1-(2-[^{18}F]Fluoro-3-pyridyl)-4-(2-isopropyl-1-oxo-isoindoline-5-yl)-5-methyl-1H-1,2,3-triazole

[^{18}F]FPIT

Kam Leung, PhD[1]

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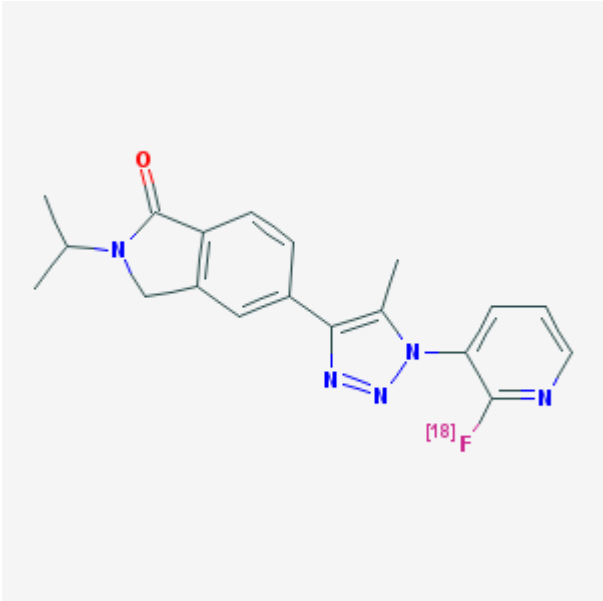
Chemical name:	1-(2-[^{18}F]Fluoro-3-pyridyl)-4-(2-isopropyl-1-oxo-isoindoline-5-yl)-5-methyl-1H-1,2,3-triazole
Abbreviated name:	[^{18}F]FPIT
Synonym:	
Agent category:	Compound
Target:	Metabotropic glutamate receptor subtype 1 (mGluR1)
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates



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.

Background

[PubMed]

Glutamate is a major excitatory neurotransmitter at neuronal synapses in the central nervous system (CNS) (1, 2). Glutamate produces excitatory effects by acting on cell-surface ionotropic glutamate or metabotropic glutamate receptors (mGluRs). The mGluRs are GTP-binding protein (G-protein)–coupled receptors that play important roles in regulating the activity of many synapses in the CNS, and many neuronal projection pathways contain mGluRs. There are eight mGluR subtypes, which are further subdivided into groups I, II, and III. The group I receptors include mGluR1 and mGluR5, and they are found predominantly in postsynaptic locations. mGluR1 is found in moderate to high density in the cerebellum, caudate, putamen, thalamus, cingulate cortex, and hippocampus, with low density in the pons. mGluR5 is usually found in moderate to high density in the frontal cortex, caudate, putamen, nucleus accumbens, olfactory tubercle, and hippocampus, with low density in the cerebellum. mGluR1 and mGluR5 are positively coupled to phospholipase C in the regulation of neuronal excitability (3). Dysfunction of mGluR1 and mGluR5 is implicated in a variety of diseases in the CNS, including anxiety, depression, schizophrenia, Parkinson's disease, and drug addiction or withdrawal (2, 4).

Positron emission tomography (PET) and single-photon emission tomography of radioligands targeting mGluR1 can visualize and analyze mGluR1 expression in normal physiological and pathological conditions. Several radioligands have been studied for *in vivo* imaging of mGluR1 in the brain. 1-(2-Fluoro-3-pyridyl)-4-(2-isopropyl-1-oxo-isoindoline-5-yl)-5-methyl-1H-1,2,3-triazole (FPIT) was shown to be a selective mGluR1 with nanomolar affinity (5.4 nM) with little inhibition to mGluR5 (5). Fujinaga et al. (6) prepared and evaluated 1-(2-[^{18}F]Fluoro-3-pyridyl)-4-(2-isopropyl-1-oxo-isoindoline-5-yl)-5-methyl-1H-1,2,3-triazole ([^{18}F]FPIT) for use with *in vivo* PET imaging of mGluR1 distribution in the brain with small animals and monkeys.

Related Resource Links:

- Chapters in MICAD (mGluR1, mGluR5)
- Gene information in NCBI (mGluR1, mGluR5)
- Articles in Online Mendelian Inheritance in Man (OMIM) (mGluR1, mGluR5)
- Clinical trials (mGluR1, mGluR5)

NLM Citation: Leung K. 1-(2-[^{18}F]Fluoro-3-pyridyl)-4-(2-isopropyl-1-oxo-isoindoline-5-yl)-5-methyl-1H-1,2,3-triazole. 2012 Nov 15 [Updated 2013 Mar 7]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

Synthesis

[PubMed]

