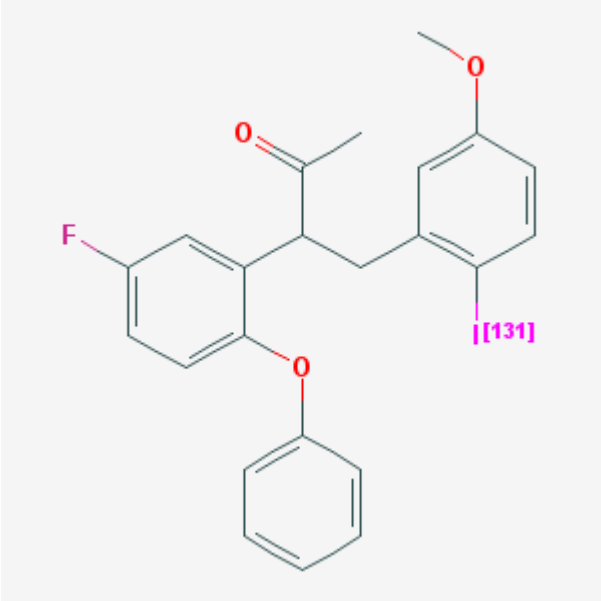
N-(5-Fluoro-2-phenoxyphenyl)-*N*-(2-[^{131}I]iodo-5-methoxybenzyl)acetamide

[^{131}I]PBR3a

Kam Leung, PhD[1]

Created: August 6, 2007; Updated: September 12, 2007.

Chemical name:	*N*-(5-Fluoro-2-phenoxyphenyl)-*N*-(2-[^{131}I]iodo-5-methoxybenzyl)acetamide
Abbreviated name:	[^{131}I]PBR3a
Synonym:	
Agent category:	Compound
Target:	Peripheral-type benzodiazepine receptor (PBR), also known as translocator protein (TSPO)
Target category:	Receptor binding
Method of detection:	Single-photon emission computed tomography (SPECT), gamma planar imaging
Source of signal:	^{131}I
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

[1] National Center for Biotechnology Information, NLM, NIH; Email: MICAD@ncbi.nlm.nih.gov.

Corresponding author.

NLM Citation: Leung K. *N*-(5-Fluoro-2-phenoxyphenyl)-*N*-(2-[^{131}I]iodo-5-methoxybenzyl)acetamide . 2007 Aug 6 [Updated 2007 Sep 12]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

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 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 probes with highly selective and specific binding to PBR. *N*-(5-Fluoro-2-phenoxyphenyl)-*N*-(2-[^{131}I]iodo-5-methoxybenzyl)acetamide ([^{131}I]PBR3a), a DAA1106 analog, has been developed for single-photon emission computed tomography (SPECT) imaging of PBR in the brain.

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 Zhang et al. (10), [^{131}I]PBR3a was synthesized by ^{131}I-iodination of the tributylstannyl precursor with [^{131}I]NaI in the presence of H_2O_2 in acetic acid. [^{131}I]PBR3a was purified with high-performance liquid chromatography for a radiochemical yield of >80%. The specific activity was >30 GBq/μmol (0.81 Ci/μmol) at the end of synthesis with >98% radiochemical purity.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro quantitative autoradiography with [^{11}C]DA1106 on rat brain sections showed that PBR3a had an inhibition concentration (IC_{50}) value of 7.8 ± 0.4 nM, which is slightly lower than DA1106 (IC_{50} = 1.6 ± 0.1 nM) and similar to PK11195 (IC_{50} = 8.3 ± 1.2 nM) (10). PBR3a has an IC_{50} value of >10,000 nM on CBR as measured by ^{11}C-labeled flumazenil binding in the rat brain sections. PBR3a has a logD value of 4.42.

Animal Studies

Rodents

[PubMed]

Zhang et al. (10) reported biodistribution studies of [^{131}I]PBR3a in mouse brains (n = 3 per group) that showed rapid accumulation of radioactivity with 1.06% injected dose per gram (ID/g) at 1 min, 1.36% ID/g at 5 min, 1.69% ID/g at 15 min, 1.28% ID/g at 30 min, and 0.75% ID/g at 60 min. Regional brain accumulation showed that the highest radioactivity level was in the olfactory bulb (3.06% ID/g), followed by the cerebellum (2.32% ID/g), hypothalamus (0.97% ID/g), cortex (0.84% ID/g), hippocampus (0.75% ID/g), striatum (0.69% ID/g), and thalamus (0.48% ID/g) at 15 min. The level of radioactivity in the blood was 1.11% ID/g at 15 min and 0.25% ID/g at 60 min. At 30 min after injection, 90–94% of total brain radioactivity was intact [^{131}I]PBR3a. Co-injection of [^{131}I]PBR3a with DAA1106 or PK11195 (1 mg/kg) decreased the accumulation in the olfactory bulb and cerebellum by 60–67% at 30 min after injection and to a lesser extent (10–30%) in the hypothalamus, cortex, hippocampus, striatum, and thalamus. *Ex vivo* autoradiography studies found the highest level of radioactivity in the choroid plexus in addition to the olfactory bulb and cerebellum at 30 min after injection. Co-injection of PK11195 clearly reduced radioactivity in the choroid plexus and olfactory bulb by 57% and in the cerebellum by 37%.

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. Zhang M.R., Kumata K., Maeda J., Haradahira T., Noguchi J., Suhara T., Halldin C., Suzuki K. *N-(5-Fluoro-2-phenoxyphenyl)-N-(2-[(131)I]iodo-5-me thoxybenzyl)acetamide: a potent iodinated radioligand for the peripheral-type*

benzodiazepine receptor in brain. J Med Chem. 2007;50(4):848–55. PubMed PMID: 17300167.