^{18}F-Labeled fluoropegylated 6-fluoroethoxy-4'-dimethylaminoflavone, 6-(2-(2-fluoro-ethoxy)-ethoxy)-4'-dimethylaminoflavone, and 6-(2-(2-(2-fluoro-ethoxy)-ethoxy)ethoxy)-4'-dimethylaminoflavone

[^{18}F]8(a–c)

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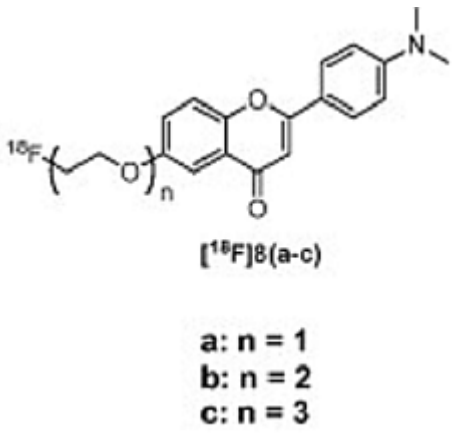
Chemical name:	^{18}F-Labeled fluoropegylated 6-fluoroethoxy-4'-dimethylaminoflavone, 6-(2-(2-fluoro-ethoxy)-ethoxy)-4'-dimethylaminoflavone, and 6-(2-(2-(2-fluoro-ethoxy)-ethoxy)ethoxy)-4'-dimethylaminoflavone
Abbreviated name:	[^{18}F]8(a–c)
Synonym:	[^{18}F]8a, [^{18}F]8b, [^{18}F]8c
Agent Category:	Compounds
Target:	β-amyloid (Aβ)
Target Category:	Accepters
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



Structure of [^{18}F]8(a–c) by Ono et al. (1).

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Background

[PubMed]

^{18}F-Labeled fluoropegylated 6-fluoroethoxy-4'-dimethylaminoflavone (compound 8a), 6-(2-(2-fluoro-ethoxy)-ethoxy)-4'-dimethylaminoflavone (compound 8b), and 6-(2-(2-(2-fluoro-ethoxy)-ethoxy)ethoxy)-4'-dimethylaminoflavone (compound 8c), abbreviated as [^{18}F]8a, [^{18}F]8b, and [^{18}F]8c, respectively, are flavone derivatives synthesized by Ono et al. for positron emission tomography (PET) of Alzheimer's disease (AD) by targeting β-amyloid (Aβ) (1).

AD is characterized in pathology by the presence of extracellular Aβ plaques, intraneuronal neurofibrillary tangles, and neuronal loss in the cerebral cortex (2, 3). Of them, Aβ deposit is the earliest neuropathological marker and is relatively specific to AD and closely related disorders. Aβ plaques are composed of abnormal paired helical filaments 5–10 nm in size. These filaments are largely made of insoluble Aβ peptides that are 40 or 42 amino acids in length (4).

In recent years, molecular imaging by targeting the extracellular Aβ has been intensively investigated in attempts to detect early AD, assess Aβ content *in vivo*, determine the timing of anti-plaque therapy, and evaluate the therapeutic efficacy (4). Radiolabeled Aβ40 peptides were tested first, but they showed poor penetration ability to cross the blood–brain barrier (BBB) (4). Based on the fact that Aβ can be specifically stained *in vitro* with dyes of Congo red, chrysamine G, and thioflavin-T, an effort was made to develop imaging agents with these dyes. This effort, however, was in general unsuccessful because the bulky ionic groups of heteroatoms in these dyes prevent them from crossing the BBB (2). Importantly, a large class of derivatives (e.g., aminonaphthalenes, benzothiazoles, stilbenes, and imidazopyridines) was synthesized with these dyes as templates (4). Clinical and preclinical studies have shown that these derivatives not only possess a high binding affinity with Aβ plaques as their parent compounds, but also exhibit good penetration ability through the BBB and rapid washout from brain with low to no plaque deposits.

