[^{11}C]*N*-Methyl-*N*-phenyl-[2-(4-chlorophenyl)-6,8-dichloroimidazo[1,2-*a*]pyridin-3-yl]acetamide

[^{11}C]PBR7

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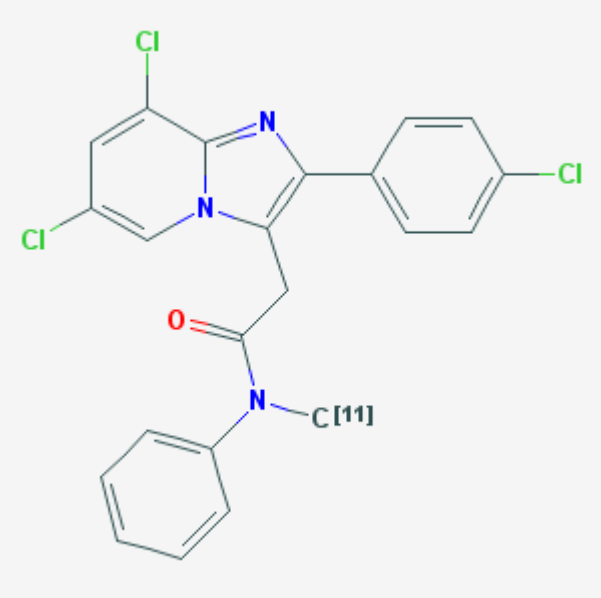
Created: October 8, 2008; Updated: December 2, 2008.

Chemical name:	[^{11}C]*N*-Methyl-*N*-phenyl-[2-(4-chlorophenyl)-6,8-dichloroimidazo[1,2-*a*]pyridin-3-yl]acetamide
Abbreviated name:	[^{11}C]PBR7
Synonym:	
Agent category:	Compound
Target:	Peripheral-type benzodiazepine receptor (PBR), also known as translocator protein (TSPO)
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

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Background

[PubMed]

Benzodiazepines are potent psychoactive drugs used for their sedative and anxiolytic properties (1, 2). There are two types of benzodiazepine receptors, which have been designated as the central benzodiazepine receptors (CBRs) and peripheral benzodiazepine receptors (PBRs). The CBR is found exclusively in the central nervous system on the membranes of neurons and is coupled to the γ-aminobutyric acid receptor/chloride channel (3). In contrast, the PBR is a mitochondrial protein found in brain and peripheral tissues (adrenal gland, heart, lung, kidney, and testis) (4). The brain has lower levels of PBRs than do peripheral tissues. Both glial cells and macrophages contain high levels of PBRs (5-7). Increased PBR expression after brain injury or neuroinflammation is associated with microglial activation, such as occurs with the neuronal damage that accompanies several neurodegenerative diseases, including Alzheimer's disease, Wernicke's encephalopathy, multiple sclerosis, and epilepsy.

PBRs have been studied *in vivo* with positron emission tomography (PET) using 1-(2-chlorophenyl)-*N*-[^{11}C]methyl-*N*-(1-methylpropyl)-3-isoquinoline carboxamide ([^{11}C]PK11195), an isoquinoline carboxamide with specific PBR-antagonistic activity. [^{11}C]PK11195 as been developed as a PET agent for non-invasive studies of microglia and macrophage activation in the brain, lung, and heart. However, accumulation of this tracer in the brain is limited. *N*-(2,5-Dimethoxybenzyl)-*N*-(5-fluoro-2-phenoxyphenyl)acetamide (DAA1106) has been found to be a selective agonist for studying PBRs in the central nervous system (8, 9). DAA1106 was reported to have a higher affinity for PBRs in mitochondrial fractions of rat and monkey brains than did PK11195 (8, 9). Therefore, both tracers are able to cross the normal cell membrane to reach the mitochondrial receptor sites. *N*-(5-Fluoro-2-phenoxyphenyl)-*N*-(2-[^{18}F]fluoroethyl-5-methoxybenzyl)acetamide ([^{18}F]FEDAA1106) and [^{11}C]DAA1106 have been developed as potential PET ligands with highly selective and specific binding to PBR. [^{11}C]*N*-Methyl-*N*-phenyl-[2-(4-chlorophenyl)-6,8-dichloroimidazo[1,2-*a*]pyridin-3-yl]acetamide ([^{11}C]PBR7, a partial agonist) with an imidazopyridine acetamide structure has been developed for imaging PBR (10, 11).

Related Resource Links:

- Chapters in MICAD (PBR)
- Gene information in NCBI (PBR)

NLM Citation: Leung K. [^{11}C]*N*-Methyl-*N*-phenyl-[2-(4-chlorophenyl)-6,8-dichloroimidazo[1,2-*a*]pyridin-3-yl]acetamide. 2008 Oct 8 [Updated 2008 Dec 2]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

- Articles in OMIM (PBR)
- Clinical trials (PBR)
- Drug information in FDA (PBR)

Synthesis

[PubMed]

Sekimata et al. (10) reported the synthesis of [^{11}C]PBR7 by ^{11}C-methylation of the *N*-desmethyl precursor with [^{11}C]iodomethane in the presence of NaH in dimethylformamide for 3 min at 80°C. [^{11}C]PBR7 was purified with high-performance liquid chromatography. The specific activity was 20–150 GBq/μmol (0.54–4.05 Ci/μmol) with >98% radiochemical purity and a radiochemical yield of 36% (decay-corrected) at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro receptor binding studies showed that PBR7 had K_i values of 0.2 nM for PBR and >6,000 nM for CBR (11). PBR7 has a moderate lipophilicity (log P = 2.2). PK11195 exhibited a K_i value of 4.3 nM.

Animal Studies

Rodents

[PubMed]

Sekimata et al. (10) reported biodistribution studies of [^{11}C]PBR7 in mice (n = 4 mice/group) that showed high accumulation of radioactivity in the lung (~22% injected dose (ID)/g), followed by the heart (~12% ID/g), spleen (~10% ID/g), kidney (10% ID/g), and liver (~7% ID/g) at 30 min after injection of 4 MBq (0.11 mCi) [^{11}C]PBR7. Radioactivity levels peaked in most tissues during the first minute and subsequently declined to constant levels. In the brain, [^{11}C]PBR7 exhibited the highest accumulation (~1.5% ID/g) in the cerebellum and olfactory bulbs at 60 min after injection, whereas the lowest accumulation was found in the thalamus and cortex (~0.8% ID/g). Co-injection of PK11195 and PBR7 (1 mg/kg) significantly decreased the accumulation ($P < 0.05$) in the heart, kidney, spleen, pancreas, and lung as well as in various brain regions at 30 min after injection. On the other hand, flumazenil (CBR antagonist) exhibited no inhibition in any examined tissue. Approximately 83% and >95% of radioactivity in the plasma and brain, respectively, was intact [^{11}C]PBR7 at 30 min after injection.

Other Non-Primate Mammals

[PubMed]

No publications are currently available.

Non-Human Primates

[PubMed]

No publications are currently available.

Human Studies

[Pub Med]

No publications are currently available.

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