^{18}F-Labeled 6-amino-2-(4′-fluorophenyl)-1,3-benzothiazole and other derivatives

[^{18}F]2

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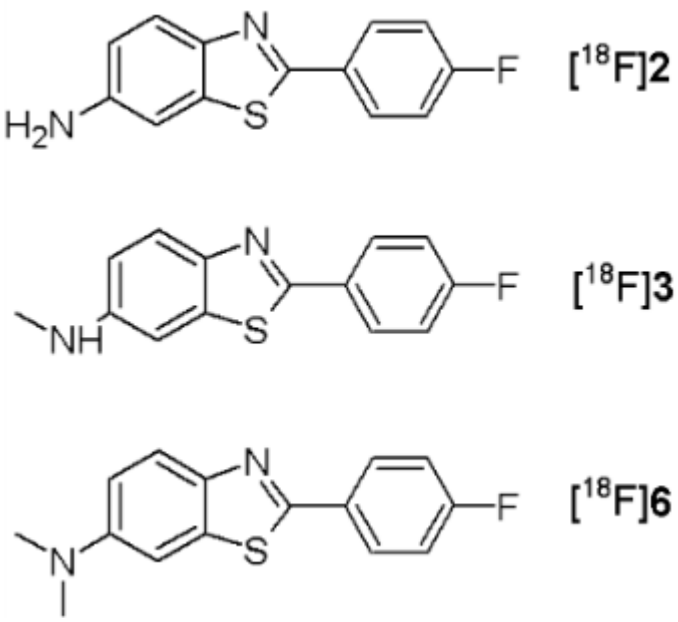
Chemical name:	^{18}F-Labeled 6-amino-2-(4'-fluorophenyl)-1,3-benzothiazole and other derivatives
Abbreviated name:	[^{18}F]**2**
Synonym:	
Agent Category:	Compound
Target:	Human amyloid β plaques
Target Category:	Protein
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates



Structures of [^{18}F]**2**, [^{18}F]**3** and [^{18}F]**6**.

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Background

[PubMed]

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 also to monitor the efficacy of drugs used to treat or delay onset of the disease (3).

The ^{11}C-labeled Pittsburgh compound B ([^{11}C]PIB) is the most commonly used PET tracer for detection of Aβ plaques, but due to the short half-life (20.4 min) of ^{11}C the use of this label is restricted to clinical facilities that have the capability to generate the agent on-site (3). Some ^{18}F-labeled compounds have also been generated for the visualization of Aβ plaques, but these labeled compounds have low specificity (3), and the PIB analogs [^{18}F]BAY94-9172 (4) and [^{18}F]GE067 (5) or its derivative, [^{18}F]flutemetamol (6), are currently under clinical evaluation. In an ongoing effort to develop ^{18}F-labeled compounds for the detection of Aβ plaques and to monitor the efficacy of drugs used to treat AD, Serdons et al. (3) synthesized three new ^{18}F-labeled derivatives of 2-phenylbenzothiazoles (designated [^{18}F]**2**, [^{18}F]**3**, and [^{18}F]**6**, respectively), determined the *in vitro* affinity of these tracers for Aβ fibrils, and investigated their biodistribution in mice, pharmacokinetics in rats, and pharmacokinetics and uptake in monkeys.

Other sources of information regarding human β amyloid protein

β Amyloid plaques in OMIM.

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]**2** (6-amino-2-(4'-[^{18}F]fluorophenyl)-1,3-benzothiazole), [^{18}F]**3** , (6-methylamino-2-(4'-[^{18}F]fluorophenyl)-1,3-benzothiazole) and [^{18}F]**6** (6-dimethylamino-2-(4'-[^{18}F]fluorophenyl)-1,3-benzothiazole), respectively, were described by Serdons et al. (3). The identity of the labeled compounds was confirmed by co-elution with the appropriate unlabeled compound using the same analytical high-performance liquid chromatography (HPLC) procedure. The time taken to obtain the pure products was reported to be between 75 and 100 min. The radiochemical purity of the tracers was reported to be >99% with a yield of 10.5 ± 5.2% for [^{18}F]**2** (specific activity, 72 GBq/μmol (1.945 Ci/μmol)), 45.0 ± 12.5% for [^{18}F]**3** (specific activity, 82 GBq/μmol (2.216 Ci/μmol)), and 19.3 ± 9.0% for [^{18}F]**6** (specific activity, 24 GBq/μmol (0.648 Ci/μmol)).

