Fluoro-pegylated (1E,4E)-1-(4-(dimethylamino)phenyl)-5-(4-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)phenyl)penta-1,4-dien-3-one and (1E,4E)-1-(4-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)phenyl)-5-(4-(methylamino)phenyl)penta-1,4-dien-3-one

[^{18}F]83, [^{18}F]85

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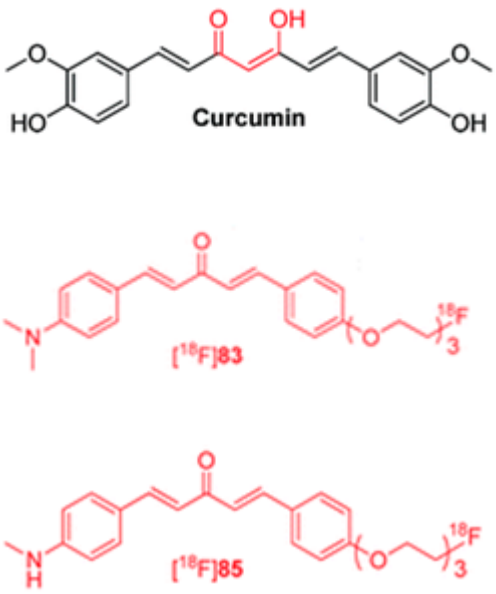
Chemical name:	Fluoro-pegylated (1E, 4E)-1-(4-(dimethylamino)phenyl)-5-(4-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)phenyl)penta-1,4-dien-3-one and (1E, 4E)-1-(4-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)phenyl)-5-(4-(methylamino)phenyl)penta-1,4-dien-3-one
Abbreviated name:	[^{18}F]83, [^{18}F]85
Synonym:	
Agent Category:	Compounds
Target:	β-amyloid (Aβ)
Target Category:	Accepters
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{18}F
Activation:	No



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Studies:	• *In vitro* • Rodents	Structures of [^{18}F]83 and [^{18}F]85 by Cui et al. (1).

Background

[PubMed]

Fluoro-pegylated (1E, 4E)-1-(4-(dimethylamino)phenyl)-5-(4-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)phenyl)penta-1,4-dien-3-one (compound 83) and (1E, 4E)-1-(4-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)phenyl)-5-(4-(methylamino)phenyl)penta-1,4-dien-3-one (compound 85), abbreviated as [^{18}F]83 and [^{18}F]85, respectively, are two dibenzylideneacetone derivatives synthesized by Cui et al. for positron emission tomography (PET) of Alzheimer's disease (AD) by targeting β-amyloid (Aβ) plaques (1).

AD is characterized in pathology by the presence of extracellular Aβ plaques, intraneuronal neurofibrillary tangles, and neuronal loss in the cerebral cortex (2, 3). Of them, Aβ deposit is the earliest neuropathological marker and is relatively specific to AD and closely related disorders. Aβ plaques are composed of abnormal paired helical filaments 5–10 nm in size. These filaments are largely made of insoluble Aβ peptides that are 40 or 42 amino acids in length (4). Aβ peptides have been shown to be toxic to neurons, and the level of Aβ peptides is closely correlated with the cognitive decline in AD. These features of Aβ prompted investigators to develop Aβ-targeted agents for AD imaging.

Curcumin is the principal component of the Indian spice turmeric, and in structure it is composed of two aromatic rings connected by two α,β-unsaturated carbonyl groups (1). In 2001, investigators at the University of California, Los Angeles, reported that curcumin is effective against neurodegeneration, oxidative damage, and diffuse plaque deposition after Aβ infusion in animals (5, 6). The anti-AD effect of curcumin has been further demonstrated to be partially due to its specific binding with Aβ, whereby it could break apart Aβ aggregates. In 2006, Ryu et al. tested eight curcumin derivatives as Aβ-specific imaging probes (7). In general, these derivatives are poor in brain–blood barrier (BBB)

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penetration and are unstable *in vivo* (1, 7). The curcumin derivatives are quickly converted to unidentified polar products, which cannot cross the BBB. The methylene moiety between the two aromatic rings is responsible for the poor stability, whereas the two aromatic rings are responsible for the binding with Aβ plaques. To improve the stability and BBB-penetrating ability of curcumin, various modifications on the curcumin structure have recently been made, including deleting the active methylene moiety in the middle of its structure (1).

