2-(4-(2-[^{18}F]Fluoroethyl)piperidin-1-yl)benzo[4,5]imidazo[1,2-a]pyrimidine

[^{18}F]T808

Kam Leung, PhD[1]

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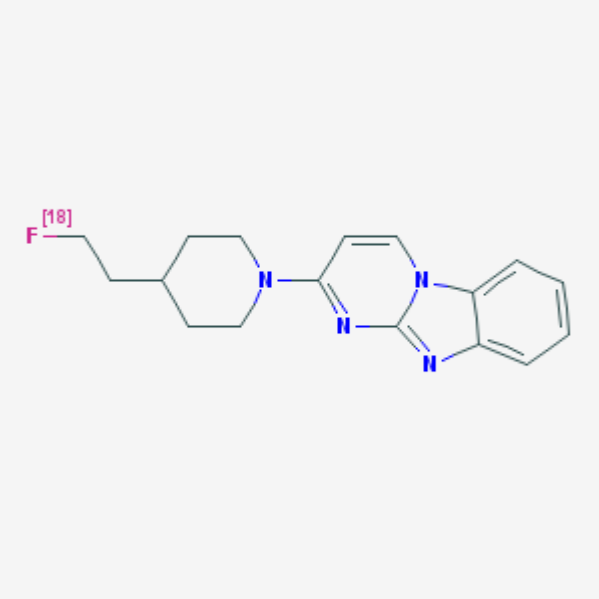
Chemical name:	2-(4-(2-[^{18}F]Fluoroethyl)piperidin-1-yl)benzo[4,5]imidazo[1,2-a]pyrimidine
Abbreviated name:	[^{18}F]T808
Synonym:	
Agent category:	Compound
Target:	Tau plaques
Target category:	Acceptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

[1] National Center for Biotechnology Information, NLM, NIH, Bethesda, MD; Email: micad@ncbi.nlm.nih.gov.

Corresponding author.

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Alzheimer's disease (AD) is a form of dementia with a gradual memory loss and a progressive decline in mental functions over time (1, 2). It is characterized pathologically by neuronal loss, extracellular senile plaques (aggregates of amyloid-β (Aβ) peptides consisting of 40–42 amino acids formed as the proteolytic cleavage of Aβ protein precursor (AβPP)), and intracellular neurofibrillary tangles (filaments of microtubule-binding hyper-phosphorylated protein tau) in the brain, especially in the hippocampus and associative regions of the cortex (3, 4). Aβ plaques and tau neurofibrillary tangles are implicated as the main causes of neuronal degeneration and cell death in AD patients (5, 6).

Early diagnosis of AD is important for treatment consideration and disease management (7). Various Aβ imaging agents have been developed for magnetic resonance imaging, single-photon emission computed tomography, and positron emission tomography (PET) (8-14). The binding properties of different derivatives of Congo red, thioflavin, stibene, and aminonaphthalene have been studied in postmortem human brain tissue and in transgenic mice (Nesterov, E.E., 2005; Ran, C., 2009). Of these analogs, 2-(1-(6-[(2-[^{18}F]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene)malono nitrile ([^{18}F]FDDNP) has been studied in humans, showing more binding in the brains of patients with AD than in those of healthy people (15). [^{18}F]FDDNP has been found to bind to both Aβ plaques and tau neurofibrillary tangles. However, [^{18}F]FDDNP exhibits low signal/noise ratios for PET imaging because it is highly lipophilic. *N*-methyl-[^{11}C]-2-(4'-methylaminophenyl)-6-hydroxybenzothiasole, an Aβ-binding compound based on a series of neutral thioflavin-T derivatives, was radiolabeled with the positron-emitting radionuclide ^{11}C ([^{11}C]6-OH-BTA-1 or [^{11}C]PIB). [^{11}C]6-OH-BTA-1 was found to be a promising imaging agent for Aβ plaques in the brain (10). Okamura et al. (16) identified a series of quinolone derivatives that bind tau neurofibrillary tangles with higher affinity than Aβ plaques. One of these derivatives, 2-(4-aminophenyl)-6-(2-([^{18}F]fluoroethoxy))quinolone ([^{18}F]THK523), was shown with PET imaging to have higher brain accumulation in tau transgenic mice than in Aβ transgenic mice (17). Zhang et al. (18) evaluated 2-(4-(2-[^{18}F]fluoroethyl)piperidin-1-yl)benzo[4,5]imidazo[1,2-a]pyrimidine ([^{18}F]T808) as a PET imaging agent for tau pathologies.

Related Resource Links:

- Chapters in MICAD (amyloid, tau)
- Gene information in NCBI (amyloid, tau)
- Articles in Online Mendelian Inheritance in Man (OMIM) (amyloid, tau)
- Clinical trials (amyloid, tau)
- Drug information in FDA (amyloid inhibitors, tau inhibitors)

Synthesis

[PubMed]

[^{18}F]T808 was readily synthesized with standard ^{18}F-fluorination of the tosylate precursor ([^{18}F]KF/Kryptofix2.2.2; 5 min at 90°C) (18). [^{18}F]T808 was purified with high-performance liquid chromatography. Average yield (n = 24) was 37.4%, with an average specific activity of 255 GBq/μmol (6.9 Ci/μmol) at the end of synthesis and a radiochemical purity of >98%. Total synthesis time was ~90 min. The Log P (lipophilicity) value of [^{18}F]T808 was not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Zhang et al. (18) performed radioautographic binding studies of [^{18}F]T808 in postmortem brain (frontotemporal cortex) tissues of AD patients (n = 33, age 64–93 years) and normal control patients (n = 12, age 64–89 years). [^{18}F]T808 localized in the "tau-rich" sections, whereas there was minimal staining in the "tau-poor/Aβ-rich" sections. The "tau-rich"/"tau-poor/Aβ-rich" ratio was determined to be 27. [^{18}F]T808 radioactivity levels colocalized with immunostaining for tau in the frontal and cingulate areas, with little colocalization with $A\beta_{42}$. Saturation binding autoradiography exhibited a K_d value of 22 nM, whereas a K_d value for Aβ could not be determined due to weak binding of [^{18}F]T808 to Aβ plaques.

Animal Studies

Rodents

[PubMed]

Zhang et al. (18) performed PET imaging over 30 minutes after intravenous injection of 7.4 MBq (200 μCi) [^{18}F]T808 into wild-type mice (n = 11) or 14.8 MBq (400 μCi) [^{18}F]T808 into wild-type rats (n = 11). [^{18}F]T808 showed an initial rapid penetration into the mouse brain, with 6.7% injected dose (ID)/g at 2.5 min and a quick washout (2.3% ID/g at 20 min). Similar kinetics was observed in the rats, with 0.7% ID/g and 0.1% ID/g at 2.5 min and 20 min after injection. Some bone accumulation was observed in the mice.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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