6-Iodo-2-[4'-*N*-(2-[^{18}F]fluoroethyl)methylamino]phenylimidazo[1,2-*a*]pyridine

[^{18}F]FEM-IMPY

The MICAD Research Team

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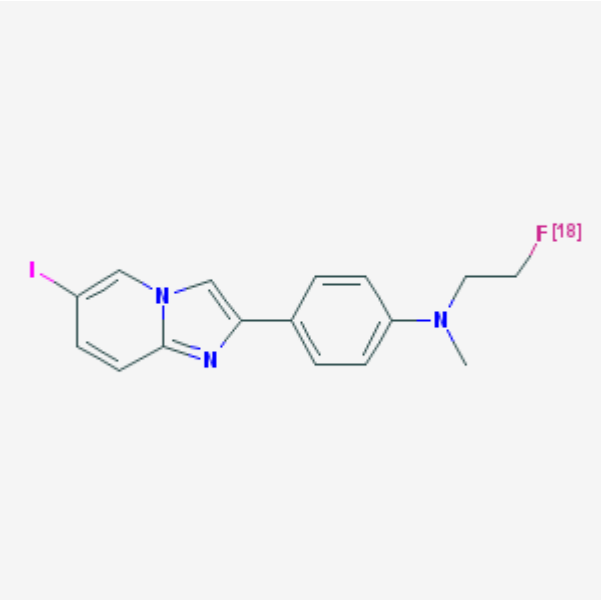
Chemical name:	6-Iodo-2-[4'-*N*-(2-[^{18}F]fluoroethyl)methylamino]phenylimidazo[1,2-*a*]pyridine
Abbreviated name:	[^{18}F]FEM-IMPY
Synonym:	
Agent Category:	Compound
Target:	Aggregates of ß-amyloid (Aß) peptides
Target Category:	Acceptor binding
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates



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Background

[PubMed]

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Alzheimer's disease (AD) is a major neurodegenerative disease associated with an irreversible decline of mental functions and with cognitive impairment (1). It is characterized by the presence in the brain of senile plaques of β-amyloid (Aβ) peptides with intracellular neurofibrillary tangles of filaments that contain the hyperphosphorylated protein tau (2, 3). Accelerated deposition of Aβ deposits seems to be a key risk factor associated with AD, and although the mechanisms of the disease are still not fully understood, reducing the deposition of amyloid plaques seems to benefit patients.

Several radioligands for positron emission tomography (PET) have been developed (4-6) and tested in humans as *in vivo* diagnostic tools for imaging and measuring the formation of Aβ deposits (6). The first agent successfully used in human studies was [^{18}F]FDDNP (7), a malonitrile derivative found to bind to both neurofibrillary tangles and Aβ plaques. The second successful attempt was made with [^{11}C]PIB (8), also known as Pittsburgh Compound B or [^{11}C]6-OH-BTA-1, which showed marked retention in areas of the cortex known to contain substantial amounts of Aβ deposits. The third PET radioligand successfully tested in humans was [^{11}C]4-*N*-methylamino-4′-hydroxystilbene, a stilbene derivative commonly named [^{11}C]SB-13 that exhibited good binding affinities for Aβ aggregates *in vitro*, moderate lipophilicity, high initial brain uptake in the normal rat cortex, and a rapid washout (9).

Benzofuran derivatives labeled with radioactive iodine have shown very good binding affinities for Aβ aggregates and good brain penetration (10). Unfortunately, their level of nonspecific binding was found to be very high, which makes them unsuitable for *in vivo* plaque imaging. However, [^{125}I]IMPY displayed a good initial brain uptake and rapid washout from normal mouse brain and postmortem AD brain sections (11). Its desirable pharmacokinetics makes [^{125}I]IMPY an attractive agent for mapping Aβ plaques. More recently, the ^{18}F-labeled analog of IMPY in which the *N*-methyl group is replaced with [^{18}F]2-fluoroethyl ([^{18}F]FEM-IMPY) has been synthesized and is currently under investigation as a prospective PET radioligand for Aβ plaques (12).

Synthesis

[PubMed]

A one-pot radiosynthesis of [^{18}F]FEM-IMPY using HM-IMPY as the precursor was developed by Cai et al. (12). In this method, HM-IMPY reacted with ethyleneglycol bis-tosylate at 130–150°C under microwave conditions. This slow reaction (5% complete after 10 min) could be enhanced by the addition of [K-(Kryptofix 222)]$^{+}$[F]$^{-}$, which accelerated the alkylation to generate FEM-IMPY with a 70–80% yield under anhydrous conditions. At the end of the synthesis, the radiochemical purity of the radiotracer was >93% and its specific radioactivity was 85–662 GBq/μmol (2.3–17.9 Ci/μmol).

