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

[^{11}C]SA6298

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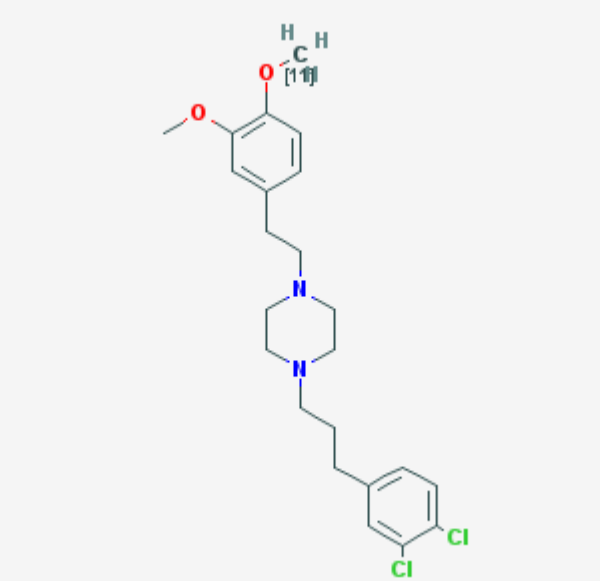
Chemical name:	1-(3,4-[^{11}C]Dimethoxyphenethyl)-4-[3-(3,4-dichlorophenyl)propyl]piperazine
Abbreviated name:	[^{11}C]SA6298
Synonym:	
Agent Category:	Compound
Target:	Sigma (σ) receptor
Target Category:	Receptor binding
Method of detection:	Positron Emission Tomography (PET)
Source of signal/ contrast:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals



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Background

[PubMed]

1-(3,4-[^{11}C]Dimethoxyphenethyl)-4-[3-(3,4-dichlorophenyl)propyl]piperazine ([^{11}C]SA6298) is a radioligand developed for positron emission tomography (PET) imaging of the sigma (σ) receptors. [^{11}C]SA6298 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).

The σ receptors are functional, membrane-bound proteins that are 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. A σ_3 receptor subtype has also been proposed (4). The precise mechanism of the functional response of these receptors is not entirely known. These receptors appear to be involved in numerous pharmacological and physiological 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 (5, 6). These receptors are also expressed on a number of human and murine tumors (7).

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, 8, 9) The σ_2 receptor subtypes have a molecular weight of ≈21.5 kDa and they have not been cloned. The σ_1 receptors are thought to be involved in certain neuropsychiatric disorders, and the σ_2 receptors are 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. (10) 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 (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). SA6298 is an analog of SA4503 with a higher but less selective affinity [inhibition constant (IC_{50}) for σ_1 = 6.9 nM; σ_1/σ_2 = 22] for σ_1 receptors than SA4503 (IC_{50} for σ_1 = 17.4 nM; σ_1/σ_2 = 103) (10, 13, 14). Kawamura et al. (13) evaluated the potential of [^{11}C]SA6298 as a PET σ_1 receptor ligand.

Synthesis

[PubMed]

Fujimura et al. (14) reported the preparation of SA6298 from phenylpropylamine. Kawamura et al. (13) designed the radiosynthesis of [^{11}C]SA6298 based on the precursor

desmethyl SA6298 (SA11726), which was obtained commercially. [^{11}C]SA6298 was prepared by methylation of SA11726 with [^{11}C]CH_3I. Briefly, [^{11}C]CH_3I was produced with an automated system and trapped in 0.2 ml of *N*,*N*-dimethylformamide containing 0.2 mg of SA11726 and 1–4 mg of sodium hydride (NaH). The mixture of SA11726 and NaH was preheated at 80°C for 2–5 min before [^{11}C]CH_3I was added. The mixture of [^{11}C]CH_3I, SA11726 and NaH was heated at 120°C for 1 min. The solution was then diluted with a solvent, and [^{11}C]SA6298 was isolated by a reversed-phase chromatography. The isolated product was purified by a high-performance liquid chromatography (HPLC). The decay-corrected radiochemical yield (based on [^{11}C]CH_3I) was 38.9 ± 5.2%, and the specific activity (n = 5) was 52.8 ± 16.8 TBq/mmol (453.6 Ci/mmol). The radiochemical purity was >97%.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Fujimura et al. (14) used guinea pig brain homogenate and [^{3}H](+)-pentazocine to determine the affinity of SA8298 to σ receptors. The IC_{50} to σ_1 receptors was 6.9 nM, and the σ_1/σ_2 ratio was 22. Kawamura et al. (13) determined that the octanol/phosphate buffered saline partition coefficient of [^{11}C]SA6298 was $logP_{7.4}$= 3.82.

