^{18}F-Labeled 6-methyl-2-(4′-fluorophenyl)-1,3-benzothiazole

[^{18}F]5

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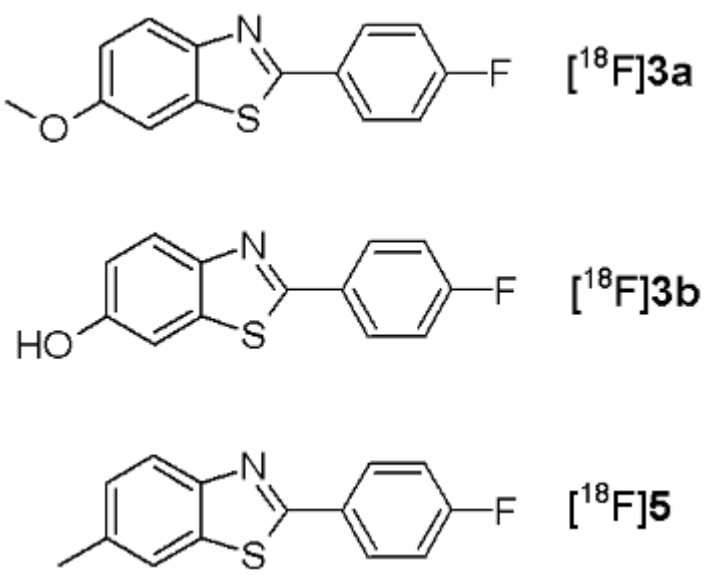
Chemical name:	^{18}F-Labeled 6-methyl-2-(4'-fluorophenyl)-1,3-benzothiazole
Abbreviated name:	[^{18}F]**5**
Synonym:	
Agent Category:	Compound
Target:	β-Amyloid plaques (Aβ)
Target Category:	Protein
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



Structures of [^{18}F]**3a**, [^{18}F]**3b** and [^{18}F]**5**.

Background

[PubMed]

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Development of Alzheimer's disease (AD) has been attributed to neurodegeneration as a result of the neuronal overexpression, secretion, and deposition of the neurotoxic amyloid β (Aβ) fragment of the Aβ protein precursor in the brain (1). No specific treatment for AD is currently available, and clinicians are increasingly focused on developing ways to either prevent or delay the formation of Aβ plaques in the brain of AD patients (2). In addition, several hundred clinical trials approved by the United States Food and Drug Administration have been completed or are in progress to develop drugs for the prevention, onset delay, or treatment of AD. Early detection of Aβ plaques by non-invasive techniques such as positron emission tomography (PET) is often used to identify individuals who are prone to get the disease and to monitor the efficacy of drugs used to treat or delay onset of the disease (3). Although several immunohistochemical fluorescent stains and an antibody directed against the Aβ have been used to detect the plaques in the brain of AD patients, this information can be obtained only during postmortem (4). Hence, the development and evaluation of a suitable agent that can non-invasively detect Aβ plaques during early onset and monitor progression and treatment of the disease is an ongoing task.

Many radiolabeled tracers have been developed and evaluated under preclinical conditions, but among these only the ^{11}C-labeled Pittsburgh compound B (6-hydroxy-2-(4'-*N*-[^{11}C]methylaminophenyl)-1,3-benzothiazole ([^{11}C]PIB)) is the most commonly used PET tracer for detection of the Aβ plaques (3, 4). However, a major limitation of labeled compound is the short half-life (20.4 min) of ^{11}C, which means that the use of [^{11}C]PIB is restricted to clinical facilities that can generate the radionuclide on-site (3). To circumvent limitations observed with the ^{11}C-labeled compounds, investigators developed several compounds labeled with ^{18}F (half-life, 109.8 min) that can be used non-invasively with PET, but these tracers either have a low specificity or are still under clinical evaluation (5-7). In an effort to develop and evaluate radiotracers that can be used to detect and monitor the progression and treatment of AD, Serdons et al. (4) synthesized three benzothiazole derivatives, 6-methoxy-2-(4'-[^{18}F]fluorophenyl)-1,3-benzothiazole ([^{18}F]**3a**), 6-hydroxy-2-(4'-[^{18}F]fluorophenyl)-1,3-benzothiazole ([^{18}F]**3b**), and 6-methyl-2-(4'-[^{18}F]fluorophenyl)-1,3-benzothiazole ([^{18}F]**5**), and evaluated the affinity of these labeled compounds for Aβ fibrils under *in vitro* conditions. In addition, the biodistribution of these radiochemicals was studied in normal mice, and the brain pharmacokinetics of these labeled compounds were investigated in normal mice and rats using micro-PET (μPET).

