2-(6-Chloro-2-(4-(3-[^{18}F]fluoropropoxy)phenyl)imidazo[1,2-*a*]pyridin-3-yl)-*N*,*N*-diethylacetamide

[^{18}F]PBR111

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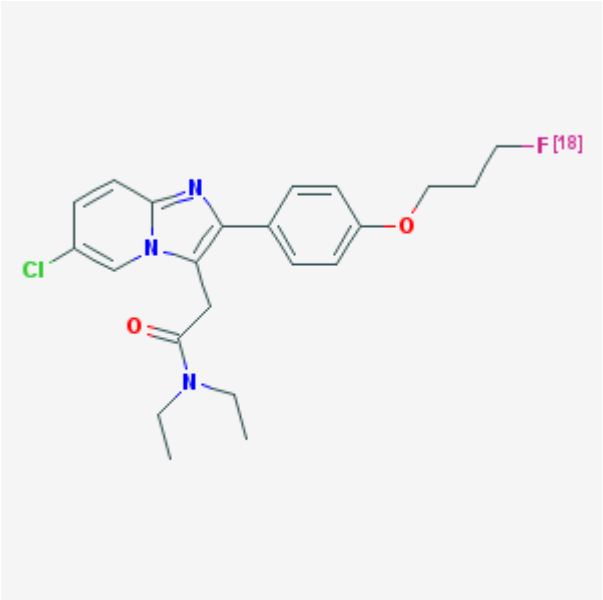
Chemical name:	2-(6-Chloro-2-(4-(3-[^{18}F]fluoropropoxy)phenyl)imidazo[1,2-*a*]pyridin-3-yl)-*N*,*N*-diethylacetamide
Abbreviated name:	[^{18}F]PBR111
Synonym:	
Agent category:	Compound
Target:	Peripheral-type benzodiazepine receptor (PBR), also known as translocator protein (TSPO)
Target category:	Receptor
Method of detection:	PET
Source of signal:	^{18}F
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 central benzodiazepine receptors (CBR) and peripheral benzodiazepine receptors (PBR). 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 PBR than do peripheral tissues. Both glial cells and macrophages contain high levels of PBR (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 has 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) was 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 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 (10, 11). 2-(6-Chloro-2-(4-(3-[^{18}F]fluoropropoxy)phenyl)imidazo[1,2-*a*]pyridin-3-yl)-*N*,*N*-diethylacetamide ([^{18}F]PBR111) has been evaluated for imaging PBR (12).

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]

Fookes et al. (12) reported the synthesis of [^{18}F]PBR111 by nucleophilic fluorination of the p-toluenesulfonyl precursor with [^{18}F]KF/Kryptofix 2.2.2./K_2CO_3 at 100°C for 5 min and purified with high-performance liquid chromatography with a radiochemical purity of >95%. The specific activity was 110–150 GBq/μmol (2.97–4.05 Ci/μmol) at the end of synthesis with 56–75% radiochemical yield. The total preparation time was ~60 min.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro [^{3}H]PK11195 PBR-binding studies using PBR111 in rat kidney and brain membranes showed inhibition constant (K_i) values of 3.7 ± 0.4 nM and 800 ± 120 nM for PBR and CBR, respectively (12).

Animal Studies

Rodents

[PubMed]

Fookes et al. (12) reported biodistribution studies of [^{18}F]PBR111 in rats that showed high accumulation of radioactivity in the adrenal gland (11.8% injected dose (ID)/g), followed by the heart (8.3% ID/g), lung (7.7% ID/g), spleen (6.0% ID/g), and kidney (5% ID/g) at 30 min after injection of [^{18}F]PBR111. The level of radioactivity was low in the brain (0.2% ID/g), blood (0.3% ID/g), and the olfactory bulbs (0.6% ID/g). In the femur, the accumulation of radioactivity was 0.4% ID/g at 15 min and 2.2% ID/g at 4 h. Pretreatment with 1 mg/kg PK11195 or 1 mg/kg PBR111 decreased the accumulation in the heart, kidney, and spleen by >75% but had no effect in the adrenal gland, blood, and brain at 60 min after injection. There was a decrease of ~50% in the olfactory bulbs in the brain. Pretreatment with flumazenil (a CBR ligand) exhibited little effect on the [^{18}F]PBR111 radioactivity level in the heart, kidney, spleen, and olfactory bulbs. The fraction of unchanged [^{18}F]PBR111 at 15 min after injection was 10% in the blood plasma, 80% in the brain cortex, and 95% in the olfactory bulbs.

Van Camp et al. (13) performed PET imaging in rats with acute neuroinflammation. PET imaging showed an increased accumulation of [^{18}F]PBR111 in the lesion as compared to the contralateral side as early as 6 min after injection. Administration of an excess of PK11195 and PBR111 (20 min after [^{18}F]PBR111 injection) induced a rapid and complete displacement of [^{18}F]PBR111 binding from the lesion. Modeling of the PET data using the simplified reference tissue model showed significant ($P < 0.001$) increase in binding potential (BP) of [^{18}F]PBR111 (2.5 ± 0.7) in comparison to [^{11}C]PK11195 (1.1 ± 0.2). Only intact [^{18}F]PBR111 was detected in the brain up to 60 min after injection.

Other Non-Primate Mammals

[PubMed]

No publications are currently available.

Non-Human Primates

[PubMed]

No publications are currently available.

Human Studies

[PubMed]

No publications are currently available.

NIH Support

Intramural research program

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