^{18}F-Labeled 4-(5-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)benzofuran-2-yl)-*N*,*N*-dimethylbenzenamine

[^{18}F]FPHBF-1

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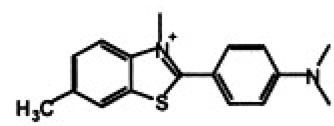
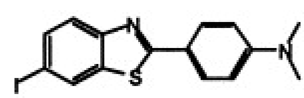
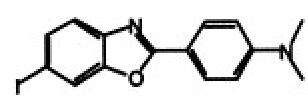
Chemical name:	^{18}F-Labeled 4-(5-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)benzofuran-2-yl)-*N*,*N*-dimethylbenzenamine
Abbreviated name:	[^{18}F]FPHBF-1
Synonym:	[^{18}F]17
Agent Category:	Compounds
Target:	β-amyloid (Aβ) plaque
Target Category:	Accepters
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{18}F



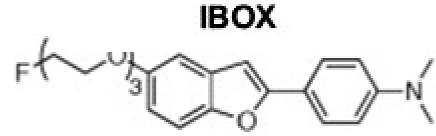
Thioflavin T



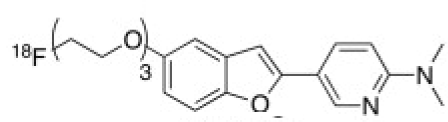
TZDM



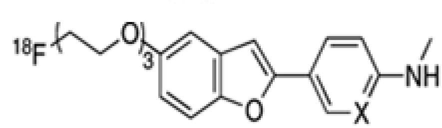
IBOX



FPHBF-1



[^{18}F]FPYBF-1



[^{18}F]**FPYBF-2**) (X = N)
[^{18}F]**FPHBF-2**) (X = CH)

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Activation:	No	
Studies:	• *In vitro* • Rodents	Structures of benzofuran derivatives by Ono and Cheng et al. (1-3).

Background

[PubMed]

^{18}F-Labeled 4-(5-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)benzofuran-2-yl)-*N*,*N*-dimethylbenzenamine (FPHBF-1), abbreviated as [^{18}F]FPHBF-1, is a fluoro-pegylated phenylbenzofuran synthesized for positron emission tomography (PET) of β-amyloid (Aβ) plaques by targeting Aβ (1-3).

Thioflavin T is a benzothiazole salt that is widely used to visualize and quantify the presence of Aβ *in vitro* (4, 5). Because of its high binding affinity with Aβ, thioflavin T has been intensively investigated as a template in the development of *in vivo* Aβ imaging agents (6-8). Ono et al. first synthesized a series of benzofuran derivatives by substituting N with CH on the heterocyclic ring of two thioflavin derivatives, TZDM (2-(4'-dimethylaminophenyl)-6-iodobenzothiazole) and IBOX (2-(4'-dimethylaminophenyl)-6-iodobenzoxazole) (4). Although these radioiodinated compounds displayed high binding affinity with Aβ *in vitro* with the inhibition constant (K_i) values in the subnanomolar range and a brain uptake ranging from 0.5% to 1.5% initial dose/organ (at 2 min after injection), they suffered from slow clearance from the normal mouse brain (<50% at 2 h after injection) (4). The investigators then modified the structures of these benzofuran derivatives by substituting the methoxy group at the 5 position with hydroxy group (5). These derivatives showed considerable tolerance for structural modification in terms of binding affinity, and their clearance from the normal mouse brain markedly improved (5).