Other sources of information regarding human β amyloid protein

β Amyloid plaques in OMIM (Online Mendelian Inheritance in Man).

Human β amyloid protein and nucleotide sequence.

Alzheimer's disease in OMIM.

Alzheimer's disease in Genome Wide Association Studies database.

FDA-approved treatments for Alzheimer's disease (from Alzheimer's Association web site; www.alz.org).

Synthesis

[PubMed]

The synthesis processes of [^{18}F]**3a** (6-methoxy-2-(4'-[^{18}F]fluorophenyl)-1,3-benzothiazole), [^{18}F]**3b** (6-hydroxy-2-(4'-[^{18}F]fluorophenyl)-1,3-benzothiazole), and [^{18}F]**5** (6-methyl-2-(4'-[^{18}F]fluorophenyl)-1,3-benzothiazole) were described by Serdons et al. (4). The decay-corrected radiochemical yields of these tracers were 24.1 ± 2.3%, 38.0 ± 0.2%, and 29.4 ± 3.2%, respectively. The time of synthesis required to obtain the labeled product was 60–80 min. The identity of each compound was confirmed by co-injection and co-elution with a corresponding nonradioactive sample of the compound using analytical reverse-phase high-performance liquid chromatography (RP-HPLC). The purity of each radiolabeled compound was reported to be >95% as determined with RP-HPLC. The average specific activity of the radiolabeled compounds at the end of synthesis was 116 GBq/μmol (3.13 Ci/μmol) (4).

Details of the biostability of [^{18}F]**5** in the plasma of mice and the brains of mice and rats (4) are provided in the appropriate Animal Studies subsections below.

[^{11}C]PIB used for comparison purposes was synthesized as described elsewhere (8), but the radiochemical yield, purity, and specific activity of the radiocompound were not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The affinities of nonradioactive compounds **3a**, **3b**, **5**, and [^{11}C]PIB for Aβ plaques, using human AD brain homogenates in a [^{125}I]IMPY binding competition assay, were reported to be 2.2 ± 0.5, 22.5 ± 4.5, 5.7 ± 1.8, and 2.8 ± 0.5 nM, respectively (4). This indicated that compound **3b** had a low affinity for the Aβ plaques, but the affinities of **3a** and **5** were comparable to that of [^{11}C]PIB.

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{18}F]**3a**, [^{18}F]**3b**, [^{18}F]**5**, and [^{11}C]PIB was studied in male NMRI mice (n = 4–6 animals/time point per radiotracer) at 2 min and 60 min after an injection through the tail vein (4). The animals were euthanized at the appropriate time point, and the various organs were removed and counted for accumulated radioactivity. Data obtained from the study were presented either as percentage of injected dose (% ID) or as

