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NLM Citation: Shan L. [^{18}F]*N*-(2-benzofuranylmethyl)-*N*'-[4-(2-fluoroethoxy)benzyl]piperazine. 2012 May 10 [Updated 2012 Jun 27]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.
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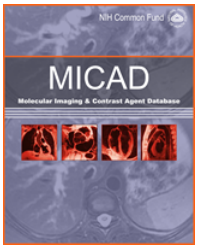

[^{18}F]*N*-(2-benzofuranylmethyl)-*N*'-[4-(2-fluoroethoxy)benzyl]piperazine

[^{18}F]**6**

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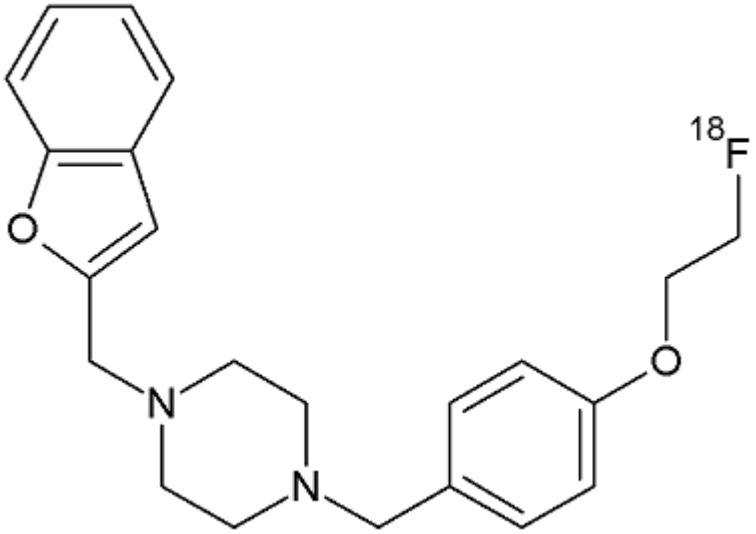
Created: May 10, 2012; Updated: June 27, 2012.

Chemical name:	[^{18}F]*N*-(2-benzofuranylmethyl)-*N*'-[4-(2-fluoroethoxy)benzyl]piperazine
Abbreviated name:	[^{18}F]**6**
Synonym:	
Agent Category:	Compounds
Target:	Sigma-1 (σ1) receptor
Target Category:	Receptors
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



Structure of [^{18}F]**6**

Background

[PubMed]

[^{18}F]*N*-(2-benzofuranylmethyl)-*N*'-[4-(2-fluoroethoxy)benzyl]piperazine, abbreviated as [^{18}F]**6**, is a piperazine derivative synthesized by Moussa et al. for positron emission tomography (PET) of sigma-1 (σ1) receptor (1).

σ1 receptor is a protein that is widely distributed in both the central nervous system (CNS) and peripheral organs. There are at least two subtypes of σ receptors, σ1 and σ2 receptors. Although the functions of σ2 receptor are poorly understood, σ1 receptor is believed to act as a modulator of the signal transduction in neurotransmitter systems (2, 3). σ1 receptor primarily resides at the interface between the endoplasmic reticulum and mitochondria, where it modulates Ca^{2+} flux by acting as a molecular chaperone for type 3

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inositol-1,4,5-triphosphate receptors. σ1 receptor can also translocate to the plasma membrane, where it regulates the voltage-dependent Ca^{2+} channels, K^+ channels, and other membrane-bound proteins (1, 2).

More and more evidence suggests that σ1 receptor is involved in a range of CNS diseases such as affective disorders, psychosis, schizophrenia, substance abuse, Parkinson's disease, and Alzheimer's disease (1, 4). Studies on postmortem human brains have shown that the density of σ1 receptor decreased in patients with schizophrenia and Alzheimer's disease (5). Discovery of specific ligands for σ1 receptor has further prompted investigations in the imaging and treatment of neuropsychiatric diseases by targeting σ1 receptor (3, 4).

