2-(4-Aminophenyl)-6-(2-([^{18}F]fluoroethoxy))quinoline

[^{18}F]THK523

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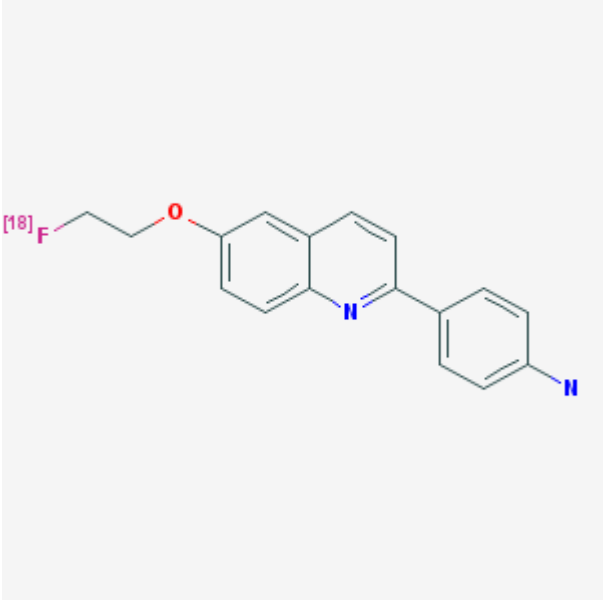
Chemical name:	2-(4-Aminophenyl)-6-(2-([^{18}F]fluoroethoxy))quinoline
Abbreviated name:	[^{18}F]THK523
Synonym:	
Agent category:	Compound
Target:	Tau fibrils
Target category:	Acceptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

Alzheimer's disease (AD) is a form of dementia with a gradual memory loss and a progressive decline in mental functions over time (1, 2). It is characterized pathologically

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by neuronal loss, extracellular senile plaques (aggregates of amyloid-β peptides consisting of 40–42 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 fibrils and tau neurofibrillary tangles 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, single-photon emission computed tomography, and positron emission tomography (PET) (8-13). The binding properties of different derivatives of Congo red, thioflavin, stibene, and aminonaphthalene have been studied in post-mortem human 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) has been studied in humans, showing more binding in the brains of patients with AD than in those of healthy people (14). [^{18}F]FDDNP has been found to bind to both β-amyloid fibrils and tau neurofibrillary tangles. 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, 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 β-amyloid fibrils in the brain (10). Okamura et al. (15) identified a series of quinolone derivatives that bind tau neurofibrillary tangles with higher affinity than β-amyloid fibrils. One of these derivatives, 2-(4-aminophenyl)-6-(2-([^{18}F]fluoroethoxy))quinolone ([^{18}F]THK523), has been evaluated for imaging of tau pathology 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, tau)
- Drug information in FDA (Amyloid inhibitors, tau inhibitors)

Synthesis

[PubMed]

[^{18}F]THK523 was readily synthesized by standard ^{18}F-fluorination of the tosylate precursor ([^{18}F]KF/Kryptofix2.2.2, 10 min at 110°C) (16). [^{18}F]THK523 was purified with high-performance liquid chromatography. Overall yield was 24%, with a specific activity of 100 GBq/μmol (2.7 Ci/μmol) at the end of synthesis and a radiochemical purity of >95%. Total synthesis time was not reported. The LogP_{oct} (lipophilicity) value was measured to be 2.91 ± 0.13 (n = 3).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Fodero-Tavoletti et al. (16) performed saturation binding studies of [^{18}F]THK523 with β-amyloid(1-40) fibrils and human recombinant K18Δ280K-tau fibrils in the presence of excess THK523. [^{18}F]THK523 exhibited two binding sites on K18Δ280K-tau fibrils, with K_{d1} and K_{d2} values of 1.67 nM and 21.74 nM, respectively. On the other hand, only one [^{18}F]THK523 binding site was identified on β-amyloid(1-40) fibrils with a K_d value of 20.7 nM. [^{18}F]THK523 was bound to tau neurofibrillary tangles but not to β-amyloid plaques in the hippocampus of post-mortem AD brain slices as visualized with *in vitro* autoradiography and immunostaining studies.

Animal Studies

Rodents

[PubMed]

Fodero-Tavoletti et al. (16) performed *ex vivo* biodistribution studies of [^{18}F]THK523 (0.68–1.32 MBq (18–36 μCi)) after intravenous injection into normal male mice (n = 4/group) at 2, 10, 30, and 60 min after injection. [^{18}F]THK523 showed an initial rapid penetration into the brain with 2.75% injected dose (ID)/g at 2 min, with a quick washout (1.5% ID/g at 60 min). The organs with high accumulation at 2 min after injection were the kidney (~6.2% ID/g), heart (~6.2% ID/g), and liver (~5% ID/g), and all of these organs exhibited a fast clearance. Accumulation in the intestine was ~2% ID/g at 2 min and increased to 10% ID/g at 60 min, suggesting elimination of [^{18}F]THK523 through biliary excretion. The radioactivity levels at 60 min were 1.7% and 2.0% in the blood and bone, respectively.

Fodero-Tavoletti et al. (16) performed PET imaging over 30 minutes in tau transgenic mice (rTg4510, n = 8) and wild-type mice (CamKII, n = 7) after injection of 3.7 MBq (0.1 mCi) [^{18}F]THK523. [^{18}F]THK523 showed an initial rapid penetration into the brain of rTg4510 mice with 4% ID/g at 2 min, with a quick washout (1.3% ID/g at 30 min). The accumulation of [^{18}F]THK523 in the brain of wild-type mice at 30 min after injection was 48% lower ($P < 0.007$) than that in the brain of rTg4510 mice at the same time point. The accumulation levels of [^{18}F]THK523 in the liver, intestine, and bone were similar in both types of mice. [^{18}F]THK523 PET imaging over 30 minutes was next performed in APP/PS1 transgenic mice (n = 3) and their wild-type littermates (n = 3). There was no difference in retention in the brains of APP/PS1 and wild-type mice. The retention was significantly lower than that of rTg4510 mice ($P < 0.0001$). Immunohistological analysis showed colocalization of radioactivity with tau deposits in the brain sections of rTg4510 mice but not with β-amyloid plaques in the brain sections of APP/PS1 mice.

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.

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