Animal Studies

Rodents

[PubMed]

Biodistribution studies of [^{11}C]SA6298 were performed in mice (n = 20) (13). Each mouse received an i.v. dose of 1 MBq(27 μCi) per 25 pmol. The lung showed the highest initial activity level of percent injected dose per g (% ID/g) at 30 min (20.67 ± 1.03%) and then decreased gradually. The radioactivity levels in the brain (1.85 ± 0.08% ID/g at 30 min) and liver (14 ± 0.81% ID/g at 30 min) increased for 60 min. The radioactivity of most other organs (spleen, pancreas, kidney, etc.) increased for the first 15–30 min and then remained constant. Co-injection of unlabeled SA6298 reduced the brain radioactivity to 1.68 ± 0.02% ID/g (30 min) at the dose of 2,000 nmol/kg. The radioactivity levels in the heart, lung, and muscle decreased significantly at doses ≥20 nmol/kg, whereas the blocking effect was found in the spleen, small intestine, liver, and kidney at doses ≥200 nmol/kg. Pretreatment with 2,000 nmol/kg of SA6298 (10 min before) significantly decreased the brain radioactivity level to 1.54 ± 0.08% ID/g. However, postreatment (10 min after) increased the brain level to 4.17 ± 0.36% ID/g. SA4503 and haloperidol at 2,000 nmol/kg also showed a large blocking effect on the brain. Metabolites of [^{11}C]SA6298 were analyzed by HPLC and showed that unchanged [^{11}C]SA6298 in the brain and plasma was 99 ± 1% and 80 ± 5% (n = 3), respectively, at 30 min after injection.

The receptor-specific uptake of [^{11}C]SA6298 was examined in rats (n = 4) (13). Each rat received an i.v. dose of 9.8–10.4 MBq/350 pmol (265–281 μCi/350 pmol). The brain

radioactivity levels were reduced to ≈80% of the control by unlabeled SA6298 and SA4503. The levels in the spleen, kidney, and muscle were significantly blocked by both ligands, but the liver level was only blocked by SA6298. *Ex vivo* autoradiograms of the rat brain after administration of 127–140 MBq/3.6–4.2 nmol (3.4–3.8 mCi/3,6–4.2 nmol) [^{11}C]SA6298 (euthanization at 30 min) showed a slightly higher density in the cortex, thalamus, and medial geniculate nucleus. The authors mentioned that cortex and thalamus were known to be rich in $\sigma_1$receptors. The co-injection of unlabeled SA6298 decreased radioactivity in all brain regions by 20–40%.

Other Non-Primate Mammals

[PubMed]

PET imaging was performed in a cat (13) A dose of 197 MBq/4.28 nmol (5.3 mCi/4.28 nmol) was injected intravenously, and the imaging was performed over a period of 60 min. There were high radioactivity levels in the cortex, thalamus, striatum, and cerebellum that remained constant for 60 min. Co-injection of SA6928 (2,000 nmol/kg) decreased these levels by only 10–20% and postinjection of SA6928 did not affect the radioactivity levels. The authors suggested that because of the high affinity of [^{11}C]SA6298 for σ_1 receptors, once it binds to the receptors, it is not easily displaced by the unlabeled SA6298. HPLC analysis of the metabolites showed that unchanged [^{11}C]SA6298 in the plasma was 87% at 1 min, 15% at 30 min, and 11% at 60 min. The authors suggested that the lack of a clear specific brain uptake of [^{11}C]SA6298 is not explained by the retention of labeled metabolite. The high nonspecific brain binding of [^{11}C]SA6298 might be caused by its high lipophilicity

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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