1-([4-methoxy-^{11}C]-3,4-Dimethoxyphenethyl)-4-(3-phenylpropyl)piperazinephenoxy)

[^{11}C]SA4503

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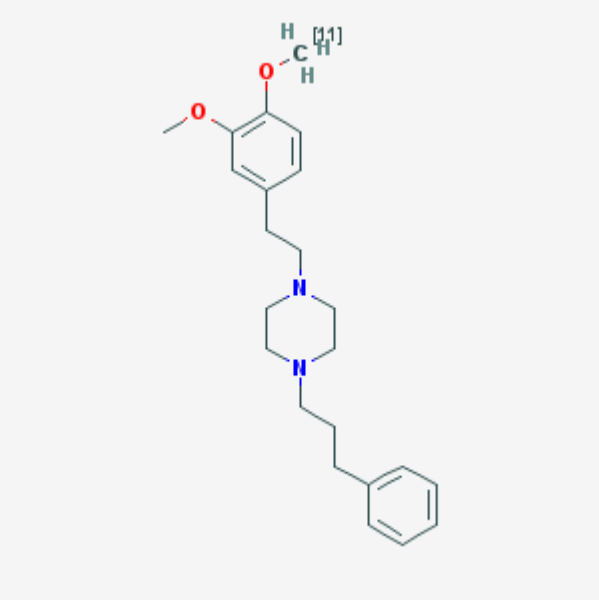
Chemical name:	1-([4-methoxy-^{11}C]-3,4-Dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine
Abbreviated name:	[^{11}C]SA4503
Synonym:	
Agent Category:	Compound
Target:	Sigma (σ) receptor
Target Category:	Receptor binding
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Non-human primates • Humans



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Background

[PubMed]

1-([4-methoxy-^{11}C]-3,4-Dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine ([^{11}C]SA4503) is a radioligand developed for positron emission tomography (PET) imaging of the sigma (σ) receptors. [^{11}C]SA4503 is a potent σ_1 receptor agonist labeled with ^{11}C, a positron emitter with a physical half-life ($t_{½}$) of 20.4 min (1).

σ receptors are functional, membrane-bound proteins distributed in the central nervous system (CNS) and peripheral organs (2). The CNS σ receptors are unique binding sites related to higher brain functions (3). They are distinct from opiate and phencyclidine binding sites. There are at least two subtypes of σ receptors: σ_1 and σ_2 receptors. The precise mechanism of the functional response of these receptors is not entirely known. These receptors appear to be involved in numerous pharmacologic and physiologic functions, and they also modulate a number of central neurotransmitter systems, including noradrenergic, glutamatergic, and dopaminergic systems. Phencyclidine and derivatives, cocaine and derivatives, some neuroleptics, atypical antipsychotic agents, and other chemically unrelated compounds can bind to the σ receptor sites. Studies have shown that these receptors may play a role in the pathogenesis of psychiatric disorders (4, 5). These receptors are also expressed on a number of human and murine tumors (6).

The σ_1 receptor subtypes have a molecular weight of ≈25 kDa, and through the process of cloning they have shown a 30% sequence homology with the yeast C89-C7 sterol isomerase (2, 7, 8) The σ_2 receptor subtypes have a molecular weight of ≈21.5 kDa and have not been cloned. The σ_1 receptors are thought to be involved in certain neuropsychiatric disorders, and the σ_2 receptors are also implicated in malignant neoplastic diseases. Because of these effects, σ receptor ligands may be useful for detection and treatment in neurology and oncology. Matsuno et al. (9) developed a potent σ_1 agonist, 1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)-piperazine dihydrochloride (SA4503), which is undergoing phase II clinical trials as a therapeutic agent for functional recovery after stroke. SA4503 is highly selective for σ_1 receptors versus σ_2 receptors (9). Small modifications in the SA4503 structure appear to have profound effects on the σ_1/σ_2 receptor affinity and selectivity (10). SA5403 can be labeled with ^{11}C for PET studies of σ receptors, and studies have shown specific localization of [^{11}C]SA4503 in animals and humans (1, 11, 12).

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Synthesis

[PubMed]

Fujimura et al. (13) reported the synthesis of SA4503 and other analogs of lefetamine. SA4503 was obtained by reacting *N*,*N*-bis(2-chloroethyl)-2-(3m4-dimethoxy)phenylethylamine with phenylpropylamine. Kawamura et al. (1, 14) prepared [^{11}C]SA4503 by methylation of the demethyl precursor, *O*-desmethyl SA4503, with [^{11}C]methyl iodide ([^{11}C]CH_3I). [^{11}C]CH_3I was synthesized with an automated system and was trapped in *N*,*N*-dimethylformamide (DMF) that contained sodium hydride (NaH) which was preheated at 80 °C for 2-5 min before reaction. The mixture was then heated at 120 °C for 1 min. The final product was purified by high- performance liquid chromatography (HPLC). The synthesis time was 20 min with a radiochemical purity >98%. The decay-corrected radiochemical yield was 25% (based on [^{11}C]CH_3I), and the specific activity was 46 TBq/mmol(1,242 Ci/mmol) 20 min after the end of bombardment.

