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

[^{18}F]FPYBF-1

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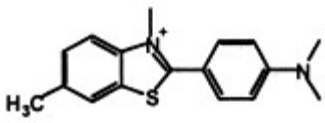
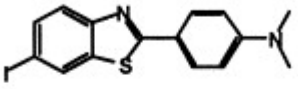
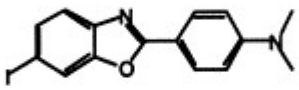
Chemical name:	^{18}F-Labeled 5-(5-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)benzofuran-2-yl)-*N*,*N*-dimethylpyridin-2-amine
Abbreviated name:	[^{18}F]FPYBF-1
Synonym:	[^{18}F]5
Agent Category:	Compounds
Target:	β-amyloid (Aβ)
Target Category:	Accepters
Method of detection:	Positron emission tomography (PET)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



Thioflavin T



TZDM



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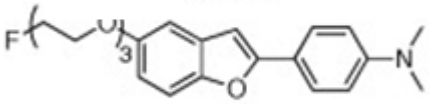
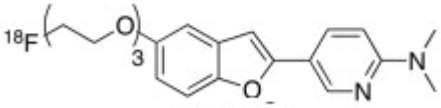
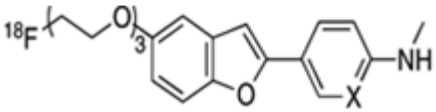


FPHBF-1



[^{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 5-(5-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)benzofuran-2-yl)-*N*,*N*-dimethylpyridin-2-amine (FPYBF-1), abbreviated as [^{18}F]FPYBF-1, is a fluoro-pegylated pyridylbenzofuran synthesized for positron emission tomography (PET) by targeting β-amyloid (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, 2). 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 (3). 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]FPYBF-1. The data obtained with [^{11}C]8, [^{18}F]FPHBF-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 FPYBF-1 was described in detail by Cheng et al. (2). The key step in the formation of the pyridylbenzofuran backbone was accomplished by Suzuki coupling between 5-methoxybenzofuran-2-boronic acid and 2-amino-5-iodopyridine. The ^{18}F-labeled FPYBF-1 was prepared from a tosyl precursor *via* a nucleophilic displacement reaction with a fluoride anion. For the final product, [^{18}F]FPYBF-1, radiochemical yield was 52%, radiochemical purity was >99%, and specific activity was 242 GBq/μmol (6.54 Ci/μmol). The identity of [^{18}F]FPYBF-1 was verified with a comparison of the retention time with the nonradioactive FPYBF-1.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The affinity of nonradioactive FPYBF-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) (2, 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).

Specific binding of [^{18}F]FPYBF-1 with human Aβ plaques was tested with postmortem brain sections (5 μm, temporal lobe) of an AD patient and a control subject (5 μm, temporal lobe). Autoradiographic images revealed extensive labeling of the Aβ plaques in the AD brain, but not in the control brain, suggesting selective binding with human Aβ plaques.

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{18}F]FPYBF-1 was analyzed in normal ddY male mice (n = 5/time point) (2). 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]FPYBF-1 displayed high brain uptake (5.16% ID/g) at 2 min after injection, and the radioactivity cleared with time (3.75%, 2.78%, and 2.44% ID/g at 10, 30, and 60 min after injection, respectively). The $\text{brain}_{2\ \text{min}}/\text{brain}_{60\ \text{min}}$ ratio (an index of washout rate) was 2.1, lower than that of agents [^{18}F]BAY94-9172 (4.8), [^{18}F]AV-45 (3.8), [^{18}F]FPYBF-2 (2.34), and [^{18}F]FPHBF-2 (2.11), but higher than that of [^{18}F]FPHBF-1 (1.0) (1-3, 10, 11). The favorable *in vivo* pharmacokinetics of [^{18}F]FPYBF-1 was achieved by changing the phenyl group in [^{18}F]FPHBF-1 to a pyridyl group. Uptake in the bone was 1.61% ID/g at 2 min and 1.42% ID/g at 60 min after injection, suggesting little *in vivo* defluorination.

The potential of [^{18}F]FPYBF-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 11.1 MBq (0.3 mCi) [^{18}F]FPYBF-1. Animals were euthanized at 30 min after injection. The Tg2576 transgenic mice typically show marked Aβ deposition in the cingulated cortex, entorhinal cortex, dentate gyrus, and CA1 hippocampal subfield by 11–13 months of age (1, 12). Autoradiography 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.

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

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