Cui et al. synthesized a series of dibenzylideneacetones by deleting the methylene moiety and one carbonyl moiety and further linking various substituents on one (forming an asymmetrical structure) or on both aromatic rings (forming a symmetrical structure) (1). Analysis of the structure–affinity relationship among these derivatives has shown that dibenzylideneacetone without any substituents have a weak affinity with Aβ (inhibition constant (K_i) = 242.5 ± 42.8 nM). Introduction of Cl or methoxy groups at the para position on both phenyl rings to form symmetrical ligands can significantly increase the binding affinity (~90 folds), and the size of substituents has no effect on the affinity for Aβ aggregates. Methylation of a primary amino group to form a secondary or tertiary amino group can also significantly increase the affinity (e.g., the agents [^{125}I]70 and [^{125}I]71 in MICAD), but methylation of the amino group at the ortho position reduces the binding affinity dramatically. Increasing the substituent size at the aromatic amino group also leads to decreased binding affinity. However, when a phenyl ring in the dibenzylideneacetone structure is changed to a heterocyclic ring, such as a thiophene, furan, pyridine, or pyrrole ring, the generated compounds maintain the high binding affinity. These results demonstrate that the para position is highly tolerant of steric bulk substitutions, which opens up the possibility of developing new, easily labeled radioligands for imaging Aβ plaques *in vivo* (1).

This chapter summarizes the data obtained with ^{18}F]83 and [^{18}F]85, two fluoro-pegylated dibenzylideneacetones (1). Another chapter summarizes the data obtained with [^{125}I]70 and [^{125}I]71, two asymmetrical dibenzylideneacetones with methylation of a primary amino group at the para position.

Related Resource Links:

- Amyloid-targeted imaging agents in MICAD
- Amyloid-targeted imaging clinical trials in ClinicalTrials.gov
- Structures and other information of amyloid peptides in PubChem
- Alzheimer's disease articles in Online Mendelian Inheritance in Man

Synthesis

[PubMed]

Synthesis of the compound precursors was described in detail by Cui et al. (1). To generate [^{18}F]83, the tosylate precursor 80 was mixed with [^{18}F]fluoride/potassium carbonate and Kryptofix2.2.2 in dimethyl sulfoxide for 5 min under heating at 120°C. The

mixture was purified with high-performance liquid chromatography. To generate [^{18}F]85, the *N*-Boc-protected mesylate precursor was first treated with aqueous HCl to remove the *N*-Boc-protecting group. The radiochemical purity of both [^{18}F]83 and [^{18}F]85 was >98%. The radiochemical yields (decay-corrected) of [^{18}F]83 and [^{18}F]85 were 49% and 13%, respectively. The partition coefficients of [^{18}F]83 and [^{18}F]85 were 2.97 and 3.08, respectively, indicating that both agents were lipophilic. The specific activity for both [^{18}F]83 and [^{18}F]85 was not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The binding affinity of unlabeled compounds 83 and 85 for $A\beta_{1-42}$ was examined with [^{125}I]IMPY (6-iodo-2-(4'-dimethylamino)phenyl-imidazo[1,2]pyridine) as the competing radioligand (1, 8). The K_i values of compounds 83 and 85 were 6.9 ± 1.4 nM and 8.6 ± 1.3 nM, respectively, which was superior to the binding affinity of IMPY (K_i = 10.5 nM) (8).

