[^{123}I/^{125}I]6-Iodo-2-(4´-dimethylamino)-phenyl-imidazo[1,2-*a*]pyridine

[^{123,125}I]IMPY

The MICAD Research Team

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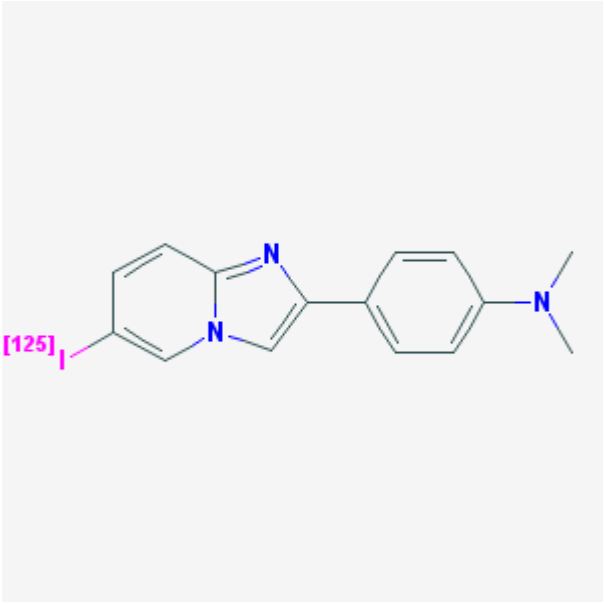
Chemical name:	[^{123}I/^{125}I]6-Iodo-2-(4´-dimethylamino)-phenyl-imidazo[1,2-*a*]pyridine
Abbreviated name:	[^{123}I]IMPY or [^{125}I]IMPY, IMPY
Synonym:	
Agent Category:	Compound
Target:	Aggregates of β-amyloid (Aβ) peptides
Target Category:	Acceptor binding
Method of detection:	SPECT
Source of signal:	^{123}I,^{125}I
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

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Alzheimer's disease (AD) is a major neurodegenerative disease associated with an irreversible decline of mental functions and with cognitive impairment (1, 2). It is characterized by the presence, in the brain, of senile plaques of β-amyloid (Aβ) peptides with intracellular neurofibrillary tangles of filaments containing the hyperphosphorylated protein tau (3, 4). Accelerated deposition of Aβ deposits seems to be a key risk factor associated with AD, and although the mechanisms of the disease are still not fully understood, reducing the deposition of amyloid plaques seems to benefit patients.

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 and Aβ deposits (7). The first successful agent used in human studies was 2-(1-(6-[(2-[^{18}F]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene)malononitrile ([^{18}F]FDDNP) (8), a malonitrile derivative found to bind to both neurofibrillary tangles and Aβ plaques. The second successful attempt in humans was made with [^{11}C]PIB (9), also known as Pittsburgh Compound B or [^{11}C]6-OH-BTA-1. [^{11}C]PIB showed marked retention in areas of association cortex known to contain substantial amounts of Aβ deposits. The third PET radioligand tested in humans was [^{11}C]4-*N*-methylamino-4′-hydroxystilbene, a stilbene derivative commonly named [^{11}C]SB-13. SB-13 was also synthesized and labeled with either I-123 or C-11 for *in vivo* imaging using PET.

The radioiodinated ligand 6-iodo-2-(4′-dimethylamino)-phenyl-imidazo[1,2-*a*]pyridine ([^{125}I]IMPY or [^{123}I]IMPY), is a novel probe displaying high specific binding for Aβ plaques and very favorable brain uptake kinetics in rodents. Published research has shown that this radioligand was a good candidate for the detection of Aβ plaques in humans when used with single-photon emission computed tomography (SPECT).

Synthesis

[PubMed]

[^{125}I]IMPY or [^{123}I]IMPY can be prepared by an iododestannylation reaction from the corresponding tin precursor using hydrogen peroxide as catalyst. Using this protocol, Kung et al. (10) obtained the no-carrier-added product with a high specific activity (81,400 GBq/mmol (2,200 Ci/mmol) for [^{125}I]IMPY and 8,140 GBq/mol (220,000 Ci/mmol) for [^{123}I]IMPY), an overall yield ranging from 30 to 45%, and a radiochemical purity greater than 95%. The method reported by the authors (10) in 2002 used a purification process that included high-pressure liquid chromatography (HPLC). The stabilities of the purified tracers (by HPLC) were 6 h at room temperature for [^{123}I]IMPY and 8 weeks for [^{125}I]IMPY stored in 100% ethanol at –20°C.