% ID per gram tissue (% ID/g). For details of the biodistribution study, see Tables 2, 3, 4, and 5 in Serdons et al. (4). Also, only data for the brain are considered here because accumulation of radioactivity in the other organs is of little consequence when detecting Aβ plaques. Briefly, the initial uptake values of [^{18}F]**3a** (5.1 ± 0.4% ID/g) and [^{18}F]**5** (5.3 ± 0.7% ID/g) were slightly higher than that of [^{18}F]**3b** (4.7 ± 0.5% ID/g). Also, [^{18}F]**5** had a significantly higher ($P < 0.05$, two-sided) uptake at 2 min postinjection (p.i.) compared with [^{11}C]PIB (3.6 ± 1.4% ID/g). The brain washout (ratio of % ID in cerebrum at 2 min to % ID in cerebrum at 60 min) of [^{18}F]**5** was higher (ratio = 23.1) than either [^{18}F]**3a** (ratio = 12.1) or [^{18}F]**3b** (ratio = 8.4), and this value was almost four-fold higher than that of [^{11}C]PIB (ratio = 6.0), indicating that [^{18}F]**5** could be a promising agent for imaging Aβ plaques under *in vivo* conditions (4). The clearance from the blood (ratio of % ID in blood at 2 min to % ID in blood at 60 min) of [^{18}F]**5** (ratio = 2.0) was between that of [^{18}F]**3a** (ratio = 1.1) and those of [^{18}F]**3b** (ratio = 3.0) and [^{11}C]PIB (ratio = 2.9). Radioactivity derived from the various labeled compounds was eliminated from the animals primarily through the hepatobiliary system (range, 48–71% ID) and to some extent through the urine (range, 5.6–26% ID).

Because [^{18}F]**5** showed superior uptake and washout characteristics in the brain of normal mice compared to the other ^{18}F-labeled compounds, Serdons et al. investigated the stability of this radiochemical in the plasma and brain of these animals (4). The animals ($n = 3$ mice/time point) were injected with the tracer through the tail vein and killed by decapitation at 2, 10, 30, or 60 min p.i. Plasma from the animals was recovered and analyzed with RP-HPLC after co-injection with a nonradioactive sample of compound **5**. Only 60% of the labeled compound remained intact at 2 min, and at least three unidentified metabolites of [^{18}F]**5** were detected. By 60 min p.i., only 1.6% of [^{18}F]**5** was intact in the plasma *versus* 80% of [^{11}C]PIB. In the mouse brain, <15% of [^{18}F]**5**-labeled metabolites were observed at either 2 min or 60 min p.i., indicating that little metabolism of the radiolabeled compound occurred in this organ and that the radiometabolites did not cross the blood–brain barrier in these animals (4). In another study using the rat ($n = 1$), ~80% of [^{18}F]**5** was reported to remain intact in the brain of this animal at 2 min p.i. (data at 60 min p.i. for this animal were not reported), which was comparable to the degree of breakdown observed for [^{11}C]PIB in these animals.

The brain pharmacokinetics of [^{18}F]**3a**, [^{18}F]**3b**, and [^{18}F]**5** were compared using μPET to those of [^{11}C]PIB in a normal rat (4). The respective tracers were administered to the animal (under anesthesia, but breathing spontaneously) through the tail vein with a time period of 5 d between each injection of ^{18}F-labeled compound. Dynamic μPET images were acquired for 120 min after the injection of each radiochemical. The data with [^{11}C]PIB (acquired for 90 min), for comparison with the ^{18}F tracers, were obtained during a μPET study performed with the same rat 2 weeks earlier. All data were expressed as standard uptake values. All the radioactive compounds, including [^{11}C]PIB, had a similar rapid brain uptake and a fast clearance profile compared to the variable uptake and clearance rates observed for these radiochemicals in the mouse brain during the biodistribution studies. The differences in uptake and washout observed between the rat and mouse brain were attributed to interspecies characteristics of the animals (4). Because

no ^{18}F was detected in the skull of the rat during the μPET study, the investigators concluded that little or no defluorination of the labeled 2-phenylbenzothiazoles was apparent under *in vivo* conditions.

With results obtained from these studies, the investigators concluded that [^{18}F]**5** could be a suitable compound for the detection of Aβ plaques in human AD patients (4). However, it is important to mention that [^{18}F]**5** would have to be evaluated in clinical trials before it can be used for the intended purpose in humans.

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.

Supplemental Information

[Disclaimers]

No information is currently available.

References

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