In some studies, [^{11}C]PIB and [^{18}F]KS28 were also used for comparison with [^{18}F]**2**, [^{18}F]**3**, and [^{18}F]**6** (3). However, the synthesis, radiochemical purity, yield, specific activity, and stability of [^{11}C]PIB and [^{18}F]KS28 were not reported.

The *in vivo* stability of [^{18}F]**2**, [^{18}F]**3**, and [^{18}F]**6** was studied in normal mice and monkeys and has been described in the appropriate Animal Studies subsections of below.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Using human AD brain homogenates in a [^{125}I]IMPY competition assay, the *in vitro* affinities of unlabeled compounds **2**, **3**, and **6** for Aβ fibrils were determined by Serdons et al. (3). The inhibition constant values for compounds **2**, **3**, and **6** were reported to be 10.0 ± 1.0, 4.1 ± 0.3, and 3.8 ± 0.4 nM, respectively.

Animal Studies

Rodents

[PubMed]

To investigate the brain pharmacokinetics of the labeled Aβ-targeting compounds, the biodistribution of [^{18}F]**2**, [^{18}F]**3**, and [^{18}F]**6** was compared to that of [^{11}C]PIB and [^{18}F]KS28 at 2 min and 60 min after intravenous (i.v.) injection of the respective tracers in normal mice (n = 4–6 animals/tracer per time point) as described by Serdons et al. (3). Data are presented as a percentage of injected dose per gram tissue (% ID/g); for complete biodistribution of the radiolabeled compounds in mice, see Tables 2, 3, 4, 5, and 6 in Serdons et al. (3). Among the Aβ tracers, [^{18}F]**2** had the highest uptake in the cerebrum (13.97 ± 0.63% ID/g) at 2 min postinjection (p.i.), followed by [^{18}F]**3** (12.13 ± 0.48% ID/g) and [^{18}F]**6** (8.84 ± 0.91% ID/g). The brain uptake of the three labeled Aβ binding compounds was significantly higher ($P < 0.05$, two-sided) than either [^{11}C]PIB (3.60 ± 1.40% ID/g) or [^{18}F]KS28 (5.33 ± 0.74% ID/g). Also, the brain uptake of [^{18}F]**2** > [^{18}F]**3** > [^{18}F]**6** ($P < 0.05$, two-sided, between each compound). The ratios of accumulated radioactivity in the cerebrum at 2 min and 60 min for [^{18}F]**2**, [^{18}F]**3**, and [^{18}F]**6** were

14.2, 7.8, and 4.5 respectively. Also, for [^{18}F]**2** this ratio was four-fold and three-fold higher than for [^{11}C]PIB and [^{18}F]KS28, respectively. This indicated that the washout of radioactivity from the brain for [^{18}F]**2** was slower than that of all the other tracers. In another study, animals pretreated with unlabeled compound **2** followed by an injection of [^{18}F]**2** (the time difference between the pretreatment and injection of the radiolabeled compound was not reported) showed there was no significant difference ($P < 0.05$, two-sided) in the biodistribution of radioactivity between the pretreated and the untreated animals at 60 min p.i., suggesting that the radioactivity accumulated at 60 min p.i. was probably due to nonspecific binding of the label. The clearance of [^{18}F]**2** from the blood was reported to be faster than that of either [^{11}C]PIB or [^{18}F]KS28. In addition, the radioactivity from the different compounds was cleared from the plasma primarily through the hepatobiliary system, and a small fraction was excreted through the urine.

The *in vivo* stability of the various Aβ tracers was investigated with HPLC analysis of the plasma and brain of normal mice. Samples were obtained from the animals at 2, 10, 30, and 60 min ($n = 3$ animals/time point) after an i.v. injection of the respective tracers (3). The percentages of intact [^{18}F]KS28, [^{18}F]**2**, [^{18}F]**3**, and [^{18}F]**6** in the plasma were 3.2 ± 1.7, 16.5 ± 2.0, 4.1 ± 1.4, and 6.0 ± 6.4, respectively, at 60 min p.i. The ^{18}F-labeled compounds **2**, **3**, and **6** were reported to have at least two, three, and four metabolites, respectively, in the plasma as determined with reverse-phase (RP)-HPLC. The percentages of intact [^{18}F]KS28, [^{18}F]**2**, [^{18}F]**3**, and [^{18}F]**6** in the brain were 86.2 ± 2.5, 86.3 ± 0.0, 60.3 ± 3.9, and 59.2 ± 17.9, respectively, at 60 min p.i. as determined with RP-HPLC. This observation indicated that the radiometabolites of [^{18}F]**2** did not efficiently cross the blood–brain barrier (BBB) in the mice.

