4-Hydroxy-, 5-hydroxy-, and 7-hydroxy- analogs of 6-hydroxy-2-(4′-[^{11}C]methylaminophenyl)-1,3-benzothiazole

[^{11}C]6a, [^{11}C]6b, and [^{11}C]6c

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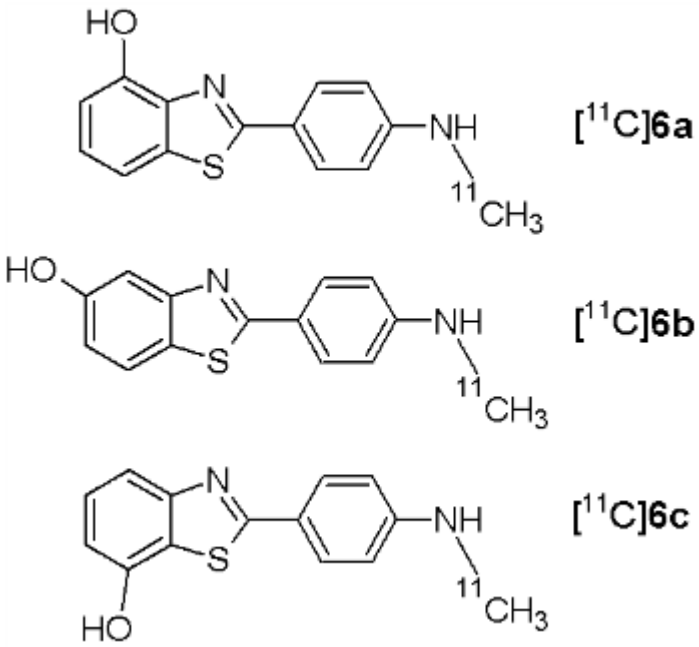
Chemical name:	4-Hydroxy-, 5-hydroxy-, and 7-hydroxy- analogs of 6-hydroxy-2-(4'-[^{11}C]methylaminophenyl)-1,3-benzothiazole
Abbreviated name:	[^{11}C]6a, [^{11}C]6b, and [^{11}C]6c
Synonym:	
Agent Category:	Compound
Target:	β-Amyloid plaques (Aβ)
Target Category:	Protein
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents



Structure of [^{11}C]**6a**, [^{11}C]**6b** and [^{11}C]**6c**.

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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 extracellular deposition of the neurotoxic amyloid-β (Aβ) fragment of the Aβ protein precursor in the brain (1). In addition, the AD brain neurons are known to form and deposit neurofibrillary tangles in the cytoplasm (2). No specific treatment for AD is currently available, and researchers and clinicians are increasingly focused on developing ways to either prevent or delay the formation of Aβ plaques in the brain of AD patients (3). 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 (4). 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 (5). Hence, the development and evaluation of a suitable agent for the non-invasive detection of Aβ plaques during early onset or to 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 agent for the PET imaging of Aβ plaques (2, 4, 5). Clinical evaluation of ^{18}F-labeled PIB derivatives for the detection of Aβ plaques is an ongoing process, and efforts are under way to develop other imaging agents that could be superior to PIB. In this regard, Serdons et al. (2) synthesized three ^{11}C-labeled structural isomers of PIB with the hydroxyl group at position 4, 5, or 7 (designated as [^{11}C]**6a**, [^{11}C]**6b**, and [^{11}C]**6c**, respectively), compared to the position 6 hydroxyl group in PIB, and investigated the binding of these labeled compounds to Aβ plaques in mouse and human AD brain sections. The biodistribution of these tracers, particularly in the brain, was also compared to that of [^{11}C]PIB in normal mice.

