2-(2'-((Dimethylamino)methyl)-4'-(3-[^{18}F]fluoropropoxy)-phenylthio)benzenamine

[^{18}F]SERT-1

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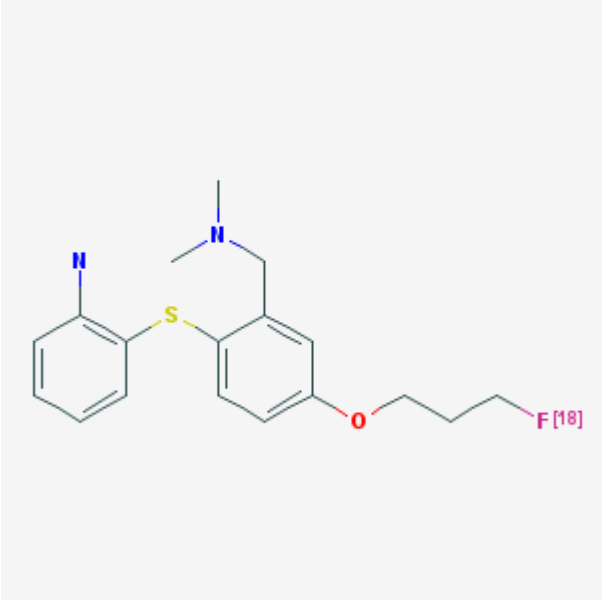
Chemical name:	2-(2'-((Dimethylamino)methyl)-4'-(3-[^{18}F]fluoropropoxy)-phenylthio)benzenamine
Abbreviated name:	[^{18}F]1, [^{18}F]SERT-1
Synonym:	
Agent category:	Compound
Target:	Serotonin transporter
Target category:	Transporter
Method of detection:	PET
Source of signal \contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

Serotonin (5-hydroxytryptamine, 5-HT) has diverse physiological roles as a neurotransmitter in the central nervous system (1). It is also a regulator of smooth muscle function and platelet aggregation. The brain 5-HT system has been implicated in several neuropsychiatric disorders, including major depression, anxiety, obsessive-compulsive disorder, and schizophrenia (2, 3). The serotonergic transmission is controlled in part by the serotonin transporter (SERT), which regulates the concentration of free, active 5-HT in the synaptic cleft. Citalopram, paroxetine, and fluoxetine were developed as selective SERT inhibitors to treat depression and anxiety disorders by blocking the reuptake of 5-HT [PubMed]. The blockade led to a higher 5-HT concentration in the synaptic cleft and subsequently to improved patient health.

trans-1,2,3,5,6,10-β-Hexahydro-6-[4-([^{11}C]methylthio)phenyl[pyrrolo-[2,1-a]isoquinoline ([^{11}C]McN5652) binds selectively to the SERT, and its regional distribution of binding in humans correlates well with the known distribution of the SERT in human brain (4). However, the usefulness of [^{11}C]McN5652 is limited by its nonspecific binding and slow release from specific binding sites (5). [^{11}C]*N*,*N*-Dimethyl-2-(2-amino-4-cyanophenylthio)benzylamine ([^{11}C]DASB) was found to be a useful tracer for SERT imaging in animals and humans (6-9). It displayed a nanomolar affinity for SERT and a >1,000-fold affinity for SERT over the dopamine transporter (DAT) and the norepinephrine transporter (NET). Uptake in the SERT-rich brain regions was both saturable and selective for SERT. However, the potential widespread use of [^{11}C]DASB is limited by the short half-life of ^{11}C (20 min). 2-(2'-((Dimethylamino)methyl)-4'-(3-fluoropropoxy)-phenylthio)benzenamine was shown to be a selective inhibitor of SERT. 2-(2'-((Dimethylamino)methyl)-4'-(3-[^{18}F]fluoropropoxy)-phenylthio)benzenamine ([^{18}F]1) is being evaluated as a useful tool for SERT imaging.

Synthesis

[PubMed]

[^{18}F]1 was synthesized by nucleophilic [^{18}F]fluorination of its *O*-mesylated precursor in acetonitrile solution of K_2CO_3/Kryptofix222 for 3 min at 100°C (10, 11). [^{18}F]1 was purified with high-performance liquid chromatography with radiochemical yields of 10–35% (decay-corrected) in a total synthesis time of ~60 min. The specific activity was 11.84–251.6 GBq/μmol (0.32–6.8 Ci/μmol) at the end of synthesis with radiochemical purities of >97%.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The transporter-binding affinity of 2-(2'-((dimethylamino)methyl)-4'-(3-fluoropropoxy)-phenylthio)benzenamine was evaluated with competitive radioaffinity assays for SERT, norepinephrine (NET), and dopamine (DAT) transporters using stably transfected cell lines (11). Binding affinity (K_i, nM) at SERT, NET, and DAT were 0.27, 11.9, and 299 nM, respectively. Selective binding of 2-(2'-((dimethylamino)methyl)-4'-(3-fluoropropoxy)-phenylthio)benzenamine to SERT over NET was also measured using rat cortical membranes with K_i values of 0.24 and 12.4 nM, respectively.

Animal Studies

Rodents

[PubMed]

Wang et al. (10) performed biodistribution studies in normal rats (n = 3 rats/group). Intravenous injection of [^{18}F]1 in rats resulted in high uptake of radioactivity in the lungs (3.86% injected dose (ID)/g) and kidneys (3.93% ID/g) at 30 min after injection; less pronounced uptake was seen in the whole brain (1.23% ID/g). Uptake in the thalamus (0.64% ID/g), hippocampus (0.79% ID/g), striatum (0.90% ID/g), cortex (1.00% ID/g), and hypothalamus (1.22% ID/g) was higher than the cerebellum (0.35% ID/g) at 30 min. The brain region radioactivity was >75% blocked with pretreatment of IDAM (SERT inhibitor) except in the cerebellum, which indicates that SERT is low in the cerebellum and the cerebellum can be used as a reference region. Pretreatment with DAT inhibitor GBR12909 did not inhibit the regional accumulation, and pretreatment with NET inhibitor nisoxetine showed only marginal inhibition. Radioactivity cleared gradually over a period of 240 min from all organs except for bone. *Ex vivo* autoradiography studies showed selective accumulation in the olfactory tubercles, thalamus, hypothalamus, substantia nigra, superior colliculus, dorsal raphe, and medial raphe as the SERT inhibitors, escitalopram, and IDAM effectively blocked [^{18}F]1 localization in these brain regions. PET analysis in rat brains was performed in rats after intravenous injection of 11.1 MBq (0.3 mCi) [^{18}F]1. The thalamus, midbrain, and striatum were clearly visualized and peaked at 10–20 min after injection with minimal accumulation in the cerebellum. The thalamus/cerebellum, midbrain/cerebellum, and striatum/cerebellum ratios of 4–4.5 peaked at 100–110 min. Injection of escitalopram and IDAM at 75 min after tracer injection caused a marked drop in radioactivity levels in the thalamus, midbrain, and striatum.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

NIH Support

MH68782

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