[^{18}F]1-(2-Fluoroethyl)-4-[(4-cyanophenoxy)methyl]piperidine

[^{18}F]SFE

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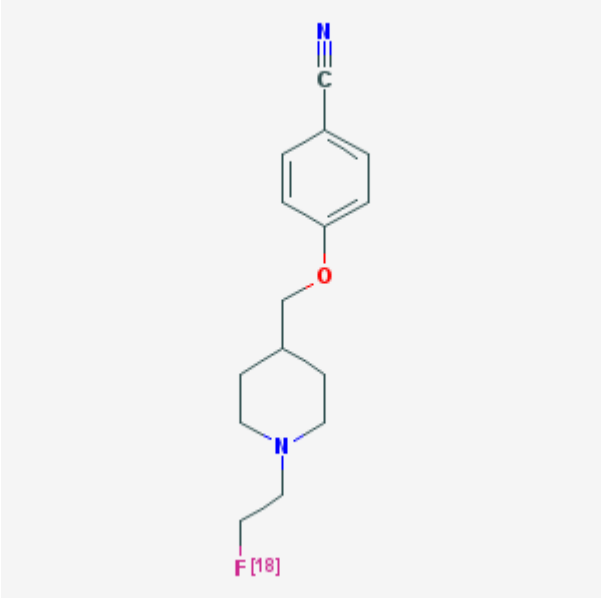
Chemical name:	[^{18}F]1-(2-Fluoroethyl)-4-[(4-cyanophenoxy)methyl]piperidine
Abbreviated name:	[^{18}F]SFE
Synonym:	[^{18}F]WLS1.002, [^{18}F]-2
Agent Category:	Compound
Target:	Sigma (σ) receptor
Target Category:	Receptor binding
Method of detection:	Positron Emission Tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals



Click on the above structure for additional information in PubChem.

Background

[PubMed]

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[^{18}F]1-(2-Fluoroethyl)-4-[4-cyanophenoxy)methyl]piperidine ([^{18}F]SFE) is a radioligand developed for positron emission tomography (PET) imaging of the sigma (σ) receptors (1-3). ^{18}F]SFE is a potent σ_1 receptor agonist labeled with ^{18}F, a positron emitter with a physical half-life ($t_{½}$) of 109.8 min.

σ receptors are functional, membrane-bound, G-protein-coupled receptors distributed in the central nervous system (CNS) and peripheral organs (4). The CNS σ receptors are unique binding sites related to higher brain functions (5). They are distinct from opiate and phencyclidine binding sites. There are at least two subtypes of sigma 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 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 (6, 7). These receptors are also expressed on a number of human and murine tumors (8).

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 (4, 9, 10). 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. A number of ligands for these receptors have been labeled with ^{11}C and ^{18}F for PET imaging to map their *in vivo* brain distribution and expression on tumors (11). Waterhouse et al. (12, 13) synthesized a number of selective σ_1 receptor ligands for both PET and single-photon emission computed tomography. [^{18}F]1-(3-Fluoropropyl)-4-(4-cyanophenoxy-methyl)piperidine ([^{18}F]FPS) was found to be a high-affinity σ_1 receptor ligand with a dissociation constant (K_d) of 0.5 nM, but it was not cleared fast enough from the CNS to reach transient equilibrium by 4 h after administration in healthy volunteers (3). In an effort to improve the CNS clearance for *in vivo* PET studies, Zhao et al. (3) synthesized and evaluated [^{18}F]SFE (K_d = 5 nM), a analog of [^{18}F]FPS analog that exhibits a lower affinity for σ_1 receptor ligands.

Synthesis

[PubMed]

Zhao et al. (3) reported the synthesis of [^{18}F]SFE from 4-(4-cyanophenoxy)methyl)piperidine, which was first prepared from ethyl isonepecotate in a five-step method. Alkylation of 4-(4-cyanophenoxy)methyl)piperidine with 2-bromo-1-ethanol in potassium carbonate and dichloromethane resulted in a 72%yield of the intermediate compound, 1-(2-hydroxyethyl)-4-[(4-cyanophenoxy)methyl]piperidine. The

alkyl mesylate precursor for [^{18}F]SFE was obtained by treating this intermediate compound with methanesulfonyl chloride in triethylamine and dichloromethane (64% yield). Radiosynthesis of [^{18}F]SFE was carried out by heating the alkyl mesylate precursor at 90°C for 15 min in an anhydrous solution of [^{18}F]fluoride and Kryptofix-potassium carbonate mixture in acetonitrile. Deionized water was added, and the mixture was heated for another 10 min to convert the unreacted precursor to the corresponding alcohol for easy purification. [^{18}F]SFE was obtained after purification by high-performance liquid chromatography (HPLC) with a yield of 59 ± 8% (n = 6) at the end of bombardment. The average time of synthesis was ≈100 min. The radiochemical purity was 98.3 ± 2.1%, and the specific activity was 106.93 ± 23.68 GBq/μmol (2.89 ± 0.80 Ci/μmol) at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Waterhouse et al. (12) reported *in vitro* receptor binding assays for several σ ligands in guinea pig membranes. The inhibition constant (K_i) of SFE for σ_1 receptors was 24.3 nM, and the K_i for σ_2 receptors was 361 nM. The K_i values of FPS were 4.3 and 144 nM for σ_1 and σ_2 receptors, respectively. Zhao et al. (3) conducted *in vitro* competitive binding assays of SFE in rat forebrain membranes. K_d for SFE was 5.0 nM, in comparison, the K_d for FPS was 0.5 nM. The lipophilicity (log *P*) of SFE was estimated to be 2.42 based on its retention time in a C18 column as compared to standards of known log *P* values.

