2-(4'-Dimethylaminophenyl)-6-[^{125}I]iodobenzothiazole

[^{125}I]TZDM

The MICAD Research Team

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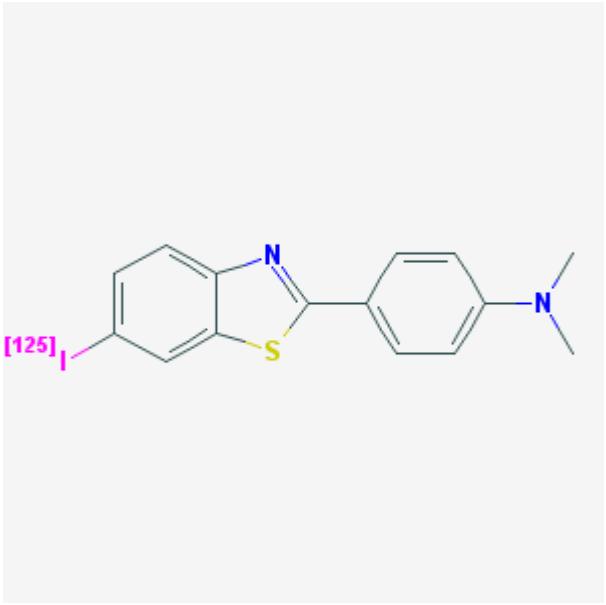
Chemical name:	2-(4'-Dimethylaminophenyl)-6-[^{125}I]iodobenzothiazole
Abbreviated name:	[^{125}I]TZDM
Synonym:	
Agent Category:	Compound
Target:	Amyloid β (Aβ) aggregates
Target Category:	Binding
Method of detection:	SPECT
Source of signal:	^{125}I
Activation:	No
Studies:	• *In vitro* • Rodents



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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 by the presence in the brain of senile plaques of β-amyloid (Aβ) peptides

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with 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, and although the mechanisms of the disease are still not fully understood, reducing the deposition of amyloid plaques seems to benefit patients.

Several radioligands have been developed (4-6) and tested in humans as *in vivo* diagnostic tools for imaging and measuring the formation of Aβ deposits (6). The first agent successfully used in human studies was [^{18}F]FDDNP (7), a malonitrile derivative found to bind to both neurofibrillary tangles and Aβ plaques. The second successful attempt was made with [^{11}C]PIB (8), 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, a stilbene derivative commonly named [^{11}C]SB-13 that exhibited good binding affinities for Aβ aggregates *in vitro*, moderate lipophilicity, high initial brain uptake in the normal rat cortex, and a rapid washout (9).

Benzofuran derivatives labeled with radioactive iodine have shown very good binding affinities for Aβ aggregates and good brain penetration (10). Unfortunately, their level of nonspecific binding was found to be very high, which makes them unsuitable for *in vivo* plaque imaging. However, [^{125}I]IMPY displayed good initial brain uptake and rapid washout from normal mouse brain and postmortem AD brain sections (11). Several conjugated thioflavin compounds based on benzothiazole have been shown to bind specifically to amyloid plaques. However, the thioflavins contain an ionic quaternary amine that is permanently charged and unfavorable to brain uptake. For that reason, several alternatives that use neutral derivatives have been synthesized and are currently being evaluated as potential ligands for imaging Aβ deposits in the AD brain. One of them, 2-(4'-dimethylaminophenyl)-6-[^{125}I]iodobenzothiazole ([^{125}I]TZDM) is currently being studied both *in vitro* and *in vivo* (12).

Synthesis

[PubMed]

[^{125}I]TZDM was prepared by Zhuang et al. (12) using a iododestannylation reaction with the tributyltin precursor 2-[4'-(dimethylamino)phenyl]-6-(tributylstannyl)benzothiazole. Briefly, hydrogen peroxide was added to a mixture of the tributyltin precursor (1 mg/ml EtOH), HCl, and Na^{125}I [0.037–0.185 MBq (1–5 μCi)] in a closed vial. The reaction was allowed to proceed at room temperature for 10 min and was ended by the addition of saturated $NaHSO_3$. The reaction mixture was then extracted after neutralization with a saturated sodium bicarbonate solution. After purification on a C4 column eluted with an isocratic solvent of 80% acetonitrile and 20% 3,3-dimethylglutaric acid (pH 7.0) at a flow rate of 0.8 ml/min, the desired fractions containing the product were collected, condensed, and re-extracted with ethyl acetate.

