1-([4-methoxy-^{11}C]3,4-Dimethoxyphenethyl)-4-[3-(4-fluorophenyl)propyl]piperazine

[^{11}C]SA5845

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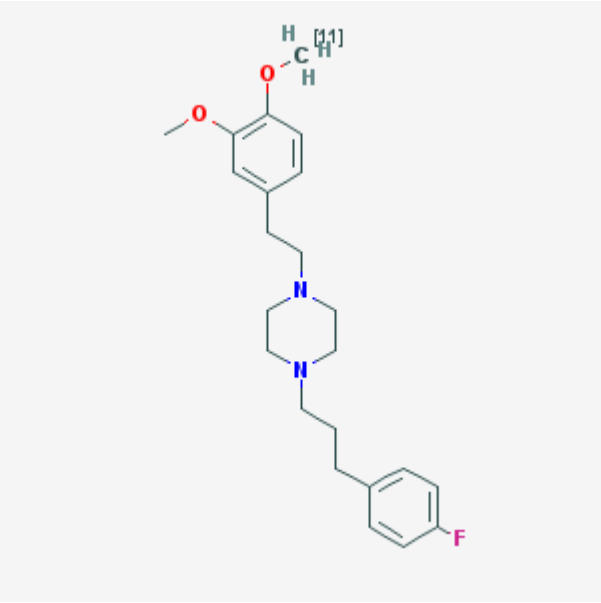
Chemical name:	1-([4-methoxy-^{11}C]3,4-Dimethoxyphenethyl)-4-[3-(4-fluorophenyl)propyl]piperazine
Abbreviated name:	[^{11}C]SA5845
Synonym:	
Agent Category:	Compound
Target:	Sigma (σ) receptor
Target Category:	Receptor binding
Method of detection:	Positron Emission Tomography (PET)
Source of signal/ contrast:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals



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Background

[PubMed]

1-([4-methoxy-^{11}C]-3,4-Dimethoxyphenethyl)-4-[3-(4-fluorophenyl)propyl]piperazine ([^{11}C]SA5845) is a radioligand developed for positron emission tomography (PET) imaging of the sigma (σ) receptors. [^{11}C]SA5845 is a potent σ 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 such as the gastrointestinal tract and immune systems (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 pharmacological 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 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 highly selective for σ_1 receptors versus σ_2 receptors. Small modifications in the SA4503 structure appear to have profound effects on the σ_1/σ_2 receptor affinity and selectivity (10). Fujimura et al. (11) prepared its fluorinated analog, SA5845, and reported that this compound had a high affinity for σ receptors. Kawamura et al. (12, 13) radiolabeled SA5845 with ^{11}C and evaluated its potential for PET studies of σ receptors in CNS and tumors.

Synthesis

[PubMed]

Kawamura et al. (12) reported the synthesis of the precursor 4-*O*-demethyl SA5845 for radiosynthesis of [^{11}C]SA5845. 4-*O*-demethyl SA5845 was prepared from 4-fluorocinnamic acid by an eight-step synthesis. In the radiosynthesis of [^{11}C]SA5845, [^{11}C]methyl iodide was prepared and trapped in 0.2 ml of *N*,*N*-dimethylformamide

containing 4-*O*-demethyl SA5845 and 1–2 mg of sodium hydride. The mixture was heated at 120°C for 1 min, and then 1.3 ml of 0.1 M hydrochloric acid/[50 mM acetic acid/ammonium acetate, 1/1](35/65) was added. The reaction mixture was purified by high-performance liquid chromatography (HPLC). [^{11}C]SA5845 was obtained with a radiochemical yield of 24 ± 4.2% (n = 6) in a synthesis time of 20 min. The radiochemical purity was >99%, and the specific activity was 135 TBq/mmol (3,645 Ci/mmol) at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Kawamura et al. (12) studied the *in vitro* properties of SA5845. The lipophilicity indicator log$P_{7.4}$ (n-octanol/phosphate buffer at 37°C) was determined to be 2.6. In comparison, the log$P_{7.4}$ of SA4503 was 2.5. Using guinea pig brain membranes, the *in vitro* binding affinity (IC_{50}) values of SA5845 to σ_1 and σ_2 receptors were 33 nM and 9.5 nM, respectively. Thus, the σ_2/σ_1 selectivity ratio was 0.29.