To further improve the pharmacokinetics of benzofuran derivatives, investigators synthesized fluoro-pegylated phenylbenzofuran FPHBF-1 and pyridylbenzofuran FPYBF-1 (1, 3). Both FPYBF-1 and FPHBF-1 possess a fluoropolyethylene glycol side chain and a dimethylaminopyridyl group. In healthy mice, FPYBF-1 displayed faster clearance than FPHBF-1 from the brain, which was explained by the lower lipophilicity of

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FPYBF-1. Because several imaging agents with a monomethylamino group (e.g., AV-45, BAY94-9172, and GE067) have been shown to be stable *in vivo*, and compounds with a monomethylamino group have a lower lipophilicity than the corresponding compounds with a dimethylamino group, Ono et al. generated *N*-monomethylated pyridylbenzofuran (FPYBF-2) and phenylbenzofuran (FPHBF-2) by replacing the dimethylaminopyridyl group in FPYBF-1 and FPHBF-1 with a monomethylamino group (2). FPYBF-2 and FPHBF-2 showed slightly less affinity than FPYBF-1 and FPHBF-1 but exhibited more favorable *in vivo* pharmacokinetics. These results further suggest that the introduction of further hydrophilic groups into the scaffold may lead to the development of more useful pyridylbenzofuran and phenylbenzofuran derivatives.

This chapter summarizes the data obtained with [^{18}F]FPHBF-1. The data obtained with [^{11}C]8, [^{18}F]FPYBF-1, [^{18}F]FPYBF-2, and [^{18}F]FPHBF-2 are summarized in other chapters on MICAD.

Related Resource Links:

- Amyloid-targeted imaging agents in MICAD
- Amyloid-targeted imaging clinical trials in ClinicalTrials.gov
- Structures and other information of amyloid peptides in PubChem
- Alzheimer's disease articles in Online Mendelian Inheritance in Man

Synthesis

[PubMed]

Synthesis of the nonradiolabeled FPHBF-1 was described in detail by Cheng et al. (1). The key step in the formation of the benzofuran backbone was accomplished by an intramolecular Wittig reaction between triphenyl phosphonium salt and 4-nitrobenzoyl chloride or 4-dimethylaminobenzoyl chloride. [^{18}F]FPHBF-1 was prepared from a tosyl precursor *via* a nucleophilic displacement reaction with a fluoride anion. For the final product, [^{18}F]FPHBF-1, radiochemical yield was 10.0%, radiochemical purity was >99%, and specific activity was 242 GBq/μmol (6.54 Ci/μmol). The identity of [^{18}F]FPHBF-1 was verified with a comparison of the retention time with the nonradioactive FPHBF-1.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The affinity of nonradioactive FPHBF-1 with Aβ(1-42) peptide was measured in solutions with [^{125}I]2-(4'-dimethylaminophenyl)-6-iodoimidazo[1,2-*a*]pyridine ([^{125}I]IMPY, dissociation constant = 4.2 nM) as the competing radioligand (1, 9). The K_i values for FPYBF-1, FPHBF-1, FPYBF-2, FPHBF-2, and IMPY were 0.9, 2.0, 2.41, 3.85, and 10.5 nM, respectively (1-3). The calculated logarithms of water–octanol partition coefficients were 3.11, 3.73, 2.32, 2.94, and 3.79 for FPYBF-1, FPHBF-1, FPYBF-2, FPHBF-2, and IMPY, respectively (1-3).

To confirm the specific binding of [^{18}F]FPHBF-1 to Aβ plaques, autoradiographic imaging of [^{18}F]FPHBF-1 with sections (10 µm) of Tg2576 mouse brain was performed (1). The Tg2576 transgenic mice typically showed marked Aβ deposition in the cingulated cortex, entorhinal cortex, dentate gyrus, and CA1 hippocampal subfield by 11–13 months of age (1, 10). Autoradiographic images with [^{18}F]FPHBF-1 showed high levels of radioactivity in the brain sections, which was confirmed for the Aβ plaque labeling with thioflavin-S staining.

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{18}F]FPHBF-1 was analyzed in normal ddY male mice (*n* = 5/time point) (1). Mice were euthanized at 2, 10, 30, and 60 min after tail vein injection of 185–370 kBq (5–10 µCi). The radioactivity of the organs of interest was measured with a gamma counter. [^{18}F]FPHBF-1 displayed high initial brain uptake (2.88% and 5.16% ID/g at 2 and 10 min after injection, respectively), and the radioactivity cleared with time (3.14% and 2.80% ID/g at 30 and 60 min after injection, respectively). The $brain_{2\ min}$/$brain_{60\ min}$ ratio (an index of washout rate) was 1.0, lower than that of agents [^{18}F]BAY94-9172 (4.8), [^{18}F]AV-45 (3.8), [^{18}F]FPYBF-2 (2.34), [^{18}F]FPHBF-2 (2.11), and [^{18}F]FPYBF-1 (2.1), indicating a less favorable *in vivo* pharmacokinetics of [^{18}F]FPHBF-1 (3, 11, 12). Uptake in the bone was 1.19% ID/g at 2 min and 2.74% ID/g at 60 min after injection, suggesting *in vivo* defluorination.

