6-(3'-[^{18}F]Fluoropropyl)-2-(4'-dimethylamino)phenylimidazol[1,2-α]pyridine

[^{18}F]FPPIP

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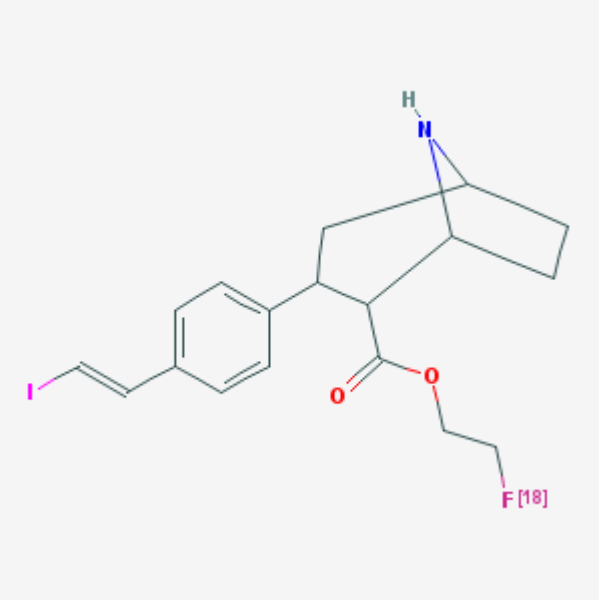
Chemical name:	6-(3'-[^{18}F]Fluoropropyl)-2-(4'-dimethylamino)phenylimidazol[1,2-α]pyridine
Abbreviated name:	[^{18}F]FPPIP
Synonym:	
Agent Category:	Compound
Target:	Amyloid-β (Aβ)
Target Category:	Specific binding
Method of detection:	Positron Emission Tomography (PET)
Source of signal/ contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Non-human primates



Click on the above structure for additional information in PubChem.

Background

[PubMed]

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

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6-(3'-[^{18}F]Fluoropropyl)-2-(4'-dimethylaminophenylimidazol[1,2-α]pyridine ([^{18}F]FPPIP) is a radioligand that was developed for positron emission tomography (PET) imaging of amyloid-β (Aβ) plaques in the central nervous system (CNS) for detection of Alzheimer's disease (AD) (1). ^{18}F is a positron emitter with a physical $t_{½}$ of 109.7 min.

Aβ-peptide was sequenced from the meningeal blood vessels of AD patients and individuals with Downs syndrome (2). Aβ peptides contain 40–42 amino acid residues and are metabolic products of the Aβ precursor protein (APP) from cleavage by β- and γ-secretases (3). Aβ is also identified as the primary component of the neuritic plaques of AD patient brain tissue (4). The cloning of the gene that encodes the APP and its localization to chromosome 21 led to the hypothesis that Aβ accumulation is the primary event in AD pathogenesis (2, 5). This hypothesis proposes that neuronal death in AD is related to the toxic effect of Aβ on the adjacent cell bodies or cell processes (6). AD is a progressive, neurodegenerative disorders of the CNS, and is characterized by a common set of clinical and pathological features (3). In addition to Aβ, the microtubule-associated protein tau is also found in the cell body and axons of neurons as neurofibrillary tangles.

The search for a cure or effective treatment of AD requires *in vivo* detection and quantification of Aβ in the brain for evaluation of the efficacy of AD therapy (3). Various amyloid-imaging probes have been developed for PET, single-photon emission computed tomography, and optical imaging. These compounds generally have high binding affinity for amyloid fibrils and adequate permeability of blood–brain barrier (BBB) (7). Klunk et al. (8) studied [^{11}C]6-OH-BTA-1 in AD patients and showed the potential usefulness of these probes. [^{123}I]6-iodo-2(4'-*N*,*N*'-dimethylamino)phenylimidazol[1,2-α]pyridine ([^{123}I]IMPY) has been reported as a potential SPECT agent for imaging Aβ plaques. Because PET can provide more accurate quantitative imaging, Zeng et al. (1) developed ^{18}F-labeled IMPY analogs for PET imaging of AD plaques. [^{18}F]FPPIP is produced by replacing the iodo group on IMPY with fluoropropyl.

Synthesis

[PubMed]

Zeng et al. (1) reported the synthesis of FPPIP from IMPY. IMPY was first prepared from condensation reaction between commercially available 2-amino-5-iodopyridine and 2-bromo-4'-dimethylaminoacetophenone in the presence of sodium bicarbonate as a mild base. IMPY was coupled with the tributyl(propylene)tin in toluene and palladium at 100°C for 20 h to produce the corresponding intermediate alkene. This alkene was then converted to a hydroxyethyl compound by a hydroboration-oxidation reaction. FPPIP was finally produced by reaction of the hydroxyethyl compound with diethylaminosulfur trifluoride in methylene chloride at −78°C to 23°C for 2 h with a yield of 44%.

The radiosynthesis of [^{18}F]FPPIP was accomplished by using the tosylate FPPIP precursor that was produced from reaction of FPPIP with tosylate chloride and triethylamine in methylene chloride at room temperature for 15 h with a yield of 52% (1). This precursor

was then reacted with anhydrous ^{18}F-labeled potassium fluoride and K_{222} in acetonitrile for 10 min at 90°C. The entire radiolabeling procedure required 105 min from the end of bombardment. The decay-corrected yield was 51% and the radiochemical purity was >98%. The specific activity was 62.9–85.1GBq/μmol (1.7–2.3 Ci/μmol) at the time of injection.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro binding studies with unlabeled FPPIP were conducted with quantitative autoradiography by binding competition with [^{125}I]IMPY in human AD cortical tissues (1). The inhibition constant (K_i) was determined to be 48.3 nM. In comparison, IMPY had a K_i value of 10.3 nM. The lipophilicity coefficient log *P* (1-octanol and phosphate buffer at pH 7.4) of FPPIP was 2.84 whereas IMPY had a value of 3.58. The *in vitro* binding of [^{18}F]FPPIP was shown in postmortem AD brain sections by autoradiography. Specific binding was found in cortical gray matter but not in the white matter. This specific binding was eliminated when the sections were pretreated with unlabeled FPPIP. No specific binding was found in normal brain sections. In a study that used *in vitro* Immunostaining with an Aβ-specific 4G8 monoclonal antibody, [^{18}F]FPPIP labeling demonstrated a good correlation with Aβ plaque labeling by AG8 in the AD brain sections.

Animal Studies

Rodents

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Zeng et al. (1) performed PET imaging of [^{18}F]FPPIP in a healthy rhesus monkey. The study showed easy brain entry and clearance from normal brain tissue. The peak standard uptake value of [^{18}F]FPPIP was 1.6–2.7 at 9 min. Relatively fast nonspecific binding clearance was observed in cerebellum, frontal cortex, and subcortical white matter. No bone radioactivity was observed in the skull, which might indicate low in *in vivo* defluorination.

Human Studies

[PubMed]

No publication is currently available.

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