Animal Studies

Rodents

[PubMed]

Zhao et al. (3) injected 555 kBq (15 μCi) [^{18}F]SFE into awake male rats (n = 4-5) for biodistribution and blocking studies. The whole-brain radioactivity concentrations, measured as percentage of injected dose per g (% ID/g) were 1.41 ± 0.05% ID/g, 1.08 ± 0.23% ID/g, and 0.33 ± 0.053% ID/g at 5 min, 60 min, and 330 min, respectively. At 5 min, the radioactivity concentrations (% ID/g) in major organs were 7.71 ± 0.93 (lung), 2.99 ± 0.10 (kidney), 1.75 ± 0.15 (heart), 1.40 ± 0.32 (intestine), 1.01 ± 0.21(spleen), 0.68 ± 0.17 (liver), and 0.14 ± 0.03% (blood). Except for the liver, radioactivity was cleared rapidly. The rapid biological clearance $t_{½}$ phase was 0.1–0.2 h, and the slow biological clearance $t_{½}$ phase was 2–4 h. The relative radioactivity concentration in the bone was low and did not significantly increase over time. Administration of the a σ_1 receptor selective compound (BD1008) 5 min before [^{18}F]SFE administration reduced brain activity by 80% at 60 min.

Waterhouse et al. (1) reported regional brain radioactivity concentrations in four rats. Each rat received 555–740 kBq (15–20 μCi) [^{18}F]SFE. The specific activity was 88.8 ± 22.2 GBq/μmol (2.4 ± 0.6 Ci/μmol) at the end of synthesis. The rats were euthanized and

specific brain regions were dissected and assayed. The regional brain radioactivity concentrations (% ID/g; $n = 4$) at 5 min were 2.02 ± 0.41 (occipital cortex), 2.00 ± 0.38 (frontal cortex), 1.66 ± 0.76 (striatum), 1.25 ± 0.25 (thalamus), 1.18 ± 0.19 (cerebellum), and 0.99 ± 0.19 (hippocampus). This appeared to be consistent with previously reported CNS σ_1 receptor distribution pattern. At 60 min, these values decreased (% ID/g) to 1.28 ± 0.08 (occipital cortex), 1.42 ± 0.12 (frontal cortex), 1.01 ± 0.06 (striatum), 1.14 ± 0.10 (thalamus), 0.96 ± 0.03 (cerebellum), and 0.87 ± 0.08 (hippocampus). Pretreatment with unlabeled SFE, FPS, and BD1407 (σ_1-selective) reduced regional brain radioactivity by ≈80%. The brain metabolite study by HPLC analysis ($n = 3$) at 60 min showed that the percentages of unchanged [^{18}F]SFE were 53 ± 5, 93 ± 1, and 97 ± 1 in the plasma, frontal cortex, and cerebellum, respectively.

Based on the rat [^{18}F]SFE distribution data from rats, Waterhouse et al. (2) reported human dosimetry estimation extrapolated from organs and the whole body. Organs with significant radioactivity generally received ≈0.02–0.04 mGy/MBq (0.054–0.108 rad/mCi). The adrenal gland was the critical organ with the highest dose of 0.044 mGy/MBq (0.163 rad/mCi), The doses of other major organs in mGy/MBq (rad/mCi) were 0.0238 (0.88), 0.0397 (0.147), 0.0382 (0.141), 0.03 (0.111), and 0.0284 (0.105) for the brain, lungs, liver, spleen, and kidneys, respectively.

Other Non-Primate Mammals

[PubMed]

Waterhouse et al. (2) studied the potential toxic effects of SFE in rabbits. The rabbits received i.v. doses of SFE at dose levels of 1.76, 17.6, and 88 μg/kg for 3 consecutive days. The no observable adverse effect level (NOAEL) and the maximum tolerated dose (MTD) were considered to be greater than 88 μg/kg per day. In studies in beagle dogs, a single i.v. dose of 52.85 μg/kg induced clear clinical signs of toxicity. No adverse cardiovascular effects were observed after individual i.v. injections of 2.64, 10.57, and 52.85 μg/kg. The NOAEL was ≈10.6 μg/kg, and the MTD was ≈53 μg/kg.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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