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 [^{11}C]**6a** (4-hydroxy-2-(4'-methylaminophenyl)-1,3-benzothiazole), [^{11}C]**6b** (5-hydroxy-2-(4'-methylaminophenyl)-1,3-benzothiazole), and [^{11}C]**6c** (7-hydroxy-2-(4'-methylaminophenyl)-1,3-benzothiazole) were described in detail by Serdons et al. (2). The identity of the labeled compounds was confirmed with radio-high-performance liquid chromatography and radio-mass spectrometry. The specific activity, radiochemical purity, and stability of the labeled compounds were not reported. The radiochemical yield of [^{11}C]**6a** was not reported, but the radiochemical yields for [^{11}C]**6b** and [^{11}C]**6c** were reported to be 5% and 7%, respectively (not decay-corrected).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Using an [^{125}I]IMPY competition assay, Serdons et al. determined the affinity of unlabeled **6a**, **6b**, and **6c** for Aβ fibrils in human AD brain homogenates (2). The inhibition constant values of **6a**, **6b**, and **6c** were reported to be 18.8 ± 3.8, 11.5 ± 3.0, and 11.2 ± 0.5 nM compared to that of 2.8 ± 0.5 for nonradioactive PIB.

The binding of nonradioactive **6a**, **6b**, and **6c** to Aβ plaques in brain sections obtained from transgenic AD mice and the brain of an AD patient was confirmed with fluorescent microscopy and in Aβ antibody co-localization studies, and it has been described by Serdons et al. (2).

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{11}C]**6a**, [^{11}C]**6b**, and [^{11}C]**6c** was compared to that of [^{11}C]PIB in normal mice (2). Groups of 4 animals/time point were injected with the different labeled compounds through the tail vein, and the mice were euthanized at 2 min and 60 min postinjection (p.i.). Various organs (kidneys, liver, intestine, cerebrum, cerebellum, and blood) were removed from the euthanized animals, and radioactivity accumulated in the different tissues was determined. Details of label uptake by the various tissues are presented in Tables 2–5 of Serdons et al. (2). Data were presented as a percentage of injected dose (% ID)/gram tissue (% ID/g). At 2 min p.i., [^{11}C]**6a**, [^{11}C]**6b**, and [^{11}C]**6c** had uptake values similar to the parent compound. With [^{11}C]**6a**, a higher amount of radioactivity was present in the cerebrum (3.8 ± 0.9% ID/g) than in the cerebellum (2.7 ± 2.1% ID/g), and the accumulated radioactivity was similar to that observed with [^{11}C]PIB (3.6 ± 1.4% ID/g in cerebrum and 1.6 ± 0.1% ID/g in cerebellum). However,

with [^{11}C]**6b** and [^{11}C]**6c** at the same time point, an equal amount of label was found to be distributed in the cerebrum (3–4%ID/g) and the cerebellum (3–4%ID/g) of the animals. At 60 min p.i., the washout rates of [^{11}C]**6b** (0.09 ± 0.02% ID/g in cerebrum and 0.08 ± 0.07% ID/g in cerebellum) and [^{11}C]**6c** (0.16 ± 0.03% ID/g in cerebrum and 0.10 ± 0.14% ID/g in cerebellum) from the brain were faster than washout of either [^{11}C]**6a** (0.30 ± 0.30% ID/g in cerebrum and 0.60 ± 0.04%ID/g in cerebellum) or [^{11}C]PIB (0.60 ± 0.20% ID/g in cerebrum and 0.30 ± 0.10% ID/g in cerebellum). The washout rate of [^{11}C]**6b** from the brain areas was approximately eight-fold faster than that of [^{11}C]PIB (by 60 min p.i.) compared to only a two-fold faster clearance rate noted with either [^{11}C]**6a** or [^{11}C]**6c**. The blood clearance ratios (% ID in blood at 2 min to % ID in blood at 60 min) of the label were 6, 12, and 8 for [^{11}C]**6a**, [^{11}C]**6b**, and [^{11}C]**6c**, respectively, compared to a ratio of 3 for [^{11}C]PIB. All of the labeled PIB analogs were excreted primarily through the hepatobiliary route, although some urinary clearance of the label was also observed.

According to Serdons et al. (2), a superior Aβ imaging agent should have a fast blood clearance with a rapid washout rate from the normal brain. On the basis of observations from this study, however, the investigators concluded that subtle structural changes introduced in PIB can have significant influence on the *in vivo* behavior of the compounds. Because none of the new PIB derivatives exhibited brain washout and blood clearance characteristics superior to [^{11}C]PIB for the imaging of Aβ plaques, further evaluation of the analogs was suggested to be necessary before any of the ^{11}C-labeled PIB derivatives could be used for the visualization of amyloid plaques in mouse or human brains with AD.

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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