N-Methyl-[^{11}C]-2-(4'-methylaminophenyl)-6-hydroxybenzothiasole

[^{11}C]6-OH-BTA-1 or [^{11}C]PIB

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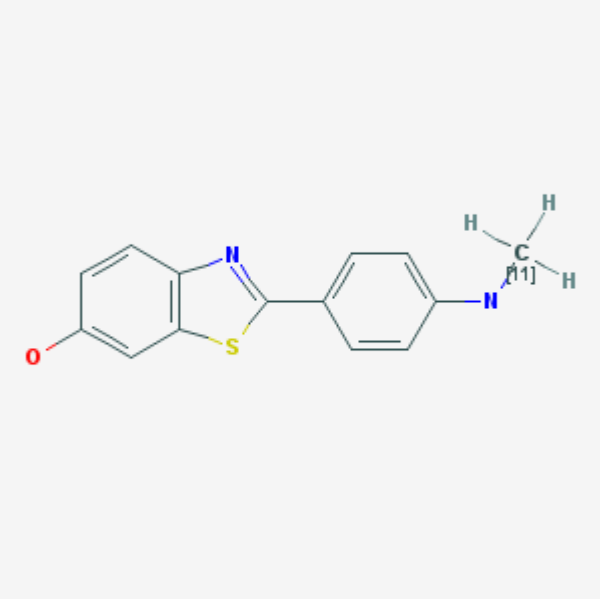
Chemical name:	*N*-Methyl-[^{11}C]-2-(4'-methylaminophenyl)-6-hydroxybenzothiasole
Abbreviated name:	[^{11}C]6-OH-BTA-1, [^{11}C]PIB
Synonym:	[^{11}C]Pittsburgh Compound-B
Backbone:	Compound
Target:	Aggregates of Amyloid-beta peptide
Mechanism:	Acceptor binding
Method of detection:	PET
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates • Humans



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Background

[PubMed]

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Alzheimer's disease (AD) is a form of dementia with a gradual memory loss and a progressive decline in mental functions overtime (1, 2). It is characterized pathologically by neuronal loss, extracellular senile plaques (aggregates of amyloid-beta peptides consisting of 40 to 42 amino acids) and intracellular neurofibrillary tangles (filaments of microtubule-binding hyper-phosphorylated protein tau) in the brain, especially in the hippocampus and associative regions of the cortex (3, 4). β-amyloid peptides and tau protein are implicated as the main causes of neuronal degeneration and cell death (5, 6).

Early diagnosis of AD is important for treatment consideration and disease management (7). Various β-amyloid imaging agents have been developed for magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), and positron emission tomography (PET) (8-13). The binding of different derivatives of Congo red, thioflavin, stibene, and aminonaphthalene has been studied in human post-mortem brain tissue and in transgenic mice. Out of these analogues, 2-(1-(6-[(2-[^{18}F]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene)malono nitrile ([^{18}F]FDDNP) was studied in humans, showing more binding in the brains of patients with AD than in those of healthy people (14). However, [^{18}F]FDDNP showed low signal-to-noise ratios for PET imaging, because it is highly lipophilic. *N*-Methyl-[^{11}C]-2-(4'-methylaminophenyl)-6-hydroxybenzothiasole, a β-amyloid binding compound based on a series of neutral thioflavin-T derivatives (15), was radiolabeled with the positron-emitting radionuclide ^{11}C ([^{11}C]6-OH-BTA-1 or [^{11}C]PIB). [^{11}C]6-OH-BTA-1 was found to be a promising imaging agent for the senile plaques in the brain (16).

Related Resource Links:

- Chapters in MICAD (Amyloid, tau)
- Gene information in NCBI (Amyloid, tau).
- Articles in Online Mendelian Inheritance in Man (OMIM) (Amyloid, tau)
- Clinical trials (Amyloid, [^{11}C]PIB)
- Drug information in FDA (Amyloid inhibitors)

Synthesis

[PubMed]

[^{11}C]6-OH-BTA-1 was readily synthesized by standard ^{11}C-methylation of 2-(4'-aminophenyl)-6-methoxymethoxybenzothiazole with [^{11}C]methyl iodide, followed by hydrolysis (15). The radiochemical yield averaged 12.1% at the end of synthesis based on [^{11}C]methyl iodide, and the specific activity averaged 85 GBq/μmol (2.3 Ci/μmol) at the end of synthesis. Radiochemical and chemical purities were >95% as determined by high-performance liquid chromatography (HPLC).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

