3-Fluoromethyl-*N*-[^{11}C]methyl-4-phenyl-*N*-(phenylmethyl)quinoline-2-carboxamide

[^{11}C]PBR6a

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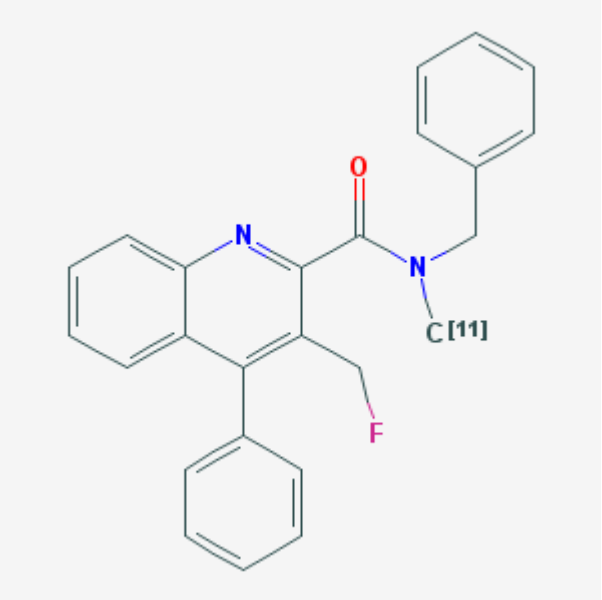
Chemical name:	3-Fluoromethyl-*N*-[^{11}C]methyl-4-phenyl-*N*-(phenylmethyl)quinoline-2-carboxamide
Abbreviated name:	[^{11}C]PBR6a
Synonym:	
Agent category:	Compound
Target:	Peripheral-type benzodiazepine receptor (PBR), also known as translocator protein (TSPO)
Target category:	Receptor
Method of detection:	PET
Source of signal:	^{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 receptor (CBR) and the peripheral benzodiazepine receptor (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 the 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* by 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 is being 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 did PK11195 (8, 9). Therefore, both compounds 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 probes with highly selective and specific binding to PBR. In this chapter, 3-Fluoromethyl-*N*-[^{11}C]methyl-4-phenyl-*N*-(phenylmethyl)quinoline-2-carboxamide ([^{11}C]PBR6a) with a 2-quinolinecarboxamide structure has been developed to image PBR in the peripheral tissues, such as the heart, lung, kidney and spleen.

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 Cappelli et al. (10), [^{11}C]PBR6a was synthesized by ^{11}C-methylation of the *N*-desmethyl precursor with ^{11}C-labeled iodomethane in the presence of tetrabutylammonium hydroxide. [^{11}C]PBR6a was purified by high-performance liquid chromatography with a 35–40% decay-corrected radiochemical yield. The specific activity was 55.5 GBq/μmol (1.5 Ci/μmol) at the end of synthesis with >99% radiochemical purity. Total synthesis time was 35 min from the end of bombardment.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro [^{3}H]PK11195 PBR-binding to rat cortical membranes showed that BR6a had an inhibition concentration (IC_{50}) value of 0.11 ± 0.02 nM (10). BR6a was ~20 times more potent than PK11195 (IC_{50} = 2.5 ± 0.4 nM).

Animal Studies

Rodents

[PubMed]

Cappelli et al. (10) reported biodistribution studies of [^{11}C]PBR6a in rats that showed high accumulation of radioactivity in the lung (1.023% injected dose (ID)/g), followed by the adrenal gland (0.523% ID/g), heart (0.489% ID/g), spleen (0.487% ID/g), and kidney (0.358% ID/g) at 30 min after injection of [^{11}C]PBR6a. The level of radioactivity was low in the brain (0.039% ID/g) and blood (0.020% ID/g). Pretreatment with PK11195 (5 mg/kg) decreased the accumulation in the heart, kidney, spleen, stomach, and lung by >74% but had no effect in the adrenal gland, blood, and brain at 30 min after injection. PET imaging in mice confirmed high levels of radioactivity in the lung, kidney, liver, heart, and spleen at 10–20 min after injection. Co-injection of PK11195 clearly reduced radioactivity in the lung, heart, and spleen, but not in the kidney or liver.

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.

References

1. Mohler H., Okada T. *Benzodiazepine receptor: demonstration in the central nervous system.* Science. 1977;198(4319):849–51. PubMed PMID: 918669.
2. Hunkeler W., Mohler H., Pieri L., Polc P., Bonetti E.P., Cumin R., Schaffner R., Haefely W. *Selective antagonists of benzodiazepines.* Nature. 1981;290(5806):514–6. PubMed PMID: 6261143.
3. Olsen R.W., Tobin A.J. *Molecular biology of GABAA receptors.* Faseb J. 1990;4(5): 1469–80. PubMed PMID: 2155149.
4. Anholt R.R., Pedersen P.L., De Souza E.B., Snyder S.H. *The peripheral-type benzodiazepine receptor. Localization to the mitochondrial outer membrane.* J Biol Chem. 1986;261(2):576–83. PubMed PMID: 3001071.
5. Jones H.A., Valind S.O., Clark I.C., Bolden G.E., Krausz T., Schofield J.B., Boobis A.R., Haslett C. *Kinetics of lung macrophages monitored in vivo following particulate challenge in rabbits.* Toxicol Appl Pharmacol. 2002;183(1):46–54. PubMed PMID: 12217641.
6. Kuhlmann A.C., Guilarte T.R. *Cellular and subcellular localization of peripheral benzodiazepine receptors after trimethyltin neurotoxicity.* J Neurochem. 2000;74(4): 1694–704. PubMed PMID: 10737628.
7. Zavala F., Lenfant M. *Benzodiazepines and PK 11195 exert immunomodulating activities by binding on a specific receptor on macrophages.* Ann N Y Acad Sci. 1987;496:240–9. PubMed PMID: 2886095.
8. Okuyama S., Chaki S., Yoshikawa R., Ogawa S., Suzuki Y., Okubo T., Nakazato A., Nagamine M., Tomisawa K. *Neuropharmacological profile of peripheral benzodiazepine receptor agonists, DAA1097 and DAA1106.* Life Sci. 1999;64(16): 1455–64. PubMed PMID: 10321725.
9. Chaki S., Funakoshi T., Yoshikawa R., Okuyama S., Okubo T., Nakazato A., Nagamine M., Tomisawa K. *Binding characteristics of [3H]DAA1106, a novel and selective ligand for peripheral benzodiazepine receptors.* Eur J Pharmacol. 1999;371(2-3):197–204. PubMed PMID: 10357257.
10. Cappelli A., Matarrese M., Moresco R.M., Valenti S., Anzini M., Vomero S., Turolla E.A., Belloli S., Simonelli P., Filannino M.A., Lecchi M., Fazio F. *Synthesis, labeling, and biological evaluation of halogenated 2-quinolinecarboxamides as potential radioligands for the visualization of peripheral benzodiazepine receptors.* Bioorg Med Chem. 2006;14(12):4055–66. PubMed PMID: 16495062.