^{99m}Tc-Labeled pyridyl benzofuran derivatives to target β-amyloid plaques

[^{99m}Tc]BAT-bp-1, [^{99m}Tc]BAT-bp-2, and [^{99m}Tc]BAT-bp-3

Arvind Chopra, PhD[1]

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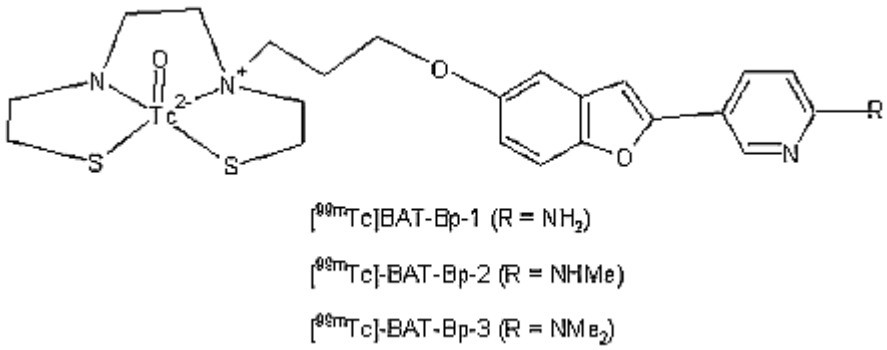
Chemical name:	^{99m}Tc-Labeled pyridyl benzofuran derivatives to target β-amyloid plaques
Abbreviated name:	[^{99m}Tc]BAT-bp-1, [^{99m}Tc]BAT-bp-2, and [^{99m}Tc]BAT-bp-3
Synonym:	
Agent Category:	Compound
Target:	β-Amyloid plaques (βA)
Target Category:	Peptides
Method of detection:	Single-photon emission computed tomography (SPECT); gamma planar imaging
Source of signal / contrast:	^{99m}Tc
Activation:	No



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Studies:	• *In vitro* • Rodents	Structures of [^{99m}Tc]BAT-bp-1, [^{99m}Tc]BAT-bp-2, and [^{99m}Tc]BAT-bp-3 according to Cheng et al. (1).

Background

[PubMed]

In developed countries, Alzheimer's disease (AD) affects ~1% of the individuals who are ≥65 years old and roughly 30% of those who are ≥80 years of age (2). The disease is characterized by slow deposition of the amyloid beta protein (βA) and formation of neurofibrillary tangles in the memory and cognition regions of the brain, which lead to memory loss and cognitive impairment in the individual (3). The generation of βA from its precursor, the amyloid precursor protein, has been illustrated by Tam and Pasternak (2), and the biochemistry of this protein and the amyloid deposits in AD has been discussed by Masters and Selkoe (4). Because the deposition of βA in the brain starts several years before the symptoms of AD are apparent, detection of the disease at an early stage can assist in the diagnosis, improved monitoring of the disease, and the development of a therapeutic regimen that can slow the advancement of AD (1). Although several drugs approved by the United States Food and Drug Administration (FDA) are available to treat the symptoms of AD, none of these medications prevent the onset and progression of the disease. Imaging probes for use with positron emission tomography (PET) have been evaluated under preclinical conditions for the noninvasive visualization of AD (1), and ^{18}F-labeled AV45 (florbetapir) was approved by the FDA to estimate the density of βA neuritic plaque in the brains of AD patients. Cheng et al. showed that ^{18}F-labeled 5-(5-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)benzofuran-2-yl)-N,N-dimethylpyridin-2-amine ([^{18}F]FPYBF), a derivative of benzofuran, had a high affinity for βA plaques, can label the plaques in postmortem human AD brain sections, and is suitable for the visualization of βA deposits in brain sections of mice (a murine model of AD) injected with [^{18}F]FPYBF (5). Similar observations have been reported from biodistribution studies with two other ^{18}F-labeled derivatives of benzofuran (6). A common limitation of these PET imaging compounds (under development or approved by the FDA) is that the tracers have a short half-life (e.g., the half-life of the most commonly used radionuclides for PET imaging, such as ^{11}C, ^{18}F, and ^{68}Ga, are 20.4 min,

1 National Center for Biotechnology Information, NLM, Bethesda, MD 20894; Email: micad@ncbi.nlm.nih.gov.

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109.8 min, and 67.6 min, respectively), may not establish the presence of βA plaques in the brain with certainty, and cannot be used to monitor the therapeutic response in an AD patient.

As an alternative to detect βA plaques with PET, investigators have evaluated the use of several ^{99m}Tc-labeled compounds (half-life of ^{99m}Tc is 6 h) with single-photon emission computed tomography (SPECT) (1). However, most of these radiolabeled chemicals have been used to visualize the plaques in *in vitro* sections of mouse and human brains with AD and do not exhibit a high affinity for the βA plaques *in vivo* or can not cross the blood–brain barrier (BBB) in the animals (1). On the basis of results obtained with the benzofuran derivatives mentioned above (5, 6), ^{99m}Tc-labeled pyridyl benzofuran (Bp) derivatives were synthesized, and the biodistribution of these tracers was investigated in normal mice (1). To label the Bp derivatives with ^{99m}Tc, a compact chelating agent, bis(aminoethanethiol) (BAT), was conjugated to the compounds to generate radiolabeled probes (designated [^{99m}Tc]BAT-Bp-1, [^{99m}Tc]BAT-Bp-2, and [^{99m}Tc]BAT-Bp-3).

