N-Acetyl-*N*-(2-[^{18}F]fluoroethoxybenzyl)-2-phenoxy-5-pyridinamine

[^{18}F]FEPPA

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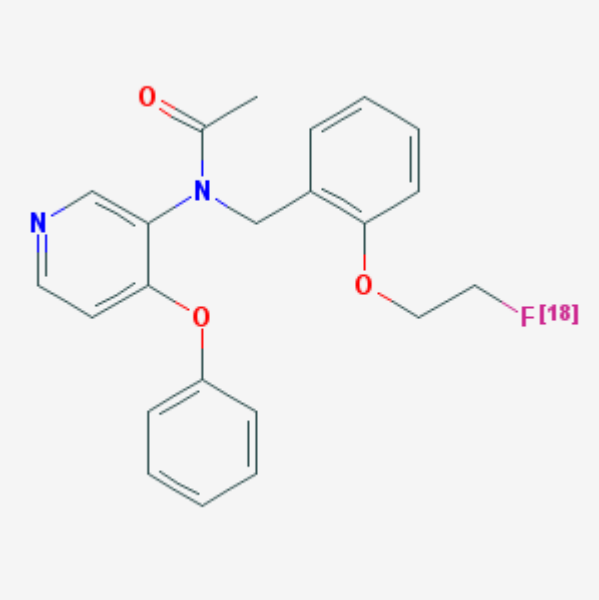
Chemical name:	*N*-Acetyl-*N*-(2-[^{18}F]fluoroethoxybenzyl)-2-phenoxy-5-pyridinamine
Abbreviated name:	[^{18}F]FEPPA
Synonym:	
Agent Category:	Compound
Target:	Peripheral-type benzodiazepine receptor (PBR)
Target Category:	Receptor-ligand binding
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

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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 (CBRs) and peripheral benzodiazepine receptors (PBRs). CBRs are found exclusively in the central nervous system on the membranes of neurons and are coupled to the γ-aminobutyric acid receptor/chloride channel (3). In contrast, PBRs are mitochondrial proteins found in the brain and peripheral tissues (adrenal gland, heart, lung, kidney, and testis) (4); the brain has lower levels of PBR than do the peripheral tissues, and 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 [PuBMed]. However, accumulation of this tracer in the brain is limited. *N*-(2,5-Dimethoxybenzyl)-*N*-(5-fluoro-2-phenoxyphenyl)acetamide (DAA1106) is a selective agonist used to study 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-labeled DAA1106 ([^{11}C]DAA1106) have been developed as potential PET ligands with highly selective and specific binding to PBR. *N*-Acetyl-*N*-(2-methoxybenzyl)-2-phenoxy-5-pyridinamine (PBR28), which has an aryloxyanilide structure, has been shown to have high affinity and selectivity for PBR (10). *N*-Acetyl-*N*-(2-[^{11}C]methoxybenzyl)-2-phenoxy-5-pyridinamine ([^{11}C]PBR28) has been developed for imaging PBR in the brain (11). *N*-Acetyl-*N*-(2-[^{18}F]fluoroethoxybenzyl)-2-phenoxy-5-pyridinamine ([^{18}F]FEPPA), an analog of [^{11}C]PBR28, is being evaluated as a PET imaging agent for PBR in the brain (12).

Synthesis

[PubMed]

Wilson et al. (12) reported the synthesis of [^{18}F]FEPPA with ^{18}F-fluorination of *N*-(2-((*n*-4-phenoxypyridin-3-yl)acetimido)methyl)phenoxy)ethyl 4-methylbenzenesulphonate in acetonitrile solution of K_2CO_3/Kryptofix222 for 10 min at 90°C. [^{18}F]FEPPA was purified with high-performance liquid chromatography (HPLC) with radiochemical yields of 50% to 60% in a total synthesis time of 40–50 min. The specific activity was 44.4–99.9 GBq/μmol (1.2–2.7 Ci/μmol) at the end of synthesis with radiochemical purities of >99%.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro [^{3}H]PK11195 PBR-binding studies showed that FEPPA and PBR28 had K_i values of 0.07 and 0.22 nM, respectively (12). FEPPA has a lipophilicity value (Log D, measured) of 2.99 and little activity against various neurotransmitters and transporters.

Animal Studies

Rodents

[PubMed]

Wilson et al. performed biodistribution studies in male rats injected with 2–3 MBq (0.054–0.081 mCi) [^{18}F]FEPPA (12). The studies showed a modest regional accumulation of radioactivity in the brain with standard uptake values of 0.6 and 0.35 at 5 min and 30 min after injection, respectively. The highest uptake value was exhibited in the olfactory bulb (0.75), followed by the hypothalamus (0.65) and the cerebellum (0.56). The fraction of unchanged [^{18}F]FEPPA in the brain as determined with HPLC was >93% at 40 min after injection. The fraction of unchanged [^{18}F]FEPPA in plasma samples as determined with HPLC was ~7% at 40 min after injection with one major hydrophilic metabolite. Blocking experiments with co-administration of 0.01–1 mg/kg PBR28 was unsuccessful in terms of the regional and total brain accumulation of radioactivity with a dramatic increase in plasma radioactivity. This may be explained by the observation that binding of [^{18}F]FEPPA to peripheral PBR sites was blocked by PBR28, thus increasing the amount of radiotracer in plasma and the amount available to accumulate in the brain.

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.

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