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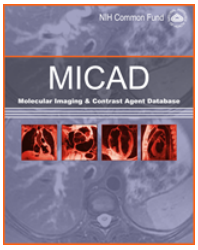

[*S-methyl*-^{11}C]*N*,*N*-Dimethyl-4-(6-(methylthio)imidazo[1,2-*a*]pyridine-2-yl)aniline

[^{11}C]MeS-IMPY

Kam Leung, PhD[1]

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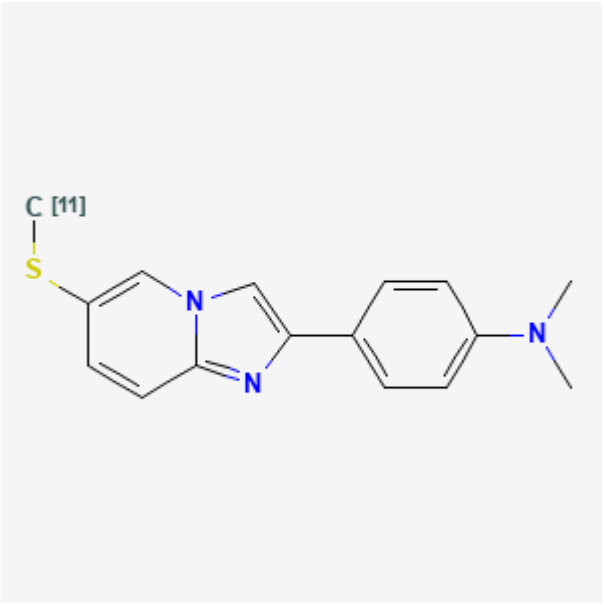
Chemical name:	[*S-methyl*-^{11}C]*N*,*N*-Dimethyl-4-(6-(methylthio)imidazo[1,2-*a*]pyridine-2-yl)aniline
Abbreviated name:	[^{11}C]MeS-IMPY
Synonym:	
Agent Category:	Compound
Target:	Aggregates of ß-amyloid (Aß) peptides
Target Category:	Acceptor binding
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Non-human primates



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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 pathologically by neuronal loss with the presence in the brain of senile plaques of β-amyloid (Aβ) peptides and 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.

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Early diagnosis of AD is important for treatment consideration and disease management (4). Several radioligands [PubMed] 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 of Aβ deposits (7). The first agent successfully used in human studies was [^{18}F]FDDNP (8), a malonitrile derivative found to bind to both neurofibrillary tangles and Aβ plaques. The second successful agent was [^{11}C]PIB (9), 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 ([^{11}C]SB-13), a stilbene derivative that exhibits good binding affinities for Aβ aggregates *in vitro*, moderate lipophilicity, high initial brain uptake in the normal rat cortex, and a rapid washout (10).

[^{125}I]6-Iodo-2-(4'-dimethylamino)-phenyl-imidazo[1,2-*a*]pyridine ([^{125}I]IMPY) displays a high specific binding for Aβ plaques and favorable brain uptake kinetics in rodents for single-photon emission computed tomography (SPECT). [*S-methyl*-^{11}C]*N*,*N*-Dimethyl-4-(6-(methylthio)imidazo[1,2-*a*]pyridine-2-yl)aniline ([^{11}C]MeS-IMPY) has been synthesized as an *S*-methyl analog of [^{125}I]IMPY and is currently being studied as a PET radioligand for Aβ plaques (11).

Synthesis

[PubMed]

[^{11}C]MeS-IMPY was synthesized from its precursor by *S*-methylation in acetonitrile with the use of ^{11}C-methyl iodide (80°C for 5 min) (11). [^{11}C]MeS-IMPY was purified by reversed-phase high-performance liquid chromatography with >98% radiochemical purity. The radiochemical yields (decay-corrected) on the basis of [^{11}C]CO_2 were 10–15% , and the specific activities were 37–148 GBq/μmol (1.0–4.0 Ci/μmol) at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

MeS-IMPY was found to have an inhibition constant (K_i) value of 7.93 nM using human AD brain homogenates (11). MeS-IMPY exhibited a moderate lipophilicity (log *D* value of 4.1 at pH 7.4). These values are comparable to those of IMPY (K_i value of 8.95 nM and log *D* value of 3.58).

Animal Studies

Rodents

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Seneca et al. (11) studied PET imaging in the brains of five young male rhesus monkeys after intravenous injection of 191 ± 75 MBq (5.16 ± 2.03 mCi) [^{11}C]MeS-IMPY. Various brain regions exhibited rapid accumulation with rapid decreases thereafter. [^{11}C]MeS-IMPY PET images (up to 120 min after injection) showed high standardized uptake values of ~500% and ~600% at 2–3 min in cortical regions and the cerebellum, respectively. The brain uptake of [^{11}C]MeS-IMPY was widespread and quite uniform across all cortical regions. Radioactivity rapidly washed out of the brain, with 20% of peak activity remaining at 40 min. Regional brain radioactivity fit well into a one-tissue compartment model. The average volume of distribution in all brain regions was 7.66 ± 2.14 ml/cm^3 (n = 4). The organs with the highest radiation exposure (μSv/MBq and mrem/mCi) were the gallbladder wall (33.4 and 123.5), urinary bladder (17.0 and 62.9), lungs (12.9 and 47.8), kidneys (11.7 and 43.4), and liver (10.7 and 39.4), with a resulting effective dose of 4.9 μSv/MBq (18.0 mrem/mCi).

Human Studies

[PubMed]

No publication is currently available.

NIH Support

Intramural Research Program

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