A simplified method was reported by Kung et al. (11) in 2004. This method improved the yield and simplified the purification process of the radioiodinated IMPY. Purification was done with a simple C_4 mini-column with stepwise washing and elution using ethanol (3 ml at 10% and 3 ml at 20% for the washing). The radiochemical yield obtained was >50%, and the total synthesis time was less than 1 h. The radiochemical purity obtained was >95% (determined by HPLC or thin-layer chromatography).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro binding assays using preformed synthetic Aβ40 aggregates (10) showed that [^{125}I]IMPY had very good binding affinities for amyloid plaques while competing well for the thioflavin binding site recognized by [^{125}I]2-(4′-dimethylaminophenyl)-6-iodobenzothiazole ([^{125}I]TZDM), a selective probe for amyloid plaques studied previously (12). The inhibition coefficient (K_i) for [^{125}I]IMPY was 15 ± 5 nM (at 25 °C). Replacement of the iodine by a methyl or hydrogen appeared to substantially decrease the binding affinity of [^{125}I]IMPY for Aβ aggregates (K_i ~242 and 1242 nM for methyl group and hydrogen, respectively).

In vitro audiography of amyloid plaques in postmortem brain sections of AD patients showed distinct labeling of the plaques after exposure to [^{125}I]IMPY, whereas no specific binding of the tracer was observed in normal brains. The specificity of Aβ plaque labeling by [^{125}I]IMPY was further supported by blocking experiments using a competing concentration of thioflavin-T (100 μM). In addition, when pretreated with formic acid (which destroys the ß-sheet structure), the AD brain sections showed no retention of [^{125}I]IMPY (10).

Animal Studies

Rodents

[PubMed]

Biodistribution studies in healthy male mice (2-3 months old; weight, 20-30 g) injected with [^{125}I]IMPY (4.9 MBq (133 μCi)) showed excellent brain uptake (2.9% of the initial injected dose (ID) at 2 min post injection) and rapid washout (0.26% and 0.2% of initial ID remaining in the brain at 30 and 60 min post injection, respectively) (10). Those results indicated that [^{125}I]IMPY had much more favorable *in vivo* kinetic properties than the other iodinated probe, [^{125}I]TZDM (12).

Plaque labeling with [^{125}I]IMPY was studied by Kung et al. (10) in an 18-month-old transgenic mouse (Tg2576) that produced excess amyloid plaques in the brain (10). *Ex vivo* autoradiograms of brain sections of the animal at 4 h after an intravenous injection of the tracer (injected dose: 4.9 MBq (133 μCi)) clearly showed distinct plaque labeling with low background activity. When the same brain section was stained with the fluorescent dye thioflavin-S, the same amyloid plaques showed prominent fluorescent labeling consistent with the results of the autoradiogram.

Zhuang et al. (13) measured the levels of radiotracer uptake (in % ID/organ) in normal mice (ICR) at 2 min, 30 min, and 2 h, respectively, and found the following values: 2.88 ± 0.25, 0.26 ± 0.00, and 0.14 ± 0.03 for the brain; 20.9 ± 2.63, 6.32 ± 0.55, and 2.90 ± 0.21

for the liver; 4.75 ± 0.49, 1.51± 0.27, and 0.53 ± 0.05 for the kidney; and 1.56 ± 0.33, 0.31 ± 0.07, and 0.20 ± 0.05 for the lung.

At 30 min after intravenous injection of 4.9 MBq (133 μCi) of [^{125}I]IMPY in 14- to 16-month-old TT mice, Kung et al. (11), found that the radiotracer uptake was the highest in the cortical region (~0.9% ID/g of tissue), followed by the hippocampal (~0.8% ID/g of tissue) and cerebellar (~0.7% ID/g of tissue) regions. The lowest binding was found in the striatal region (~0.5-0.6% ID/g of tissue).

In that same research study, Kung et al. (11) investigated the effect of the carrier IMPY on several factors affecting the uptake of [^{125}I]IMPY by measuring the plasma input function and brain metabolites, with or without added carrier in the injected dose. Results showed that when the carrier was co-injected with [^{125}I]IMPY, degradation of [^{125}I]IMPY was significantly reduced and more tracer was retained by the brains of TT mice.

At 30 min post injection, approximately 0.97 ± 0.11% ID/organ (n = 3) was present in the brain with no carrier added, whereas approximately 1.36 ± 0.05% ID/organ (n = 3) and 1.93 ± 0.09% ID/organ (n = 3) were retained with 2 and 10 mg/kg IMPY, respectively. In the blood, those values were 6.46, 7.20, and 8.48% for 0, 2, and 10 mg/kg carrier, respectively. At 2 min post injection, adding the carrier IMPY to the [^{125}I]IMPY injection significantly increased the amount of nonmetabolized radiotracer in the plasma.

As proposed by Kung et al. (11) in 2004, the fact that *in vivo* binding of [^{125}I]IMPY to amyloid plaques cannot be blocked by co-injection of the carrier may be attributable to the following: (*a*) the binding capacity or number of sites for [^{125}I]IMPY is very high; or (*b*) the amount of injected carrier is limited by its solubility and therefore is not high enough to reach the minimal necessary blocking dose. As pointed out by the authors, the binding capacity of [^{125}I]IMPY is clearly high in the cortex and other brain tissues affected by the disease.

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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