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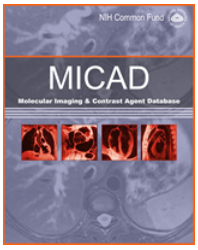


# *N*-[$^{18}$F]Fluoroacetyl-*N*-(2,5-dimethoxybenzyl)-2-phenoxyaniline

## [$^{18}$F]PBR06

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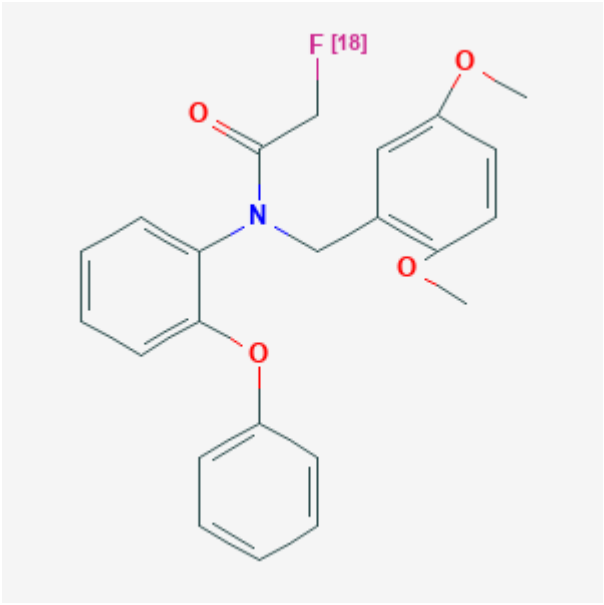
| **Chemical name:** | *N*-[$^{18}$F]Fluoroacetyl-*N*-(2,5-dimethoxybenzyl)-2-phenoxyaniline |
| **Abbreviated name:** | [$^{18}$F]PBR06 |
| **Synonym:** | |
| **Agent category:** | Compound |
| **Target:** | Peripheral-type benzodiazepine receptor (PBR), also known as translocator protein (TSPO) |
| **Target category:** | Receptor |
| **Method of detection:** | PET |
| **Source of signal:** | $^{18}$F |
| **Activation:** | No |
| **Studies:** | • *In vitro*<br>• Non-human primates<br>• Humans |

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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). PBR is also known as translocator protein (TSPO). 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

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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 (8). [$^{11}$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 (9, 10). DAA1106 was reported to have a higher affinity for PBRs in mitochondrial fractions of rat and monkey brains than PK11195 (9, 10). 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, 12). *N*-[$^{18}$F]Fluoroacetyl-*N*-(2,5-dimethoxybenzyl)-2-phenoxyaniline ([$^{18}$F]PBR06), which has an aryloxyanilide structure, has been evaluated for imaging PBR in the brain.

### Related Resource Links:

- Chapters in MICAD
- Gene information in NCBI (PBR)
- Articles in OMIM
- Clinical trials (PBR)

## Synthesis

[PubMed]

Imaizumi et al. (13) reported the synthesis of [$^{18}$F]PBR06 by nucleophilic displacement of the bromo precursor with [$^{18}$F]KF/Kryptofix 2.2.2./$K_2CO_3$ at 110°C for 10 min and purified by high-performance liquid chromatography. The specific activity was 26.8 ± 17.5 GBq/μmol (0.72 ± 0.47 Ci/μmol) at the time of injection with 10–20% radiochemical yield.

## *In Vitro* Studies: Testing in Cells and Tissues

[PubMed]

*In vitro* [$^{3}$H]PK11195 PBR-binding studies using monkey brain mitochondrial homogenates showed inhibition constant ($K_i$) values of 0.30 ± 0.08nM and 3.84 ± 1.26 nM for PBR06 and PK11195, respectively.

## Animal Studies

### Rodents

[PubMed]

No publications are currently available.

### Other Non-Primate Mammals

[PubMed]

No publications are currently available.

## Non-Human Primates

[PubMed]

Imaizumi et al. (13) reported PET studies of [18F]PBR06 in the monkey brain. The radioactivity level of [18F]PBR06 in the monkey brain was 300% of the standard uptake value with greater radioactivity in gray matter than in white matter. [18F]PBR06 exhibited the highest uptake in the choroid plexus, a region rich in PBR. Accumulation of [18F]PBR06 in the cerebellum, putamen, and choroid plexus was inhibited significantly (~80%) by pretreatment of DAA1106 (3 mg/kg), indicating that the binding of [18F]PBR06 in the monkey brain was mainly attributable to PBR. Averaged distribution volume ($V_T$) values by a two-tissue compartment model were 60, 80, and 78 ml/cm$^3$ in the cerebellum, putamen, and choroid plexus, respectively. $V_T$ values by a one-tissue compartment model were 49, 65, and 49 ml/cm$^3$ in the cerebellum, putamen, and choroid plexus, respectively. In the blocking experiment, $V_T$ values by a one-tissue compartment model were 2.0, 2.4, and 2.3 ml/cm$^3$ in the cerebellum, putamen, and choroid plexus, respectively. Therefore, ~95% of $V_T$ in the baseline scans was PBR-specific binding. The $V_T$ value was more stable and more reliably determined with 200 min of baseline scanning using the two-compartment model than the one-compartment model. Approximately 20–30% of radioactivity in the plasma was intact [18F]PBR06 at 5 min after injection. The metabolites were more hydrophilic than the parent compound.

# Human Studies

[PubMed]

Fujimura et al. (14) performed PET kinetics studies of the brain for 5 h after injection of 185 MBq (5 mCi) of [18F]PBR06 in 9 healthy subjects. A 2-tissue compartment model was shown to be better than a 1-tissue compartment model. A brain scan of 120 min exhibited the best estimation of $V_T$ value, which was stable during 60-120 min.

Fujimura et al. (15) later performed 2-dimensional dynamic scans for radiation dosimetry after injection of 185 MBq (5 mCi) of [18F]PBR06 in 7 healthy subjects. The highest radiation doses were in the gallbladder wall (367.0 μSv/MBq, 1380 mrem/mCi), spleen (64.5 μSv/MBq, 239 mrem/mCi), liver (46.1 μSv/MBq, 170 mrem/mCi), kidneys (39.3 μSv/MBq, 146 mrem/mCi), lung (36.5 μSv/MBq, 135 mrem/mCi), and urinary bladder wall (31.0 μSv/MBq, 115 mrem/mCi). The effective dose was 18.5 μSv/MBq (69 mrem/mCi).

# NIH Support

Intramural research program

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