2-(2-(2-(4-((4-(Methylamino)phenyl)ethynyl)phenoxy)ethoxy)[^{18}F]fluoroethoxy)ethyl-4-methylbenzenamine

[^{18}F]AV-138

Kam Leung, PhD[1]

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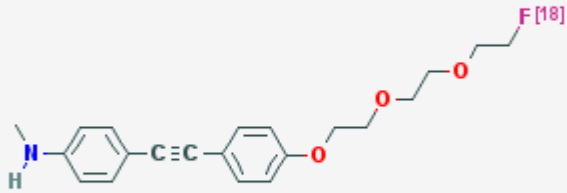
Chemical name:	2-(2-(2-(4-((4-(Methylamino)phenyl)ethynyl)phenoxy)ethoxy)[^{18}F]fluoroethoxy)ethyl-4-methylbenzenamine
Abbreviated name:	[^{18}F]AV-138
Synonym:	
Agent category:	Compound
Target:	Amyloid-beta peptide
Target category:	Acceptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Non-human primates • Humans



Click on the above structure for additional information in PubChem.

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

Corresponding author.

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Background

[PubMed]

Alzheimer's disease (AD) is a form of dementia with gradual memory loss and progressive decline in mental functions over time (1, 2). It is characterized pathologically by neuronal loss, extracellular senile plaques (aggregates of β-amyloid peptides consisting of 40–42 amino acids), and intracellular neurofibrillary tangles (filaments of microtubule-binding hyperphosphorylated 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 single-photon emission computed tomography and positron emission tomography (PET) (8-13). The binding performance of different derivatives of Congo red, thioflavin, stibene, and aminonaphthalene has been studied in human post-mortem brain tissue and in transgenic mice. Of these analogs, 2-(1-(6-[(2-[^{18}F]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene)malono nitrile ([^{18}F]FDDNP) was studied in humans and showed more binding in the brains of patients with AD than in those of healthy people (14). However, [^{18}F]FDDNP showed low signal/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, [^{11}C]PIB). [^{11}C]6-OH-BTA-1 was found to be a promising agent for the imaging of senile plaques in the brain (16). Zhang et al. (17) reported the development of a series of fluorinated polyethylene glycol units (n = 2–5) for PET imaging of β-amyloid plaques in the brain. 2-(2-(2-(4-((4-(Methylamino)phenyl)ethynyl)phenoxy)ethoxy) [^{18}F]fluoroethoxy)ethyl-4-methylbenzenamine ([^{18}F]AV-138) was validated as a PET imaging agent for β-amyloid plaques in the brain (18).

Related Resource Links:

- Chapters in MICAD (amyloid)
- Gene information in NCBI (amyloid)
- Articles in Online Mendelian Inheritance in Man (OMIM) (amyloid)
- Clinical trials (amyloid)
- Drug information in U.S. Food and Drug Administration (amyloid inhibitors)

Synthesis

[PubMed]

[^{18}F]AV-138 was readily synthesized by standard ^{18}F-fluorination of the *O*-tosylated derivative with [^{18}F]KF/Kryptofix 2.2.2 for 10 min at 130°C (18). [^{18}F]AV-138 was purified with high-performance liquid chromatography. Overall radiochemical yield was

3.3%–8.5%, with a specific activity of >55 GBq/μmol (1.5 Ci/μmol) at the end of synthesis and a radiochemical purity of >98%. Total synthesis time was ~90 min.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

[^{18}F]AV-138 has a binding affinity (K_i) value of 2.4 ± 0.7 nM for aggregated β-amyloid fibrils (n = 3 postmortem AD brain homogenates) in competition with [^{125}I]IMPY (18). The binding signal in AD gray matter homogenates was approximately nine-fold higher than in AD white matter homogenates. [^{18}F]AV-138 was bound to the cortex of postmortem AD brain slices but not to control brain slices, as visualized with autoradiography studies. Plaque labeling with [^{18}F]AV-138 correlated very well with thioflavin-S fluorescent labeling (r > 0.9).

Animal Studies

Rodents

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

PET imaging was performed in the brains of healthy young female rhesus monkeys after injection of [^{18}F]AV-138 (19). The radioactivity peaked in the cortex at ~15 min after injection and exhibited slow washout.

Human Studies

[PubMed]

Carpenter et al. (19) reported PET imaging with [^{18}F]AV-138 in a study of 14 AD patients, with 12 healthy, elderly patients as controls. [^{18}F]AV-138 binding was quantified with the use of the standardized uptake value ratio (SUVR), which was calculated for the neocortex, with the cerebellum as reference region. Widespread neocortical binding was observed in all AD patients, with a SUVR peak at ~90 min after injection with ~370 MBq (10 mCi) [^{18}F]AV-138. A higher neocortical SUVR was observed in AD patients (~2) than in healthy controls (~1) at 90 min. However, the 90 min to reach maximal SUVR is

considered to be suboptimal for routine clinical PET imaging. Furthermore, [^{18}F]AV-138 exhibits substantial non-cortical (nonspecific) binding.

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