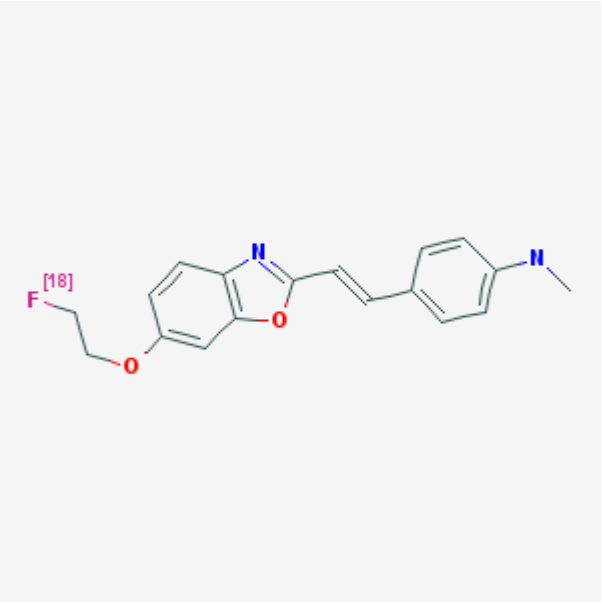
6-(2-[^{18}F]Fluoroethoxy)-2-[2-(4-methylaminophenyl)ethenyl]benzoxazole

[^{18}F]BF-168

Kenneth T. Cheng, PhD[1]

Created: October 3, 2006; Updated: January 28, 2008.

Chemical name:	6-(2-[^{18}F]Fluoroethoxy)-2-[2-(4-methylaminophenyl)ethenyl]benzoxazole
Abbreviated name:	[^{18}F]BF-168
Synonym:	
Agent Category:	Compound
Target:	Amyloid-β (Aβ)
Target Category:	Specific binding
Method of detection:	Positron Emission Tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

Background

[PubMed]

6-(2-[^{18}F]Fluoroethoxy)-2-[2-(4-methylaminophenyl)ethenyl]benzoxazole ([^{18}F]BF-168) is a radioligand that was developed for positron emission tomography (PET) imaging of

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

NLM Citation: Cheng KT. 6-(2-[^{18}F]Fluoroethoxy)-2-[2-(4-methylaminophenyl)ethenyl]benzoxazole . 2006 Oct 3 [Updated 2008 Jan 28]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

amyloid-β (Aβ) plaques in the central nervous system (CNS) for detection of Alzheimer's disease (AD) (1). ^{18}F is a positron emitter with a physical $t_{½}$ of 109.7 min.

Aβ peptide was sequenced from the meningeal blood vessels of AD patients and individuals with Downs syndrome (2). Aβ peptides contain 40–42 amino acid residues and are metabolic products of Aβ precursor protein (APP) from cleavage by β and γ secretases (3). Aβ is also identified as the primary component of the neuritic plaques of AD patient brain tissue (4). Cloning of the gene that encodes the APP and its localization to chromosome 21 led to the hypothesis that Aβ accumulation is the primary event in AD pathogenesis (2, 5). This hypothesis proposes that neuronal death in AD is related to toxic effect of Aβ on the adjacent cell bodies or cell processes (6). AD is a progressive, neurogenerative disorder of the CNS that is characterized by a common set of clinical and pathological features (3). In addition to Aβ, the microtubule-associated protein tau (τ) is also found in the cell body and axons of neurons as neurofibrillary tangles.

The search for a cure or effective treatment of AD requires *in vivo* detection and quantification of Aβ in the brain for efficacy evaluation of AD therapy (3). Various amyloid-imaging probes have been developed based on PET, single-photon emission computed tomography, and optical imaging. These compounds generally have high binding affinity for amyloid fibrils and adequate permeability of the blood-brain barrier (1). There is evidence that suggests substantial deposition of diffuse plaques may be the initial pathological change in AD that precedes cognitive deterioration (7). Thus, imaging agents that can detect diffuse amyloid plaques may be useful for early detection of AD. Okamura et al. (1) synthesized a series of styrylbenzoxazole derivatives that target amyloid plaques, including diffuse plaques. They found that BF-168 recognized both neuritic and diffuse plaques *in vivo*. [^{18}F]BF-168 appeared to be a promising candidate for PET imaging of AD.

Synthesis

[PubMed]

Okamura et al. (1) reported the radiosynthesis of [^{18}F]BF-168. 2-(4-Methylaminophenyl)-6-(2-tosyloxyethoxy)benzoxazole obtained commercially was reacted with potassium [^{18}F]fluoride and Kryptofix 222 in acetonitrile at 80°C for 20 min. The labeled compound was purified by high-performance liquid chromatography. The radiochemical yield was 30–40%, and the radiochemical purity was >95%. The maximum specificity was 106 TBq/mmol (2,865 Ci/mmol) at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Okamura et al. (8) evaluated unlabeled BF-168 and several other quinoline and benzimidazole derivatives. The octanol/water (1-octanol/phosphate–buffered saline) partition coefficient of BF-168 was determined to be 62.6.