Fujinaga et al. (6) reported an one-step automated synthesis of [^{18}F]FPIT. The bromo-precursor was subjected to nucleophilic fluorination with K[^{18}F]F for 10 min at 150°C, with a radiochemical yield of 58 ± 21% (n = 16) and a specific activity of 80–280 GBq/μmol (2.2–7.6 Ci/μmol) after purification with high-performance liquid chromatography. The radiochemical purity of [^{18}F]FPIT was >98%. The total synthesis time was 77 min. [^{18}F]FPIT exhibited a Log $D_{7.4}$ value of 2.53 ± 0.19 (n = 3).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro [^{18}F]FPIT autoradiographic imaging studies were performed on rat brain sections (n = 8/group) (6). [^{18}F]FPIT bound heterogeneously to the brain sections, with the highest accumulation of radioactivity in the mGluR1-rich cerebellum (333 ± 47 PSL/mm^2) and thalamus (237 ± 35 PSL/mm^2), followed by the hippocampus (158 ± 30 PSL/mm^2), striatum (98 ± 27 PSL/mm^2), cerebral cortex (49 ± 10 PSL/mm^2) and pons-medulla (26 ± 5 PSL/mm^2). FPIT and JNJ-16259685 (1,000 nM, mGluR1 antagonists) completely blocked radioactive signals to background levels in these brain regions. On the other hand, mGluR5 antagonist MPEP (1,000 nM) only demonstrated only marginal inhibition of the signals. *In vitro* autoradiographic studies were also performed on monkey brain sections (n = 10/group) with similar results as those of the rat brain sections.

Animal Studies

Rodents

[PubMed]

Fujinaga et al. (6) performed *ex vivo* biodistribution studies in rats (n = 4/group) at 1-90 min after intravenous injections of 3.4 MBq (0.46 mCi) [^{18}F]FPIT (0.014 nmol). The radioactivity levels in most tissues were highest at 1-5 min and thereafter decreased quickly. The highest accumulation at 5 min was observed in the liver (2.07% injected dose/gram (ID/g)), followed by the small intestine (1.64% ID/g), kidney (1.55% ID/g), lung (1.54% ID/g), pancreas (1.28% ID/g), brain (0.98% ID/g), spleen (0.95% ID/g), heart (0.61% ID/g), muscle (0.33% ID/g), blood (0.32% ID/g), and bone (0.39% ID/g). [^{18}F]FPIT remained 42% and 93% intact in the plasma and brain at 60 min, respectively.

Fujinaga et al. (6) performed dynamic PET imaging studies for 90 min in rats (n = 4/group) after intravenous injection of 19 MBq (0.51 mCi) [^{18}F]FPIT (0.08 nmol). Blocking studies were performed by pretreatment (0.5 min) with 1 mg/kg FPIT, JNJ-16259685 or MPEP. Baseline tissue time-activity curves revealed a high accumulation of radioactivity

peaked at 30 min in the cerebellum, and decreased to 87% of the maximum at 90 min. On the other hand, moderate radioactivity levels in the thalamus, striatum, hippocampus and cerebral cortex peaked at 5-10 min and decreased to 60-70% of the maximum at 90 min. The cerebellum/medulla, thalamus/medulla, striatum/medulla, hippocampus/medulla, and cerebral cortex/medulla ratios at 10-15 min were 4.27, 2.32, 1.82, 1.61, and 1.42, respectively. The non-displacement binding potential (BP_{nd}) values were 2.10 ± 0.18 and 0.60 ± 0.04 for the cerebellum and thalamus as determined with the simplified reference-tissue model, respectively. Pretreatment with FPIT reduced the radioactivity signals by 83%, 71%, 62%, 61% and 53% in the cerebellum, thalamus, striatum, hippocampus, and cerebral cortex, respectively. Pretreatment with JNJ-16259685 also showed reduced radioactivity levels in all brain regions, whereas pretreatment with MPEP showed little inhibition.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Fujinaga et al. (6) performed dynamic PET imaging studies for 90 min in one male rhesus monkey after intravenous injection of 152 MBq (4.1 mCi, 0.63 nmol) [^{18}F]FPIT. Blocking studies were performed by pretreatment (0.5 min) with FPIT (1 mg/kg), JNJ-16259685 (3 mg/kg) or MPEP (1 mg/kg). Baseline tissue time-activity curves revealed high accumulation of radioactivity in the cerebellum, followed by the thalamus. However, little difference in radioactivity levels was observed among the striatum, hippocampus, cingulate cortex, and pons. The maximum uptake ratios to the pons were 1.62, 1.43 and 1.00-1.25 for the cerebellum, thalamus, and the rest of brain regions, respectively. Pretreatment with JNJ-16259685 or FPIT reduced the radioactivity signals of all brain regions by 40-70%, whereas pretreatment with MPEP did no change the distribution of radioactivity in the brain. [^{18}F]FPIT remained 89% and 50% intact in the brain and plasma at 90 min, respectively.

Human Studies

[PubMed]

No publication is currently available.

References

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