The potential of [^{18}F]FPHBF-1 for imaging Aβ plaques in living brain tissue was examined in Tg2576 mice (36 months old, male) and in wild-type mice (36 months old, male) after tail vein injection of 9.29–11.1 MBq (0.25-0.3 mCi) [^{18}F]FPHBF-1 (1). Animals were euthanized at 30 min after injection. Autoradiography *ex vivo* showed clear labeling of the Aβ plaques in the Tg2576 mouse brain, but not in the wild-type mouse brain. Aβ plaques were confirmed by co-staining the sections with thioflavin-S. No blocking studies were performed.

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

References

1. Cheng Y.et al. *Fluorinated benzofuran derivatives for PET imaging of β-disease amyloid plaques in Alzheimer's disease brains.* ACS Med Chem Lett. 2010;1(7):321–5. PubMed PMID: 24900214.
2. Ono M.et al. *Novel 18F-labeled benzofuran derivatives with improved properties for positron emission tomography (PET) imaging of beta-amyloid plaques in Alzheimer's brains.* J Med Chem. 2011;54(8):2971–9. PubMed PMID: 21428407.
3. Cheng Y.et al. *A novel 18F-labeled pyridyl benzofuran derivative for imaging of beta-amyloid plaques in Alzheimer's brains.* Bioorg Med Chem Lett. 2010;20(20):6141–4. PubMed PMID: 20817524.
4. Ono M.et al. *Benzofuran derivatives as Abeta-aggregate-specific imaging agents for Alzheimer's disease.* Nucl Med Biol. 2002;29(6):633–42. PubMed PMID: 12234587.
5. Ono M.et al. *Novel benzofuran derivatives for PET imaging of beta-amyloid plaques in Alzheimer's disease brains.* J Med Chem. 2006;49(9):2725–30. PubMed PMID: 16640332.
6. Mathis C.A., Wang Y., Klunk W.E. *Imaging beta-amyloid plaques and neurofibrillary tangles in the aging human brain.* Curr Pharm Des. 2004;10(13):1469–92. PubMed PMID: 15134570.
7. Ono M. *Development of positron-emission tomography/single-photon emission computed tomography imaging probes for in vivo detection of beta-amyloid plaques in Alzheimer's brains.* Chem Pharm Bull (Tokyo). 2009;57(10):1029–39. PubMed PMID: 19801854.
8. Vallabhajosula S. *Positron emission tomography radiopharmaceuticals for imaging brain Beta-amyloid.* Semin Nucl Med. 2011;41(4):283–99. PubMed PMID: 21624562.
9. Newberg A.B.et al. *Safety, biodistribution, and dosimetry of 123I-IMPY: a novel amyloid plaque-imaging agent for the diagnosis of Alzheimer's disease.* J Nucl Med. 2006;47(5):748–54. PubMed PMID: 16644743.
10. Hsiao K.et al. *Correlative memory deficits, Abeta elevation, and amyloid plaques in transgenic mice.* Science. 1996;274(5284):99–102. PubMed PMID: 8810256.
11. Zhang W.et al. *18F-labeled styrylpyridines as PET agents for amyloid plaque imaging.* Nucl Med Biol. 2007;34(1):89–97. PubMed PMID: 17210465.
12. Zhang W.et al. *F-18 Polyethyleneglycol stilbenes as PET imaging agents targeting Abeta aggregates in the brain.* Nucl Med Biol. 2005;32(8):799–809. PubMed PMID: 16253804.