Okamura et al. (1) conducted *in vitro* binding assays with [^{125}I]BF-168 using synthetic Aβ1-42 (diffuse plaques were exclusively positive) and Aβ1-40 for binding. The dissociation constant (K_d) values were 6.8 ± 1.4 nM and 10.6 ± 1.5 nM for Aβ1-42 and Aβ1-40, respectively. The maximum specific binding (B_{max}) values were 3.2 ± 0.55 nM and 4.1 ± 1.3 nM for Aβ1-42 and Aβ1-40, respectively. The inhibition constant (K_i) for Aβ fibrils was determined to be 6.4 ± 1.0 nM (8). The effective concentration to achieve 50% maximal fluorescence intensity at optimal excitation wavelength (EC_{50}) for Aβ fibrils was 346 ± 2.21 nM. In comparison, the EC_{50} for ? fibrils was 1010 ± 1.72 nM.

In vitro neuropathological staining studies of unlabeled BF-168 were performed in postmortem brain tissue from four autopsy-confirmed AD cases (1). The experiments showed BF-168 clearly stained both neuritic and diffuse amyloid plaques in AD temporal brain tissue sections. BF-168 bound both Aβ1–40-positive and Aβ1–42 positive plaques. The staining and distribution patterns corresponded well to those of Aβ and ? immunostaining in the serial sections. Little nonspecific binding of BF-168 was found in the aged normal brain sections. The results also indicated that BF-168 recognized the β-pleated sheet structure of senile plaques and neurofibrillary tangles, but not nonfibrillar forms of Aβ and ?.

Ishikawa et al. (9) reported that BF-168 also appeared to have a high affinity for the CNS protease-resistant isoforms of prion protein (PrP) which is associated with transmissible spongiform encephalopathies. Using a cellular PrP model, the IC_{50} of BF-168 to PrP was determined to be 0.4 nM.

Animal Studies

Rodents

[PubMed]

The *in vivo* binding of unlabeled BF-168 was studied in PS1/APP double transgenic mice (1). Each mouse received 4 mg/kg BF-168 by i.v. injection. Brain sections were then obtained and examined using immunostaining with anti–Aβ antibodies (6F/3D). The distribution of BF-168 corresponded well to that of both compact and diffuse Aβ. The amount of BF-168 binding appeared to reflect the density of Aβ fibrils. When the same experiment was performed in APP23 single transgenic mice with only mild depositions of amyloid plaques, BF-168 successfully detected early plaque formation in the entorhinal cortex hippocampus. No binding of BF-168 was found in the brain slices of normal wild-type mice.

In vivo brain uptake studies were done by injecting 0.240.38 MBq (6.48–10.27 μCi) of [^{18}F]BF-168 into normal mice (1). Brain radioactivity levels were measured to be 3.9 ± 0.22% injected dose per gram (ID/g) at 2 min after injection. There was a good brain clearance from the normal brain slices with a clearance $t_{½}$ of 24.7 min. The brain/blood ratio dropped from 2.0 at 10 min to 0.72 at 60 min after injection.

When [^{18}F]BF-168 was injected into APP23 transgenic mice with Aβ plaques, autoradiographic images of brain sections at 180 min after injection showed high radioactivity levels in the cerebral cortex, hippocampus, and entorhinal cortex (1). The distribution closely corresponded ($r = 0.923$; $P<0.001$) with those of *in vitro* thioflavin-S staining. There was little nonspecific accumulation of [^{18}F]BF-168 in the brain.

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.

References

1. Okamura N., Suemoto T., Shimadzu H., Suzuki M., Shiomitsu T., Akatsu H., Yamamoto T., Staufenbiel M., Yanai K., Arai H., Sasaki H., Kudo Y., Sawada T. Styrylbenzoxazole derivatives for in vivo imaging of amyloid plaques in the brain. J Neurosci. 2004;**24**(10):2535–41. PubMed PMID: 15014129.
2. Hardy J., Selkoe D.J. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002;**297**(5580):353–6. PubMed PMID: 12130773.
3. Wu C.Y., Pike V.W., Wang Y.M. Amyloid imaging: From benchtop to bedside. Current Topcis in Developmental Biology. 2005;**70**:171–213.
4. Masters C.L., Multhaup G., Simms G., Pottgiesser J., Martins R.N., Beyreuther K. Neuronal origin of a cerebral amyloid: neurofibrillary tangles of Alzheimer's disease contain the same protein as the amyloid of plaque cores and blood vessels. Embo J. 1985;**4**(11):2757–63. PubMed PMID: 4065091.
5. Kang J., Lemaire H.G., Unterbeck A., Salbaum J.M., Masters C.L., Grzeschik K.H., Multhaup G., Beyreuther K., Muller-Hill B. The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. Nature. 1987;**325**(6106):733–6. PubMed PMID: 2881207.
6. Carter J., Lippa C.F. Beta-amyloid, neuronal death and Alzheimer's disease. Curr Mol Med. 2001;**1**(6):733–7. PubMed PMID: 11899259.
7. Price J.L., Morris J.C. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. Ann Neurol. 1999;**45**(3):358–68. PubMed PMID: 10072051.

8. Okamura N., Suemoto T., Furumoto S., Suzuki M., Shimadzu H., Akatsu H., Yamamoto T., Fujiwara H., Nemoto M., Maruyama M., Arai H., Yanai K., Sawada T., Kudo Y. Quinoline and benzimidazole derivatives: candidate probes for in vivo imaging of tau pathology in Alzheimer's disease. J Neurosci. 2005;**25**(47):10857–62. PubMed PMID: 16306398.
9. Ishikawa K., Kudo Y., Nishida N., Suemoto T., Sawada T., Iwaki T., Doh-Ura K. Styrylbenzoazole derivatives for imaging of prion plaques and treatment of transmissible spongiform encephalopathies. J Neurochem. 2006;**99**(1):198–205. PubMed PMID: 16987247.