[^{11}C]methyl triflate ([^{11}C]CH_3Tf) was used by Kawamura and Ishiwata (15) to improve the radiosynthesis of [^{11}C]SA4503. The precursor, 4-*O*-demethyl SA4503, was prepared from 3-phenyl-1-propanol (16). [^{11}C]CH_3Tf) was prepared by passing [^{11}C]CH_3I through silver triflate at 200 °C with a nitrogen flow. [^{11}C]CH_3Tf was trapped in DMF that contained 4-*O*-demethyl SA4503 at −17 to −12°C, and then the mixture was heated for 1 min at 120°C. The reaction mixture was separated by HPLC. The radiochemical yield of [^{11}C]SA4503 was increased to 56.2 ± 2.3%.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Kawamura et al. (16) reported that the lipophilicity $logP_{7.4}$ (n-octanol and phosphate buffer, pH 7.4 at 37°C) of [^{11}C]SA4503 (specific activity = 135 ± 82 TBq/mmol(3,645 ± 2,214Ci/ mmol) was 2.5, and the *in vitro* affinity IC_{50} values in guinea pig brain membranes were 17 and 1800 nM for σ_1 and σ_2 receptors, respectively. Ishiwata et al. (17) reported an age-related increase in the binding of [^{11}C]SA4503 to σ receptors in the rat brain membrane binding assay studies. The K_d values (n = 3) were 4.5 ± 0.1, 9.5 ± 0.6, 5.8 ± 0.6, and16.9 ± 0.9 nM for rats of 1.5, 6, 12, and 24 months of age, respectively. The B_{max} values were 234 ± 4, 421± 24, 545 ± 41, and 1069 ± 56 fmol/mg, respectively.

Kawamura et al. (11) studied the effects of SA4503 on proliferation of AH109A hepatoma cells (810 fmol/mg σ_1 and 1,200 fmol/mg σ_2), and found that SA4503 showed little tendency toward tumor growth inhibition. Van Waarde et al. (12) reported rapid association of [^{11}C]SA4503 with rat glioma C6 and human small cell lung carcinoma N417 cell lines. *In vitro* cell binding assays indicated that the binding occurred at a single site with IC_{50} values in the 10^{-5} to 10^{-4} mol/L range.

Animal Studies

Rodents

[PubMed]

Mouse radiation dosimetry studies indicated that the liver received the highest radiation dose of 20.5 μGy/MBq (75.9 mrad/mCi) (18). The pancreas, kidneys, lungs, and bones received 19.9 μGy/MBq (73.7 mrad/mCi), 19.1 μGy/MBq (70.7 mrad/mCi), 4.19 μGy/MBq (15.5 mrad/mCi), and 17.1 μGy/MBq (63.3 mrad/mCi), respectively. In tissue distribution studies of [^{11}C]SA4503 at dosage levels of 1–2 MBq/8.2–34 pmol (27–54 μCi)/8.2–34 pmol) in mice showed radioactivity levels (n = 4) of 3.61 ± 0.39% injected dose (ID/g) at 5 min, 3.54 ± 0.38% ID/g at 15 min, 3.36 ± 0.26% ID/g at 30 min, 3.10 ± 0.23% ID/g at 60 min, and 2.79 ± 0.35% ID/g at 90 min in the brain (16, 18). Whereas the radioactivity levels in the lungs and kidneys decreased over time, radioactivity levels in the liver and pancreas increased over time. Brain uptake was significantly decreased by co-injection of unlabeled SA4503 (60% decrease) or haloperidol (a σ_1 and σ_2 receptor ligand). Metabolite analysis showed that 97 ± 0.9% and 54 ± 5.8% of [^{11}C]SA4503 remained unchanged at 30 min after injection into the brain and plasma, respectively. Kawamura et al. (19) found that the mouse brain uptake of [^{11}C]SA4503 radioactivity was not affected by cyclosporine A, a P-glycoprotein modulator. Ishiwata et al. (20) also reported that raclopride (dopamine D_2-receptor ligand) had no effect on [^{11}C]SA4503 radioactivity uptake in the mouse brain.

