[^{11}C]2-(2-[2-Dimethylaminothiazol-5-yl]ethenyl)-6-(2-[fluoro]ethoxy)benzoxazole

[^{11}C]BF-227

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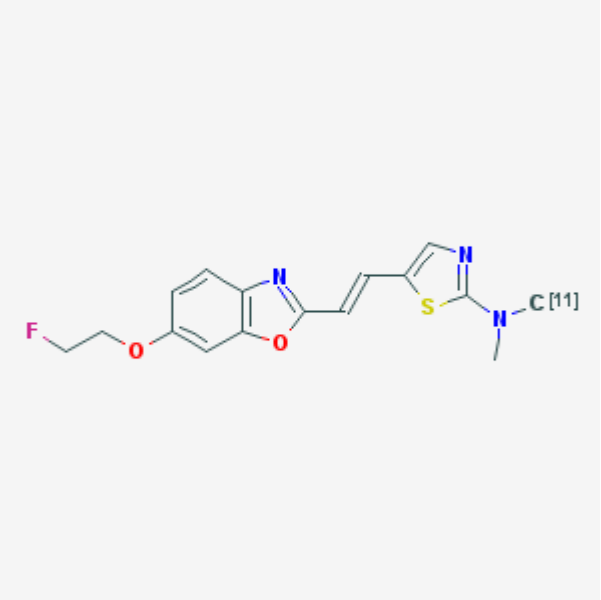
Chemical name:	[^{11}C]2-(2-[2-Dimethylaminothiazol-5-yl]ethenyl)-6-(2-[fluoro]ethoxy)benzoxazole
Abbreviated name:	[^{11}C]BF-227
Synonym:	
Agent Category:	Compound
Target:	Aggregates of ß-amyloid (Aß) peptides
Target Category:	Acceptor binding
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Humans



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Background

[PubMed]

Alzheimer's disease (AD) is a major neurodegenerative disease associated with an irreversible decline of mental functions and with cognitive impairment (1). It is characterized pathologically by neuronal loss with the presence in the brain of senile plaques of β-amyloid (Aβ) peptides and intracellular neurofibrillary tangles of filaments that contain the hyperphosphorylated protein tau (2, 3). Accelerated deposition of Aβ deposits seems to be a key risk factor associated with AD.

Early diagnosis of AD is important for treatment consideration and disease management (4). Several radioligands for positron emission tomography (PET) have been developed (5-7) and tested in humans as *in vivo* diagnostic tools for imaging and measuring the formation of Aβ deposits (7). The first agent successfully used in human studies was [^{18}F]FDDNP (8), a malonitrile derivative found to bind to both neurofibrillary tangles and Aβ plaques. The second successful attempt was made with [^{11}C]PIB (9), also known as Pittsburgh Compound B or [^{11}C]6-OH-BTA-1, which showed marked retention in areas of the cortex known to contain substantial amounts of Aβ deposits. The third PET radioligand successfully tested in humans was [^{11}C]4-*N*-methylamino-4′-hydroxystilbene ([^{11}C]SB-13), a stilbene derivative that exhibits good binding affinities for Aβ aggregates *in vitro*, moderate lipophilicity, high initial brain uptake in the normal rat cortex, and a rapid washout (10).

Benzoxazole derivatives have shown very good binding affinities for Aβ aggregates and Aβ plaques, as well as good brain penetration (11). An optimized derivative, [^{11}C]2-(2-[2-dimethylaminothiazol-5-yl]ethenyl)-6-(2-[fluoro]ethoxy)benzoxazole ([^{11}C]BF-227), has been synthesized and is currently being studied as a PET radioligand for Aβ plaques (12).

Synthesis

[PubMed]

[^{11}C]BF-227 was synthesized from its precursor by *N*-methylation in dimethyl sulfoxide by use of ^{11}C-methyl triflate (12). [^{11}C]BF-227 was purified by reverse-phase high-performance liquid chromatography and solid-phase extraction with >95% radiochemical purity. The radiochemical yields on the basis of [^{11}C]methyl triflate were >50% , and the specific activities were 119–138 GBq/μmol (3.2–3.7 Ci/μmol) at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

BF-227 was found to compete well with [^{125}I]BF-180, a ligand selective for Aβ plaques (12). Studies of binding to Aβ1–42 fibrils in solution showed an inhibition constant (K_i)

value of 4.3 ± 1.5 nM. BF-227 exhibited a moderate lipophilicity (log *P* value of 1.75 at pH 7.4).

Animal Studies

Rodents

[PubMed]

Kudo et al. (12) performed *in vivo* biodistribution studies in normal male C57B6 mice injected intravenously with a saline solution of [^{11}C]BF-227. Results showed that the radiotracer easily penetrated the blood–brain barrier, and a peak of the brain uptake of 7.9% injected dose/g (% ID/g) was observed at 2 min after injection. This value compared well with [^{125}I]6-iodo-2-(4′-dimethylamino)-phenyl-imidazo[1,2-*a*]pyridine ([^{125}I]IMPY) (7.2% ID/g at 2 min). Accumulation in the brain was 3.7% ID/g at 10 min, 1.4% ID/g at 30 min, and 0.64% ID/g at 60 min.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

The first human study with [^{11}C]BF-227 in 10 patients with probable AD and 11 healthy control subjects was reported. Subjects were given an intravenous injection of 211–366 MBq (5.7–9.9 mCi) of [^{11}C]BF-227 (12). Dynamic PET images showed that [^{11}C]BF-227 retention (measured as the ratio of regional standard uptake value [SUV] to cerebellar SUV) is significantly higher in brain regions that are known to contain Aβ plaques in AD patients (e.g., the frontal, lateral temporal, parietal, temporooccipital, occipital, anterior and posterior cingulate cortices, and striatum) than in control subjects. The lateral temporal cortex SUV ratio showed no overlap between AD patients and normal control subjects. There was a similar retention of [^{11}C]BF-227 in the medial temporal cortex, thalamus, cerebellum, and white matter that contained few Aβ deposits in AD patients and control subjects. No significant difference was observed in any brain regions between young normal (n = 3) and aged normal subjects (n = 8).

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