The binding of [^{18}F]83 and [^{18}F]85 to Aβ plaques in brain tissue sections of transgenic mice (APP/PS1) was evaluated *in vitro* with autoradiography (1). Both ligands showed effective labeling of the plaques with minimal background, consistent with the findings from thioflavin S staining. The brain sections from normal mice were void of any notable Aβ labeling.

Autoradiographic studies of [^{18}F]83 and [^{18}F]85 were also performed in human AD brain sections to test their binding with human Aβ plaques (1). Specific labeling of the plaques was observed, and immunohistochemical staining confirmed the presence of plaques in the sections.

Animal Studies

Rodents

[PubMed]

Biodistribution of [^{18}F]83 and [^{18}F]85 was analyzed in normal mice (n = 4/time point for each agent) (1). Both [^{18}F]83 and [^{18}F]85 exhibited good initial penetration of the BBB with initial brain uptakes of 4.13% and 5.15% ID/g at 2 min after injection, respectively, showing improved initial uptake than the previously reported radiofluorinated curcumin (0.52% ID/g at 2 min) (7). The radioactivity was then washed out rapidly (0.90% and 1.27% ID/g at 60 min for [^{18}F]83 and [^{18}F]85, respectively). The $brain_{2min}/brain_{60min}$ ratios were 4.59 and 4.06 for [^{125}I]70 and [^{125}I]71, respectively. The defluorination, as reflected by bone uptake, was low (2.33% and 2.54% ID/g in the bone at 1 h for [^{18}F]83 and [^{18}F]85, respectively). Both agents were cleared predominantly by the hepatobiliary system (14.07% and 19.24% ID/g in the liver at 30 min for [^{18}F]83 and [^{18}F]85, respectively). The hepatobiliary excretion to the intestines was also rather fast, and radioactivity was observed to accumulate within the intestines at later time points

(21.57% and 26.26% ID/g in the intestines at 60 min for [^{18}F]83 and [^{18}F]85, respectively). A moderate uptake of the two agents was also observed in the kidneys (7.13% and 11.51% ID/g at 30 min for [^{18}F]83 and [^{18}F]85, respectively), indicating that they were also excreted *via* the renal system.

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

References

1. Cui M.et al. *Synthesis and structure-affinity relationships of novel dibenzylideneacetone derivatives as probes for beta-amyloid plaques.* J Med Chem. 2011;54(7):2225–40. PubMed PMID: 21417461.
2. Ono M. *Development of positron-emission tomography/single-photon emission computed tomography imaging probes for in vivo detection of beta-amyloid plaques in Alzheimer's brains.* Chem Pharm Bull (Tokyo). 2009;57(10):1029–39. PubMed PMID: 19801854.
3. Mathis C.A., Wang Y., Klunk W.E. *Imaging beta-amyloid plaques and neurofibrillary tangles in the aging human brain.* Curr Pharm Des. 2004;10(13):1469–92. PubMed PMID: 15134570.
4. Vallabhajosula S. *Positron emission tomography radiopharmaceuticals for imaging brain Beta-amyloid.* Semin Nucl Med. 2011;41(4):283–99. PubMed PMID: 21624562.
5. Frautschy S.A.et al. *Phenolic anti-inflammatory antioxidant reversal of Abeta-induced cognitive deficits and neuropathology.* Neurobiol Aging. 2001;22(6):993–1005. PubMed PMID: 11755008.
6. Lim G.P.et al. *The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse.* J Neurosci. 2001;21(21):8370–7. PubMed PMID: 11606625.
7. Ryu E.K.et al. *Curcumin and dehydrozingerone derivatives: synthesis, radiolabeling, and evaluation for beta-amyloid plaque imaging.* J Med Chem. 2006;49(20):6111–9. PubMed PMID: 17004725.

8. Newberg A.B.et al. *Safety, biodistribution, and dosimetry of 123I-IMPY: a novel amyloid plaque-imaging agent for the diagnosis of Alzheimer's disease.* J Nucl Med. 2006;47(5): 748–54. PubMed PMID: 16644743.