To investigate the brain pharmacokinetics of the new ^{18}F-labeled Aβ binding tracers, micro-PET (μPET) imaging was performed on a normal male Wistar rat (under anesthesia with isoflurane in oxygen) injected with either [^{18}F]**2**, [^{18}F]**3**, or [^{18}F]**6** through the tail vein (time interval of 1 d or 3 d between each radiocompound injection) as described by Serdons et al. (3). Dynamic μPET images of the animal were acquired at 120 min p.i. Data obtained from this study were compared to data obtained earlier with [^{11}C]PIB and [^{18}F]KS28, respectively, during a μPET imaging study (7). For a blocking study, a spontaneously breathing rat was given an intraperitoneal injection of excess (0.35 mg) unlabeled compound **2** followed by i.v. injection of [^{18}F]**2** 30 min later, and μPET images were obtained as before. Time-activity curves for the various tracers in the frontotemporal cortex of the animal were obtained, and the values were expressed as standard uptake values (SUVs). The brain uptake values of [^{18}F]**2**, [^{18}F]**3**, or [^{18}F]**6** were reported to be approximately two-fold higher than either [^{11}C]PIB or [^{18}F]KS28 at 2 min p.i. A comparison of the SUVs for the mouse cerebrum (for details see above) and the rat frontotemporal cortex were similar, but at 60 min p.i. these values were lower for the mice than those obtained with the rats, indicating there was an interspecies difference in clearance of the labeled compounds from the brain of these animals. Similar to the biodistribution study with mice, no significant ($P < 0.05$, two-sided) difference between the SUVs of the pretreated and the untreated rats was noticed, indicating that the

prolonged retention of [^{18}F]2 was due to nonspecific binding of radioactivity. No blocking studies were reported.

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

Because of the interspecies brain washout differences observed with the mice and rats, the brain uptake values of [^{18}F]**2**, [^{18}F]**3**, and [^{18}F]**6** were studied with μPET imaging in a normal rhesus monkey (*Maccaca mulatta*; initially sedated with ketamine and later anesthetized with isoflurane) (3). The monkey was injected with [^{18}F]**2**, [^{18}F]**3**, [^{18}F]**6**, or [^{11}C]PIB through the vena saphena with a 1-d interval between each tracer. Dynamic μPET imaging was performed for 180 min with [^{18}F]**2**, [^{18}F]**3**, and [^{18}F]**6** and for 90 min for [^{11}C]PIB. Data analysis was performed as described for the rat μPET study (see above). None of the new tracers were detected in the monkey skull, indicating that these labeled compounds or their metabolites did not cross the BBB. For a detailed description and discussion of the results from this study, see Serdons et al. (3). Briefly, although [^{18}F]**3** had the highest initial uptake, [^{18}F]**2** had the fastest clearance from the brain. In addition, [^{18}F]**2** had the highest ratio between the cerebrum and the brain white matter, indicating that this radiolabeled compound had the lowest nonspecific binding in the monkey white matter, which is considered a favorable characteristic for the detection of Aβ plaques by imaging in AD patients.

The pharmacokinetics of [^{18}F]**2**, [^{18}F]**3**, [^{18}F]**6**, and [^{11}C]PIB were investigated in monkey plasma by analyzing samples taken at different time points (varying from 2–180 min p.i.) as described by Serdons et al. (3). Among the new Aβ tracers, only [^{18}F]**2** was 66.9% intact at 180 min after the injection as determined with RP-HPLC(at 2 min [^{18}F]**2** was 91.8% intact), and its rate of metabolism was comparable to that of [^{11}C]PIB (3).

On the basis of the results obtained from this study, Serdons et al. concluded that [^{18}F]**2** is probably a suitable PET imaging agent for the detection of Aβ plaques in AD patients (3). However, it is appropriate to mention here that the use of this labeled compound in humans will have to be evaluated in clinical trials before [^{18}F]**2** can be utilized for the detection of Aβ plaques in humans.

Human Studies

[PubMed]

No references are currently available.

Supplemental Information

[Disclaimers]

No information is currently available.

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