Ono et al. first synthesized a class of radioiodinated flavone derivatives that present a high binding affinity with Aβ plaques and good penetration ability through the BBB (5). However, these flavone derivatives display poor clearance from the brain, which leads to a high brain background. The investigators then explored another class of flavonoids with aurone as the core structure (1, 6). Aurone is a heterocyclic chemical compound that

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contains a benzofuran element associated with a benzylidene linked in position 2 and a chalcone-like group being closed into a five-member ring. The aurone derivatives possess a nucleophilic group (NH_2, NHMe, or NMe_2) at the 4' position and a radioiodine at the 5 position. Although these aurone derivatives exhibit a strong binding affinity with Aβ (inhibition constant (K_i) = 1.2–6.8 nM), high penetration ability through the BBB (1.9% –4.6% injected dose per gram tissue (ID/g) at 2 min), and a fast washout from the brain (0.3%–0.5% ID/g at 30 min), the pharmacokinetics of these compounds are less favorable for brain imaging than the pharmacokinetics of the agent [123I]IMPY (6-iodo-2-(4'-dimethylamino)phenyl-imidazo[1,2]pyridine), which is the only SPECT agent to be tested in humans to date (7-9). The investigators also modified the flavone and aurone derivatives by pegylating them with 1–3 units of ethylene glycol at the 4' position or by conjugating them with the chelating agent bis-amino-bis-thiol (BAT). Favorable pharmacokinetics for brain imaging was observed for the pegylated derivatives ([18F]8(a–c)) but not for the BAT-chelated derivatives ([99mTc]BAT-FL and [99mTc]BAT-AR) (1, 6).

This series of chapters summarizes the data obtained with flavone and aurone derivatives, including [125I]15, [125I]9, [125I]14, [125I]16, [125I]17, [99mTc]BAT-FL, [99mTc]BAT-AR, [18F]8(a–c), [125I]3, and [18F]3 (1, 6-8). This chapter presents the data obtained with [18F]8(a–c) (1).

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]

The synthesis of the compound precursors with chemical yields was described in detail by Ono et al. (1). [18F]8(a–c) was obtained with the reaction of the corresponding tosylate precursors with [18F]fluoride. The reaction mixture was purified with reversed phase high-performance liquid chromatography. The radiochemical purities of the final products were >99%; radiochemical yields ranged from 5% to 13%; total synthesis times were 70 min; and specific activities were 33.3–55.5 GBq/mmol (900–1,500 mCi/mmol) at the end of synthesis.

[125I]6-Iodo-4'-dimethylaminoflavone ([125I]DMFV, K_d = 12.3 nM) was prepared as the radioligand in binding assays using the standard iododestannylation reaction (10). The specific activity and radiochemical purity of [125I]DMFV were 81.4 TBq/mmol (2.2 kCi/mmol) and >95%, respectively.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The binding of [^{18}F]8(a–c) with Aβ aggregates was carried out with [^{125}I]DMFV in solutions (1, 10). The K_i values were measured to be 5.3, 14.4, and 19.3 for [^{18}F]8a, [^{18}F]8b, and [^{18}F]8c, respectively. The results of K_i measurement for [^{18}F]8(a–c) and other derivatives indicate that the affinities of flavone derivatives for Aβ(1–42) aggregates were affected by the group substituted at the 4' position in the flavone structure, not by the length of ethylene glycol introduced into the flavone backbone (1).

The affinity of [^{18}F]8(a–c) for brain Aβ plaques was analyzed with brain sections of *Tg2576* transgenic mice with fluorescence staining (1). Many fluorescent spots were observed, and these findings were consistent with those obtained with immunohistochemical labeling with an antibody specific for Aβ. No spots were observed in the brain sections of wild-type mice (data not shown). These results indicate that [^{18}F]8(a–c) can bind specifically with Aβ plaques in the mouse brain.

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{18}F]8(a–c) was examined in normal mice (n = 4–5/time point for each agent) (1). All three ligands displayed high radioactivity in the brain at 2 min after injection (2.89%–4.17% ID/g). Low radioactivity was observed at 30 min after injection (1.89%, 2.00%, and 1.31% ID/g for [^{18}F]8a, [^{18}F]8b, and [^{18}F]8c, respectively). These values were equal to 45.3%, 56.5%, and 45.3% of the initial uptake peak for [^{18}F]8a, [^{18}F]8b, and [^{18}F]8c, respectively, indicating a rapid initial uptake in normal brain tissue coupled with a fast washout, which is highly desirable for Aβ imaging. [^{18}F]8(a–c) also showed high bone uptake (3.74%–6.21% ID/g) at 60 min after injection, suggesting there may be *in vivo* defluorination. However, the interference from this free fluoride is expected to be relatively low for brain imaging because the free fluorine was not taken up by brain tissue (1).

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.

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