemia in 10 anesthetized baboons between days 1 and 91 after unilateral middle cerebral artery occlusion. The studies consisted of successive assessments, in the same PET session, of [^{11}C]PK11195, [^{11}C]flumazenil, cerebral blood flow, and oxygen consumption. Late computed tomographic scans were obtained to map the approximate contours of infarction and to define a concentric peri-infarct area. There was a significant time-dependent increase in [^{11}C]PK11195 accumulation in the peri-infarcted area, which reached its maximum at 20 to 40 days after occlusion, presumably attributable to the presence of glial cells/macrophages. In contrast, there was a time- and perfusion-independent significant decrease in [^{11}C]flumazenil accumulation in the infarcted area, which remained stable from day 2 onward, representing synaptic damage. Both accumulations were blocked by saturating doses of cold ligands, which confirmed that these changes represented alterations in specific binding.

Human Studies

[PubMed]

Charbonneau et al. (16) reported on PET studies in 7 healthy male volunteers after injection of 259-777 MBq (7-21 mCi) of [^{11}C]PK11195. Accumulation in the lung was high up to 10 min post injection. The radioactivity in the myocardium became detectable at 2 min. The radioactivity in the heart decreased for 20 min and remained constant at 75 min. Injection of excess unlabeled PK11195 (650 nmol/kg) 30 min after [^{11}C]PK11195 (0.94 nmol/kg) led to a rapid decrease (48%) in the radioactivity in the myocardium. In a different study (19), formation of plasma metabolites from [^{11}C]PK11195 was analyzed in 2 healthy controls and 3 stroke patients. At 5, 20, and 35 min after injection of [^{11}C]PK11195 (370 MBq or 1 mCi), 5%, 22% and 32% of the plasma activity, respectively, was attributable to at least two more polar metabolites. However, no metabolites were found in the hearts, lungs, and brains of mice that received injections of [^{11}C]PK11195 (10).

[^{11}C]PK11195 or *R*-[^{11}C]PK11195 PET has been used mainly for assessing microglia/macrophage activation as an indication of neuronal and tissue damage in various neurodegenerative disorders (such as Alzheimer's disease, Wernicke's encephalopathy, multiple sclerosis, lateral sclerosis, Huntington's disease, HIV-associated dementia, and epilepsy), pulmonary diseases, and ischemic stroke [PubMed]. Most of these human studies used a reference tissue (cerebellum or other cortical regions) to measure the accumulation of radioactivity. Kropholler et al. (20) reported that a kinetic plasma (metabolite-corrected) input with a reversible two-tissue compartment model was best for analyzing *R*-[^{11}C]PK11195 kinetics in PET brain studies of 13 human subjects.

Hirvonen et al. (21) performed dynamic whole-body scans after injection of *R*-[^{11}C]PK11195 in five healthy subjects for radiation dosimetry measurement. The mean effective dose was 4.8 μSv/MBq and the highest equivalent organ doses were recorded in the kidneys (14.0 μSv/MBq), spleen (12.5 μSv/MBq) and small intestine (12.2 μSv/MBq).

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