Noninvasive imaging of σ1 receptor *in vivo* would enable better understanding of the pathogenesis of neuropsychiatric diseases as well as how the expression and function of σ1 receptors change during disease progression (2). Early in 1998, Baziard-Mouysset et al. synthesized a series of disubstituted 1,4-piperazines, flanked by a chromene ring and a benzyl group (6). Of this series, the simplest compound that contained an unsubstituted benzyl ring displayed high affinity for σ receptors (K_i = 3 nM) and negligible off-target activity. Substitution of the benzyl ring was generally detrimental to σ binding, with the exception of 4-chloro or 4-methoxy substitution, which marginally improved σ receptor binding (K_i = 1 nM and 0.6 nM, respectively). The chromene ring was shown to have little effect on σ binding, and it was well tolerated for substitution with a large number of alternate aromatic groups (7). With the 2-benzofurylmethyl group–substituted compound as a lead compound, Moussa et al. generated a series of *N*-(2-benzofuranylmethyl)-*N*'-(alkoxybenzyl)piperazines as selective σ1 receptor ligands (1, 4, 8). Two compounds in this series, *N*-(2-benzofuranylmethyl)-*N*'-[4-(2-fluoroethoxy)benzyl]piperazine (compound **6**) and *N*-(benzofuran-2-ylmethyl)-*N*'-(4'-methoxybenzyl)piperazine (compound **13**), were further radiolabeled and tested for their feasibilities as imaging probes for σ1 receptors.

This chapter summarizes the data obtained with [^{18}F]**6**.

Related Resource Links:

The nucleotide and protein sequences of sigma-1 (σ1) receptors

Sigma-1 (σ1) receptor-related compounds in PubChem

Synthesis

[PubMed]

Moussa et al. described the synthesis of piperazine derivatives in detail (1, 4). Compound **6** was synthesized by *O*-alkylation of *N*-(2-benzofuranylmethyl)-*N*'-(4-hydroxybenzyl)piperazine (compound **7**) with 2-fluoroethyl tosylate. The synthesis of [^{18}F]**6** was achieved in two steps from compound **7**. Mono-alkylation of compound **7** with 1,2-ethylene glycol bis-tosylate furnished tosylated precursor compound **8**. Compound **8** was then radiofluorinated with a Tracerlab FXF-N module. The overall synthesis time for [^{18}F]**6** was 45 min, and the radiochemical yield was 18%. Both radiochemical and chemical purities were >98%, with a specific activity of 45 GBq/μmol (1.22 Ci/μmol) at end of synthesis. [^{18}F]**6** was formulated by dilution of the radioactive fraction of the high-performance liquid chromatography (HPLC) mobile phase with water for injection. The final preparation was free from precursor **8**. Administration to the animal was performed within 30 min after the end of synthesis.

The lipophilicity of compound **6** was evaluated with HPLC, which gave a log D value of 3.35 (1). To ensure high uptake in the brain and to minimize non-specific binding, the optimal log D value for therapeutic CNS-active compounds is reported to be between 2 and 3.5.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Affinities of compound **6** for σ1 and σ2 receptors were determined with competitive displacement of [^{3}H](+)-pentazocine in a rat brain homogenate preparation (to determine σ1 receptor affinity) and with competitive displacement of [^{3}H]1,3-di-(2-tolyl)-guanidine in a PC12 cell preparation (a rat pheochromocytoma cell line known to overexpress σ2 receptors) (1, 4). Compound **6** had K_i values of 2.6 nM and 486 nM for σ1 and σ2 receptors, respectively, indicating selectivity for σ1 over σ2. The K_i values of compound **6** for 5-HT_{1A}, 5-HT_{2B}, and D_2 receptors were 2,439, 96, and >10,000 nM, respectively (4).

Animal Studies

Rodents

[PubMed]

No references are currently available.

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

MicroPET studies were conducted in an anaesthetized *Papio hamadryas* baboon to evaluate the *in vivo* regional distribution kinetics of [^{18}F]6 after intravenous administration of 100 MBq (2.7 mCi) [^{18}F]6 (1). The microPET images confirmed the ability of [^{18}F]6 to penetrate the blood–brain barrier with accumulation in the baboon brain. The time-activity curve showed that [^{18}F]6 reached the maximal level within 5 min after injection and remained at a plateau to the end of the PET scan (60 min after injection). Homogenous uptake of [^{18}F]6 was observed in the cortex, striatum, thalamus, and cerebellum, which are known to express σ receptors.

The *in vivo* specificity of [^{18}F]**6** uptake was evaluated in a single blocking study in the same baboon (1). Pretreatment with haloperidol (1 mg/kg) 5 min before [^{18}F]6 administration resulted in increased radioligand uptake within 3 min, followed by a rapid decline to the washout level within 5 min after injection. The net result was an 80% reduction in radioligand uptake in all regions of the brain at the end of the imaging experiment (60 min.) when compared to [^{18}F]6 administration alone, indicating the *in vivo* specificity of [^{18}F]6 for σ receptors. Haloperidol is a high-affinity ligand for σ receptors.

Human Studies

[PubMed]

No references are currently available.

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