Related Resource Links

Related chapters in MICAD

What is Alzheimer's disease? [PubMed Health]

Alzheimer's disease clinical trials

Human amyloid beta (A4) precursor protein; Gene ID: 351 (NCBI Gene database)

Alzheimer's disease in Online Mendelian Inheritance in Man Database (OMIM)

Synthesis

[PubMed]

The synthesis of [^{99m}Tc]BAT-Bp-1, [^{99m}Tc]BAT-Bp-2, and [^{99m}Tc]BAT-Bp-3 (BAT-Bp-2 and BAT-Bp-3 are the *N*-monomethylated- and *N,N*-dimethylated derivatives of BAT-Bp-1, respectively) has been described by Cheng et al. (1). The radiochemical purity of these tracers was reported to be >99% as determined with high-performance liquid chromatography. The radiochemical yield and specific activity of the different probes were not reported.

For *in vitro* studies, rhenium (Re) complexes of the Bp derivatives (Re-BAT-Bp-1, Re-BAT-Bp-2, and Re-BAT-Bp-3) were prepared as detailed elsewhere (1). The yields of purified Re-BAT-Bp-1, Re-BAT-Bp-2, and Re-BAT-Bp-3 were 46.0%, 26.7%, and 33.0%, respectively.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The binding affinities of Re-BAT-Bp-1, Re-BAT-Bp-2, and Re-BAT-Bp-3 for the βA aggregates were determined in a competition assay with [^{125}I]IMPY as the binding ligand (1). All the Re compounds inhibited the binding of [^{125}I]IMPY to the βA aggregates in a dose-dependent manner. The inhibition constants (K_i) of Re-BAT-Bp-1, Re-BAT-Bp-2, and Re-BAT-Bp-3 were reported to be 149.6 ± 34.4 nM, 32.8 ± 5.80 nM, and 13.6 ± 1.60 nM, respectively.

Using a 1-octanol/phosphate-buffered saline (pH 7.4) mixture, the partition coefficients (log *P* values) of [^{99m}Tc]BAT-Bp-1, [^{99m}Tc]BAT-Bp-2, and [^{99m}Tc]BAT-Bp-3 were determined to be 0.68, 1.35, and 2.09, respectively, indicating that the radiolabeled compounds were probably suitable for penetration of the BBB (1).

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{99m}Tc]BAT-Bp-1, [^{99m}Tc]BAT-Bp-2, and [^{99m}Tc]BAT-Bp-3 was investigated in normal ddY mice (1). The animals (n = 5 mice/time point; under isoflurane anesthesia) were injected with 148 kBq (4 μCi) of the tracer through the tail vein and euthanized at predetermined time points ranging from 2 min postinjection (p.i.) to 60 min p.i. Organs of interest were harvested from the animals, and the amount of label accumulated in the various tissues was determined. The uptake of radioactivity in the organs was presented as percent of injected dose per gram tissue (% ID/g). [^{99m}Tc]BAT-Bp-1 and [^{99m}Tc]BAT-Bp-2 showed maximum uptake of tracer in the brain at 2 min p.i. (1.59 ± 0.21% ID/g and 1.80 ± 0.16% ID/g, respectively). With [^{99m}Tc]BAT-Bp-3, the peak uptake of radioactivity in the brain was 1.64 ± 0.27% ID/g at 10 min p.i. Among the ^{99m}Tc-labeled Bp derivatives, [^{99m}Tc]BAT-Bp-2 showed the maximum uptake in the brain, and it was concluded that this labeled compound was superior to any ^{99m}Tc-labeled tracer previously used for βA imaging (1).

In another study, Tg2576 transgenic mice (used as a murine model of AD; number of animals not reported) and wild-type mice (number of animals not reported) under anesthesia were injected with 16.6 MBq (448.6 μCi) [^{99m}Tc]BAT-Bp-2 through the tail vein (1). The rodents were euthanized at 30 min p.i., and the brains were removed, frozen immediately, and used to prepare sections for *ex vivo* autoradiography. After autographic examination, the brain sections were stained with thioflavin-S to confirm the presence of βA plaques in the organs. From the autoradiograms it was clear that the radioactive spots were present only in brain sections of the Tg2576 mice. Thioflavin-S staining of the autoradiographed sections confirmed that the location of the radiolabeled spots in the brain sections corresponded to the βA deposits in the tissue.

From these studies, the investigators concluded that [^{99m}Tc]BAT-Bp-2 was probably suitable to detect βA plaques with SPECT in the brains of rodents with AD (1).

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

Supplemental Information

[Disclaimers]

No information is currently available.

References

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