The synthesis of the precursor HM-IMPY could be achieved in one step under mild conditions by bromination of the secondary amine 4-methylaminocetaphenone using tetra-*n*-butylammonium tribromide in MeOH (13). This bromination was regioselective

(only on the methyl group) and did not produce any byproducts on the ring from bromination.

An alternative synthesis of HM-IMPY is to follow one of the methods reported in the literature for the demethylation of *N,N*-dimethylanilines to perform a monodemethylation of the imidazopyridine IMPY (14). One of the approaches used $TiCl_4/CH_2Cl_2$ and only produced polymerized compounds (15). In the other approach, tetra-*n*-butylammonium periodate, a potent oxygen donor, was used to hydroxylate one of the methyl groups in the presence of a metalloporphyrin catalyst. Those two methods were not very successful: the first produced polymerized products only and the second led to low yields with many side reactions and had to be abandoned.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

FEM-IMPY was found to compete well with [^{125}I]TZDM, a probe selective for Aβ plaques previously reported in the literature (16). Studies of binding to Aβ-40 aggregates in solution and AD brain homogenates led to an inhibition constant (K_i) of 27 ± 8 nM. The high lipophilicity (Log D value of 4.41 ± 0.10 at pH 7.4) of FEM-IMPY might explain the relatively high nonspecific binding of [^{18}F]FEM-IMPY to human AD brain homogenates (~50% of the total binding) (12).

Incubation of mouse brain homogenates with [^{18}F]FEM-IMPY at 37°C for various lengths of time resulted in radioactive polar and lipophilic metabolites and parent [^{18}F]FEM-IMPY (12). A mass spectrum analysis of the metabolites showed the presence of a dealkylated aromatic amino group, consistent with the fact that tertiary amino groups are unstable in an oxidative environment. Complete N-dealkylation of [^{18}F]FEM-IMPY was not observed *in vitro*; the metabolism ended after the radioligand was degraded to ~10% conversion.

Animal Studies

Rodents

[PubMed]

Cai et al. (12) performed *in vivo* biodistribution studies on 4 normal male ICR mice (2–3 months-old) injected intravenously with a saline solution of [^{18}F]FEM-IMPY [14.8–16.5 MBq (0.4–0.5 mCi)]. Results showed that the radiotracer easily penetrated the blood–brain barrier, and a peak of the brain uptake [~6.4% injected dose/g (% ID/g)] was observed at 0.5 min after injection. This value compared well with [^{123,125}I]IMPY (7.2% ID/g in 2 min). However, the washout of radioactivity for [^{18}F]FEM-IMPY in normal mice was found to be biphasic (rapid over the first 20 min and much slower thereafter), whereas a single-exponential washout was observed for [^{123,125}I]IMPY. Residual brain radioactivity was 4.5% ID/g for [^{18}F]FEM-IMPY at 2 h after injection.

A high-performance liquid chromatography analysis of homogenates of *ex vivo* mouse brain after injection of the radioligand showed that the residual activity represented polar metabolites (presumably a fluoride ion or a related small-molecule ionic species such as $[^{18}F]FCH_2CO_2^-$) and was not the result of nonspecific binding. Lipophilicity of the ligands did not seem to play a role, and the contribution of the lipophilic intermediate was unclear at the time of the study. Given its low concentration observed both *in vivo* and *in vitro*, it might not have contributed significantly to the TACs.

Substantial bone uptake of [^{18}F]FEM-IMPY was observed in the skull. Substitution of the 4-ethylene protons by deuterium led to a 34% reduction of the radioactivity in the skull, while there was no effect on brain uptake or clearance of the radiotracer.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Cai et al. (12) performed brain PET scans on a male rhesus monkey (7.12 kg) after intravenous administration of 107.3 MBq (2.9 mCi) of [^{18}F]FEM-IMPY. The experiment involved acquiring dynamic transaxial images over a period of 120 min with scan duration ranging from 30 s to 5 min.

Results showed a rapid increase of brain activity, with peak values of 0.26–0.35% ID/g at 3–6 min after injection. [^{18}F]FEM-IMPY appeared to be washed out of all brain regions in a similar fashion, with a monoexponential washout rate of 0.05–0.09 min^{-1} (0.0488 ± 0.0020 min^{-1} for the brain stem, 0.0606 ± 0.0024 min^{-1} for the frontal cortex, 0.0859 ± 0.0037 min^{-1} for the striatum, and 0.0488 ± 0.0020 min^{-1} for the cerebellum), which corresponds to a half-life ($t_{1/2}$) of 8–14 min. Activity in bone increased exponentially and reached levels of ~0.1% ID kg/g, which is similar to residual activity in the brain and substantially less than what was observed in mice. The studies by Cai et al. (12) showed that the metabolism of [^{18}F]FEM-IMPY was significantly slower in rhesus monkeys than in mice.

Human Studies

[PubMed]

No publication is currently available.

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