6-OH-BTA-1 has a binding affinity (K_i) of 4.5 nM for aggregated amyloid-beta(1-40) fibrils in competition with [*N*-methyl-^{3}H]BTA-1 (15). The K_i Value for thioflavin-T was found to be 580 nM. Saturation binding studies with [*N*-methyl-^{3}H]6-OH-BTA-1 to amyloid-beta(1-40) peptide showed a K_d value of 4.7 nM and a B_{max} value of 2.7 pmol of 6-OH-BTA-1 per nmol of amyloid-beta(1-40) peptide. 6-OH-BTA-1 showed no inhibition in an array of neurotransmitter receptor and transporter assays. Saturation binding studies with [*N*-methyl-^{3}H]6-OH-BTA-1 to homogenates of frontal cortex from postmortem advanced AD brain showed a K_D value of 1.4 nM and a B_{max} value of 1900 pmol per g tissue. There was no specific binding of [*N*-methyl-^{3}H]6-OH-BTA-1 to homogenates of frontal cortex from age-matched control brain as well as to homogenates of cerebellum from AD brain or control brain. Klunk et al (16) showed that [^{11}C]6-OH-BTA-1 bound specifically to frontal cortex of postmortem AD brain slices, and its binding could be blocked by excess unlabeled BTA-1. There was little binding of [^{11}C]6-OH-BTA-1 to frontal cortex of normal elderly control brain slices.

Animal Studies

Rodents

[PubMed]

[^{11}C]-labeled BTA derivatives (0.37-3.7 MBq, 10-100 µCi) were injected intravenously into mice to study their accumulation into brain of normal mice (15). 6-OH-BTA-1 has an apparent lipophilicity (log P_{c18}) of 1.2. It is expected to enter the brain readily. The radioactivity in excised brain samples was measured at 2 and 30 min after injection. [^{11}C]6-OH-BTA-1 showed the lowest 30-min brain value of 0.018% injected dose (ID)-kg/g, with the highest 2 min-to-30 min ratio of 12. [^{11}C]BTA-1 was the second best tracer, with a 2 min-to-30 min ratio of 7.6. The peripheral metabolism of [^{11}C]6-OH-BTA-1 in normal mice was rapid, with intact [^{11}C]6-OH-BTA-1 composing 73% of the total plasma activity at 2 min after injection and 6% at 30 min. All [^{11}C]6-OH-BTA-1 metabolites were polar and are not expected to cross the blood-brain barrier because the brain homogenates at 2 and 10 min contained >95% unmetabolized [^{11}C]6-OH-BTA-1.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

PET studies were performed in six adult baboons after injection of 185 MBq (5 mCi) of [^{11}C]6-OH-BTA-1 or [^{11}]BTA-1 and co-registered with MRI anatomical brain images (15). A dynamic series of PET scans were acquired over 60 min. At early time points (0-9 min), radioactivity was uniformly distributed throughout the baboon brains, whereas at

the later time points, radioactivity became more heterogeneously distributed. Regions of brain containing higher levels of white matter (such as pons) exhibited 20-30% higher accumulation of radioactivity than regions that were mainly gray matter (such as the temporal, mesial-temporal, and occipital cortex). In the baboon brains, radioactivity concentrations of [^{11}C]BTA-1 and [^{11}C]6-OH-BTA-1 at 30 min were 0.45 and 0.27% ID-kg/g, respectively. These values were similar to those in mice. [^{11}C]6-OH-BTA-1 showed a faster rate of clearance of radioactivity than [^{11}C]BTA-1.

Human Studies

[PubMed]

The first human study with [^{11}C]6-OH-BTA-1 in 16 patients with mild AD and 9 healthy people was reported (16). The subjects were given an intravenous injection of 300 MBq (8.1 mCi) of [^{11}C]6-OH-BTA-1. Plasma metabolism of [^{11}C]6-OH-BTA-1 was rapid and similar in the AD patients and normal subjects. The amount of intact [^{11}C]6-OH-BTA-1 was 7.2 ± 3.6% (normal control subjects) and 9.8 ± 3.0% (AD) at 60 min after injection. The dynamic PET data showed that [^{11}C]6-OH-BTA-1 retention is 1.52-1.94-fold greater in brain regions (such as frontal, parietal, temporal, and occipital cortex and the striatum) that are known to contain amyloid plaques in AD patients than in controls. The frontal cortex had the highest tracer uptake. There was a similar retention of [^{11}C]6-OH-BTA-1 in the cerebellum and white matter containing little amyloid deposits in AD and controls. There is an inverse correlation of [^{11}C]6-OH-BTA-1 retention with cerebral FDG metabolism in the cortical regions. However, the differences between AD and controls were greater with [^{11}C]6-OH-BTA-1 than with FDG.

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