The no-carrier-added products were evaporated to dryness and redissolved in 100% EtOH. This reaction produced a no-carrier-added tracer with a specific activity comparable to that of Na^{125}I [59.4 MBq/mmol (2,200 Ci/mmol)] at the end of reaction. [^{125}I]TZDM was found to be stable *in vitro* for up to 2 months (storage at -20°C), with a radiochemical purity >95% as determined by high-performance liquid chromatography (12).

The precursor was prepared from a solution of 2-[4'-(dimethylamino)phenyl]-6-bromobenzothiazole (60 mg, 0.18 mmol) in 1,4-dioxane (2 ml), toluene (2 ml), and triethylamine (2 ml) with successive additions of $(Bu_3Sn)_2$ and $Pd(Ph_3P)_4$. After stirring at 90°C overnight, the solvent was removed and the residue purified by preparative thin-layer liquid chromatography (12).

In Vitro Studies

[PubMed]

Zhuang et al. (12) performed i*n vitro* binding assays of [^{125}I]TZDM to Aβ aggregates using Aβ(1–40) and Aβ(1–42) peptides in solution. Results showed that the ligand displayed a saturable binding, probably with one-site binding (as suggested by the linearity of the transformation of the saturation binding to Scatchard plots) and a preference for Aβ(1–42) aggregates. The estimated dissociation constants reported by Zhuang et al. (12) were 0.06 nM for aggregates of Aβ(1–40) and 0.14 nM for Aβ(1–42) aggregates.

Zhuang et al. (12) also performed competitive studies to evaluate the two styrylbenzene derivatives, chrysamine G and (*E*,*E*)-1-iodo-2,5-bis(3-hydroxycarbonyl-4-hydroxy)styrylbenzene (IMSB), *versus* [^{125}I]TZDM with respect to binding properties on Aβ (1–40) and Aβ (1–42) aggregates. High inhibition constants (K_i) were observed, which indicated poor binding competition. Similarly, high K_i values were obtained for [^{125}I]TZDM compared with binding of [^{125}I]IMSB [K_i (25°C) >2000 for Aβ(1–40) and K_i (25°C) >2000 for Aβ(1–40)]. The reported K_i values for TZDM *versus* [^{125}I]TZDM were 0.9 ± 0.2 for Aβ(1–40) and 2.2 ± 0.4 for Aβ(1–42). Three sets of experiments were performed, each carried out in duplicate.

The observations and results reported by Zhuang et al. (12) highlighted that fact that [^{125}I]TZDM displayed distinctive and mutually exclusive binding sites for Aβ(1–40) and Aβ(1–42) aggregates. Because increased production and deposition of Aβ(1–42) relative to Aβ(1–40) may be crucial for the generation of senile plaques, [^{125}I]TZDM and other related derivatives may be attractive imaging probes for *in vivo* plaque labeling. Zhuang et al. (12) pointed out the need for additional studies to provide further insight into structural information of the potential binding sites and the extent of functional linkages of benzothiazole binding sites on Aβ aggregates.

Animal Studies

Rodents

[PubMed]

To test the permeability of [^{125}I]TZDM through the intact blood–brain barrier, Zhaung et al. (12) injected 0.18–0.37 MBq (5–10 μCi) of the radioligand into the tail vein of normal mice (2–3 months old, 20–30 g each). The mice were euthanized at various times after injection, the organs of interest were excised and weighed, and their radioactivity was measured. Brain uptake results (in % dose/organ, average of 3 or 4 mice) were: 0.6 ± 0.11 (at 2 min postinjection), 0.9 ± 0.29 (30 min), 1.57 ± 0.24 (60 min), 0.65 ± 0.11 (6 h), and 0.04 ± 0.01 (24 h). Brain uptake peaked at 60 min, and blood levels were relatively low throughout the evaluated time period. Radioactivity uptake values (in % dose/organ) for other organs of interest included 0.6 ± 0.11 (at 2 min postinjection), 0.9 ± 0.29 (30 min), 1.57 ± 0.24 (60 min), 0.65 ± 0.11 (6 h), and 0.04 ± 0.01 (24 h) for the kidney; 0.6 ± 0.11 (at 2 min postinjection), 0.9 ± 0.29 (30 min), 1.57 ± 0.24 (60 min), 0.65 ± 0.11 (6 h), and 0.04 ± 0.01 (24 h) for the liver; 0.6 ± 0.11 (at 2 min postinjection), 0.9 ± 0.29 (30 min), 1.57 ± 0.24 (60 min), 0.65 ± 0.11 (6 h), and 0.04 ± 0.01 (24 h) for the heart.

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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