N-Benzyl-*N*-ethyl-2-[7,8-dihydro-7-(2-[^{18}F]fluoroethyl)-8-oxo-2-phenyl-9*H*-purin-9-yl]acetamide

[^{18}F]FEAC

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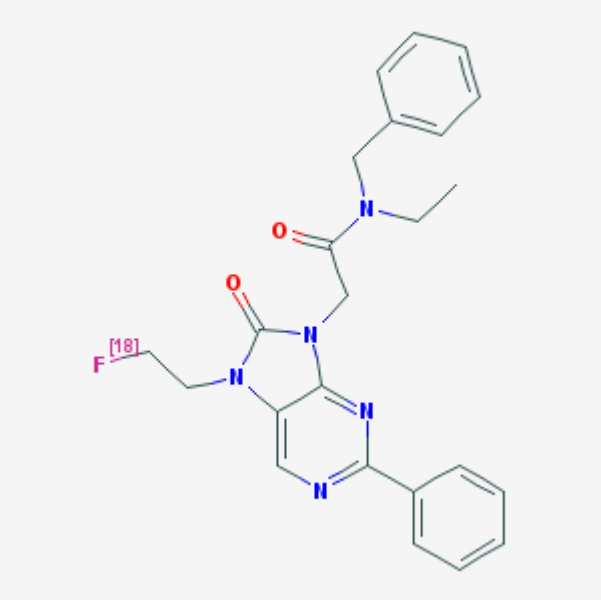
Chemical name:	*N*-Benzyl-*N*-ethyl-2-[7,8-dihydro-7-(2-[^{18}F]fluoroethyl)-8-oxo-2-phenyl-9*H*-purin-9-yl]acetamide
Abbreviated name:	[^{18}F]FEAC
Synonym:	
Agent category:	Compound
Target:	Peripheral-type benzodiazepine receptor (PBR), also known as translocator protein (TSPO)
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates



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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 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* 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 (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 did 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*-Benzyl-*N*-ethyl-2-[7,8-dihydro-7-(2-[^{18}F]fluoroethyl)-8-oxo-2-phenyl-9*H*-purin-9-yl]acetamide ([^{18}F]FEAC), which has an acetamide structure, has been evaluated for imaging PBR in the brain (13).

Related Resource Links:

- Chapters in MICAD

NLM Citation: Leung K. *N*-Benzyl-*N*-ethyl-2-[7,8-dihydro-7-(2-[^{18}F]fluoroethyl)-8-oxo-2-phenyl-9*H*-purin-9-yl]acetamide. 2010 May 6 [Updated 2010 Aug 19]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

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

Synthesis

[PubMed]

Yanamoto et al. (13) reported the synthesis of [^{18}F]FEAC by alkylation of the precursor with [^{18}F]FCH_2CH_2Br. [^{18}F]FEAC was purified with high-performance liquid chromatography with 35% radiochemical yield (decay-corrected) based on [^{18}F]F^-. The total synthesis time was ~45 min. The radiochemical purity was >98% with the specific activity of 30–95 GBq/μmol (0.81–2.43 Ci/μmol) at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro [^{11}C]PK11195 PBR-binding studies using rat brain homogenates showed inhibition constant (K_i) values of 0.49 ± 0.05 nM and 0.31 ± 0.03 nM for FEAC and PK11195, respectively (13). Log D was determined to be 3.6 and 3.7 for FEAC and PK11195, respectively.

Animal Studies

Rodents

[PubMed]

Yui et al. (14) showed that [^{18}F]FEAC had high accumulation as expressed in % injected dose/gram (ID/g) in the lung (35.3), heart (9.6), kidney (17.1), liver (9.3) and small intestine (5.4) in normal mice at 5 min after injection. The brain exhibited 1% ID/g at 1 min and ~0.45% for next 89 min. The radioactivity in the bone was 1.1% ID/g at 1 min and 1.4% ID/g at 90 min. PET imaging scans were performed in rats with infarcted brain. Maximum uptake (1-3 min after injection) on the ipsilateral and contralateral sides was about 0.87 and 0.49 standardized uptake value (SUV), respectively. The SUV ratio of radioactivity between ipsilateral and contralateral sides reached 3.03 for [^{18}F]FEAC at 20 min after injection. The ratio was reduced to ~1 with PK11195 pretreatment (~1 min). The binding potential was estimated to be 1.70 ± 0.19 (n = 4).

Yanamoto et al. (13) performed PET imaging in rats (n = 4) with acute neuroinflammation in the striatum. PET imaging showed an increased accumulation of [^{18}F]FEAC in the lesion as compared with the contralateral side as early as 1 min after injection with rapid clearance. The maximum ratio of 2.5 was achieved within 10–20 min after injection. No blocking experiment was performed.

Other Non-Primate Mammals

[PubMed]

No publications are currently available.

Non-Human Primates

[PubMed]

PET imaging was performed in a male rhesus monkey (14). The maximum uptake (0.016% dose/mL) of [18F]FEAC in the occipital cortex was at ~5 min after injection. At 90 min after injection, the radioactivity decreased to 70% of the maximum.

Human Studies

[PubMed]

No publications are currently available.

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