N-(6-[^{18}F]Fluoro-4-phenoxypyridin-3-yl)-N-(2-methoxybenzyl)acetamide

6-[^{18}F]Fluoro-PBR28

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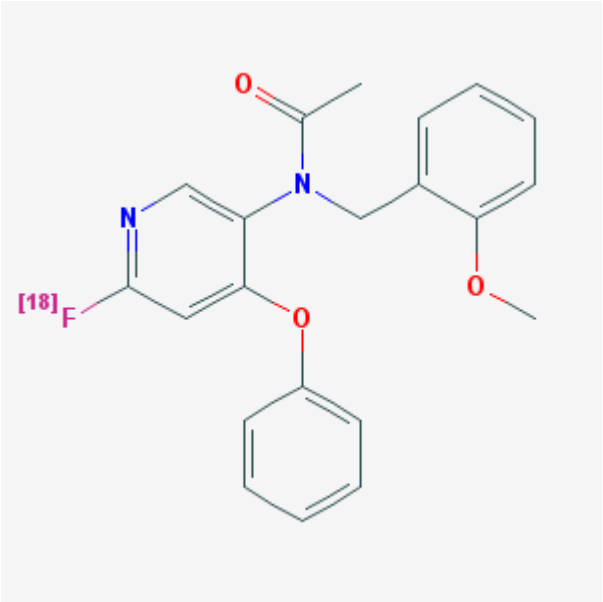
Chemical name:	N-(6-[^{18}F]Fluoro-4-phenoxypyridin-3-yl)-N-(2-methoxybenzyl)acetamide
Abbreviated name:	6-[^{18}F]Fluoro-PBR28
Synonym:	[^{18}F]**15**
Agent Category:	Compound
Target:	Peripheral-type benzodiazepine receptor (PBR; 18-kDa translocator protein (TSPO))
Target Category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



Click on above structure of 6-[^{18}F]fluoro-PBR28 for more information in PubChem.

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Background

[PubMed]

The 18-kDa translocator protein (TSPO; also known as the peripheral benzodiazepine receptor (PBR)) is evolutionarily conserved and is found mainly in the outer membrane of the mitochondria of steroid-synthesizing tissues, including the brain (1). Although the TSPO is involved in neuroinflammation and axonal regeneration after brain injury (2), the best characterized function of this protein is the transport of cholesterol from the outer membrane of the mitochondria to the inner membrane of these organelles, where it is used for steroid and neurosteroid hormone synthesis (2). Very low levels of TSPO are expressed in healthy brain tissue, but, in the event of an injury, the protein is overexpressed at the site of injury (3) both in the peripheral nervous system (in Schwann cells, macrophages, and neurons) and in the central nervous system (in activated microglia and infiltrating macrophages) (1). In addition, TSPO is overexpressed in different types of neuroinflammatory diseases such as Alzheimer's disease, Parkinson's disease, stroke, and various cancers, including those of the brain (3), but the expression of this protein is downregulated in psychiatric disorders such as anxiety, schizophrenia, depression, and bipolar disorder (1). Because the TSPO density is altered during neuronal injury or disease, it has been suggested that TSPO may serve as a biomarker of neuroinflammation and may be used to determine the efficacy of drugs used to monitor the progression and treatment of neuroinflammatory diseases (3). Several TSPO-selective ligands with diverse chemical structures have been synthesized, radiolabeled with ^{11}C or ^{18}F, and evaluated with positron emission tomography (PET) for the noninvasive imaging of this receptor in the brain of various species of animals (mouse, rat, and monkey) (4). For a detailed discussion of the chemistry of different TSPO ligands, see Dolle et al. (3). It is not clear, however, how the labeled ligands interact with the TSPO, and much is unknown about the changes that take place within this protein during neuroinflammation and related disorders (5).

[^{11}C]PK11195 targets TSPO and is commonly used with PET for the imaging of neurological disorders, but its uptake in the brain can be difficult to quantify because the tracer has high lipophilicity and exhibits high nonspecific binding (6). Much effort has been devoted to develop and screen new tracers that can be used for the imaging and quantification of TSPO (such as [^{11}C]DAA1106, [^{18}F]DAA1106, [^{18}F]FEDAA1106, [^{11}C]PBR28, etc.) (4, 6). However, these radioligands have to be synthesized with multi-step procedures, and all of them are still under investigation for use in animals (4). Using a single-step procedure, Damont et al. synthesized N-(6-[^{18}F]fluoro-4-phenoxypyridin-3-yl)-N-(2-methoxybenzyl)acetamide (6-[^{18}F]Fluoro-PBR28), a radiofluorinated derivative of PBR28, studied its characteristics *in vitro*, and evaluated the tracer for the imaging of TSPO in the rat brain (4).

Related Resource Links

Related chapters in MICAD

Human TSPO in Gene Database. Gene ID: 706

TSPO in Online Mendelian Inheritance in Man Database (OMIM)

Clinical trials related to PET imaging of TSPO

Synthesis

[PubMed]

The synthesis and ^{18}F-labeling of 6-Fluoro-PBR28 has been detailed by Damont et al. (4). The radiochemical yield of the labeled compound was 16%–18% ($n > 10$ reactions), with a radiochemical purity of >99%. The specific activity of 6-[^{18}F]Fluoro-PBR28 was reported to be 74–148 GBq/μmol (2–4 Ci/μmol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The log $D_{7.4}$ (*n*-octanol/buffer pH 7.4 partition coefficient) and log P (*n*-octanol/water partition coefficient) of 6-[^{18}F]Fluoro-PBR28 were determined to be 2.82 ± 0.14 and 2.77 ± 0.10, respectively (4).