Animal Studies

Rodents

[PubMed]

Ex vivo brain autoradiography was carried out in rats with a [^{11}C]SA5845 dose of 98–180 MBq/2.1–7.6 nmol (2.64–4.86 mCi/2.7–7.6 nmol) (12). The radioligand showed a higher density in the vestibular nucleus, temporal cortex, cingulated cortex, inferior colliculus, thalamus, and frontal cortex. A lower level of density was found in the hippocampus and cerebellum. The study indicated that this regional brain distribution pattern was very similar to other σ ligands.

In a mouse biodistribution study, each mouse (n = 4-5) received a dose of 1.0-2.0 MBq/ 8.2-34 pmol (27–54 μCi/8.2–34 pmol) (12). At 5 min after injection, the radioactivity levels measured as percentage of injected dose per g (% ID/g) were 2.87 ± 0.39 (brain), 0.85 ± 0.11 (blood), 21.4 ± 3.82 (lung), 7.18 ± 1.22 (liver), 12.5 ± 1.87 (kidney), and 1.63 ± 0.22 (muscle). At 60 min, these levels changed to 3.79 ± 0.32 (brain), 0.28 ± 0.08 (blood), 6.83 ± 1.65 (lung), 13.5 ± 1.49 (liver), 7.05 ± 0.78 (kidney), and 0.81 ± 0.13 (muscle). The brain radioactivity level increased for 60 min, whereas the radioactivity levels in the lung and kidney rapidly decreased. The brain radioactivity level was significantly decreased (60%) by co-injection of unlabeled SA5845 (2000 nmol/kg). Loading of haloperidol, a non-subtype-selective σ receptor ligand, loading also significantly decreased the brain radioactivity level.

Each mouse received 4.5–19 MBq/0.13–2.0 nmol (122–513 μCi/0.13–2.0 nmol) in a metabolite study using HPLC analysis (12). The percentages of unchanged [^{11}C]SA5845

in the brain and plasma 30 min after injection were 98 ± 0.2 (n = 3) and 69 ± 3.1, respectively. [^{11}C]SA5845 appeared to be very stable in the brain.

Kawamura et al. (13) performed tissue distribution studies of [^{11}C]SA5845 in rats bearing the AH109A hepatoma.. The AH109A hepatoma was found to express a moderate density of both σ_2 and σ_1 receptors. Each mouse (n = 5) received 11 MBq/0.3 nmol (0.3 mCi/0,3 nmol) of [^{11}C]SA5845. The tumor radioactivity levels (% ID/g) were 0.24 ± 0.08, 0.26 ± 0.06, 0.37 ± 0.04, and 0.49 ± 0.05 at 5, 15, 30, and 60 min after injection, respectively. PET images (14 MBq/1.28 nmol (0.38 mCi/1.28 nmol)) visualized the AH109A hepatoma on the rat thigh. The brain radioactivity levels were 0.94 ± 0.12, 0.88 ± 0.29, 0.89 ± 0.04, and 0.98 ± 0.07 at 5, 15, 30, and 60 min after injection, respectively. Co-injection with 1 mg/kg haloperidol significantly decreased the radioactivity levels at 30 min in the brain, kidney, and muscle. The radioactivity levels in the tumor and blood were significantly increased. The 30−min tumor/blood ratio decreased from 9.7 without haloperidol to 5.6 with haloperidol whereas the 30−min tumor/muscle ratio increased from 1.3 without haloperidol to 3.5 with haloperidol. At 30 min after injection, HPLC analysis showed that 95.4 ± 1.9% and 75.1 ± 7.9% of [^{11}C]SA5845 remained unchanged in the tumor and plasma, respectively.

Other Non-Primate Mammals

[PubMed]

Kawamura et al. (13) used PET imaging to study [^{11}C]SA5845 in rabbits bearing the VX-2 carcinoma. In the VX-2 carcinoma the density of σ_2 receptors was >10-fold than that of σ_1 receptors. Each rabbit received 86 MBq/0.78 nmol (2.3 mCi/0.78 nmol) of [^{11}C]SA5845. PET images clearly visualized VX-2 carcinoma on the rabbit thigh. The radioactivity level of the tumor increased for the first 10 min and then remained constant for 60 min. Pretreatment with 1 mg/kg haloperidol decreased the initial radioactivity level of [^{11}C]SA5845 by 26% which then decreased further with time. Treatment with 1 mg/kg unlabeled SA5845 decreased the tumor radioactivity level by 53%. The authors concluded that [^{11}C]SA5845 might be a potential radioligand for PET imaging of σ receptor−rich tumors.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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