Ex vivo autoradiography in rat brains (98–180 MBq/2.1–7.6 nmol [2.6-4.9 mCi/2.1–7.6 nmol]) at 30 min after injection showed a higher density in the vestibular nucleus, temporal cortex, cingulated cortex, inferior colliculus, thalamus, and frontal cortex (16). Moderate levels were found in the caudate putamen and parietal cortex. In a separate study, unlabeled SA4503 reduced 80% of the density in the regions with high and moderate levels (1). Kawamura et al. (1) reported the tissue distribution study of 10 mBq/140 pmol (270 μCi/140 pmol, 0.54 nmol/kg) of [^{11}C]SA4503 in rats. At 30 min after injection, the radioactivity levels (n = 4) were 0.30 ± 0.02% ID (brain), 3.84 ± 0.29% ID(pancreas), 1.40 ± 0.09% ID(liver), 1.05 ± 0.12% ID(lung), and 0.86 ± 0.04% ID(kidney), 0.98 ± 0.09% ID(spleen). The brain activity was reduced to ≈30% of the control by unlabeled SA4503 or haloperidol. In PET imaging of the rat brain 9.4 MBq/230 pmol [254 μCi/230 pmol], 0.91 nmol/kg), the rat brain was clearly visualized.

In a distribution study of 20 MBq (0.54 mCi) [^{11}C]SA4503 in nude rats with C6 glioma the standardized uptake value (SUV = cpm/g tissue divided by cpm/g of body weight) was 0.65 ± 0.15 (n = 5) for the tumor at 60 min after injection (12). The ratios of tumor/plasma and tumor/muscle were 13.3 ± 3.1 and 5.0 ± 2.5, respectively. In another study, van Waarde et al. (21) found that [^{11}C]SA4503 was fairly tumor selective for tumor cells from inflammation caused by turpentine. The SUV values (n = 6) were 0.73 ± 0.32 and 0.20 ± 0.07 for C6 tumor and inflammation, respectively.

Other Non-Primate Mammals

[PubMed]

Kawamura et al. (18) evaluated PET imaging of [^{11}C]SA4503 in a cat with a dose of 200 MBq/57 nmol (5.4 mCi/57 nmol). A high radioactivity uptake was observed in the cortex. With co-injection dose of 1 mg/kg unlabeled SA 4503, the radioactivity rapidly decreased with 67%, 47%, and 41% remaining at 30 min, 60 min, and 90 min, respectively. The blood and plasma radioactivity rapidly decreased after injection. Percentages of unchanged [^{11}C]SA4503 in the blood were 26.3% (15 min), 21.9% (30 min), 12.5% (60 min), and 11.0% (90 min).

In a VX-2 carcinoma rabbit model (11,000 fmol/mg σ receptor density in cells), Kawamura et al. (11) showed that PET imaging with [^{11}C]SA4503 clearly visualized VX-2 tumor tissue. Pretreatment with haloperidol or unlabeled SA4503 decreased the uptake of the radioactivity at 30 min after injection by 22% and 41%, respectively.

Non-Human Primates

[PubMed]

Ishiwata et al. (22) performed [^{11}C]SA4503 PET imaging in a conscious monkey with a dose of 600 MBq/20 nmol(16.2 mCi/20 nmol). Images were acquired at 60 min after injection for 20 min. The accumulated radioactivity levels were relatively high in the thalamus, parietal cortex, and vermis but were relatively low in the frontal cortex and cerebellar hemisphere. The plasma radioactivity was lower than the radioactivity of blood. The radioactivity in both the blood and plasma decreased for the first 30 min. When a second dose of 140 MBq/12 μmol (3.8 mCi/12 μmol) was given to the same monkey along with 5.4 mg unlabeled SA4503 (90 min after the first scan), the initial radioactivity uptake rapidly decreased and the brain accumulation disappeared. The overall radioactivity level was ≈50–60% of the level of [^{11}C]SA4503 injection alone at 60–80 min. The plasma radioactivity was slightly higher than the radioactivity of blood. The radioactivity in the blood and plasma rapidly decreased for the first 5 min and then remained constant. The authors suggested there was a saturable uptake by the blood cells or a saturable binding to the membrane. In another monkey, 1 mg/kg haloperidol was given after injection of 560 MBq/22 nmol (15.1 mCi/22 nmol) [^{11}C]SA4503 was injected. The radioactivity level gradually decreased in all brain regions studied. Similarly, the radioactivity level rapidly decreased when haloperidol was given before the dose of [^{11}C]SA4503.

Human Studies

[PubMed]

Van Waarde et al (12) performed [^{11}C]SA4503 PET imaging in a healthy human volunteer. A dose of 560 MBq/9/7 nmol (15.1 mCi/9.7 nmol) with specific activity >10 TBq/mmol (270 Ci/mmol) was administered. Imaging showed that there was high uptake

in the brain, heart, liver, and kidneys. There was relatively low radioactivity in the thorax, extremities, and lower abdomen.

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