Using [^{3}H]PK11195 as the ligand in a competition assay, the binding affinities (K_i) of 6-Fluoro-PBR28 for TSPO in rat heart homogenate, rat kidney mitochondrial-enriched fraction, and the mitochondrial fraction of HEK293 cells (originating from human embryonic kidney) were reported to be 0.44 ± 0.01 nM, 3.90 ± 0.30 nM, and 1.19 ± 0.03 nM, respectively (4). The K_i values of PK11195 in these preparations were determined to be 1.80 ± 0.04 nM, 9.30 ± 0.50, and 7.11 ± 0.35, respectively. This indicated that 6-Fluoro-PBR28 had a higher binding affinity for TSPO compared with PK11195.

In another study with rat glioma C6 cells, 6-Fluoro-PBR28 was observed to have a lower stimulation of pregnenolone (a precursor of steroid hormones) synthesis (16.46 ± 1.77% above controls) compared with PK11195 (37.0 ± 1.0% above control) (4). This indicated that the PBR28 derivative had a lower potency than PK11195 to stimulate steroidogenesis in the rat cells.

Ex vivo binding studies were performed with brain sections obtained from rats treated with α-amino-3-hydroxy-5-methylisoxazol-4-propionate (AMPA; 7.5 nmol) to induce inflammatory lesions in the organ (4). Autoradiography of brain sections exposed to 6-[^{18}F]Fluoro-PBR28 in presence or absence of nonradioactive 6-Fluoro-PBR28 or PK11195 (20 nM) showed that only those sections that were exposed to 6-[^{18}F]Fluoro-PBR28 alone had a high ipsi/contralateral ratio (value not reported). This indicated that the ^{18}F-labeled derivative of PRB28 had a high specificity of binding to TSPO.

Animal Studies

Rodents

[PubMed]

Acute neuroinflammatory lesions were induced with a stereotaxic injection of 7.5 nmol AMPA in rats for micro-PET imaging with 6-[^{18}F]Fluoro-PBR28 and [^{11}C]PK11195, respectively (4). The animals (number not reported) were injected with one of the two labeled compounds (concentration of tracer and route of injection were not reported), and micro-PET images of the brain were acquired for up to 60 min postinjection (p.i.). At 60 min p.i., the AMPA-induced lesions were clearly visible in the axial, coronal, and sagittal PET images of the animals (results for [^{11}C]PK11195 were not reported). Time-activity curves of 6-[^{18}F]Fluoro-PBR28 showed that maximum uptake of radioactivity (~0.5% injected dose per cubic centimeter of tissue (% ID/cc)) from the tracer was reached within 1–2 min p.i. and remained constant for the duration of the study (60 min p.i.), and the ipsi/contralateral uptake ratio at the 1-2 min time point was 2.2. Uptake kinetics observed with [^{11}C]PK11195 within the first 1–2 min p.i. (maximum uptake, ~0.4% ID/cc) were similar to uptake kinetics observed with [^{18}F]Fluoro-PBR28, but a rapid clearance of label from the lesions was observed with the ^{11}C-labeled compound; by 60 min p.i., the amount of radioactivity in the lesions decreased to ~0.25% ID/cc.

From these preliminary studies, the investigators concluded that 6-[^{18}F]Fluoro-PBR28 was probably suitable for the PET imaging of neuroinflammatory lesions in the brain of rodents (4).

Other Non-Primate Mammals

[PubMed]

No reference is currently available.

Non-Human Primates

[PubMed]

No reference is currently available.

Human Studies

[PubMed]

No reference is currently available.

Supplemental Information

[Disclaimers]

No information is currently available.

References

1. Rupprecht R., Papadopoulos V., Rammes G., Baghai T.C., Fan J., Akula N., Groyer G., Adams D., Schumacher M. *Translocator protein (18 kDa) (TSPO) as a therapeutic target for neurological and psychiatric disorders.* Nat Rev Drug Discov. 2010;9(12):971–88. PubMed PMID: 21119734.
2. Girard C., Liu S., Adams D., Lacroix C., Sineus M., Boucher C., Papadopoulos V., Rupprecht R., Schumacher M., Groyer G. *Axonal regeneration and neuroinflammation: roles for the translocator protein 18 kDa.* J Neuroendocrinol. 2012;24(1):71–81. PubMed PMID: 21951109.
3. Dolle F., Luus C., Reynolds A., Kassiou M. *Radiolabelled molecules for imaging the translocator protein (18 kDa) using positron emission tomography.* Curr Med Chem. 2009;16(22):2899–923. PubMed PMID: 19689272.
4. Damont A., Boisgard R., Kuhnast B., Lemee F., Raggiri G., Scarf A.M., Da Pozzo E., Selleri S., Martini C., Tavitian B., Kassiou M., Dolle F. *Synthesis of 6-[(1)(8)F]fluoro-PBR28, a novel radiotracer for imaging the TSPO 18 kDa with PET.* Bioorg Med Chem Lett. 2011;21(16):4819–22. PubMed PMID: 21741237.
5. Scarf A.M., Kassiou M. *The translocator protein.* J Nucl Med. 2011;52(5):677–80. PubMed PMID: 21498529.
6. Doorduin J., de Vries E.F., Dierckx R.A., Klein H.C. *PET imaging of the peripheral benzodiazepine receptor: monitoring disease progression and therapy response in neurodegenerative disorders.* Curr Pharm Des. 2008;14(31):3297–315. PubMed PMID: 19075709.