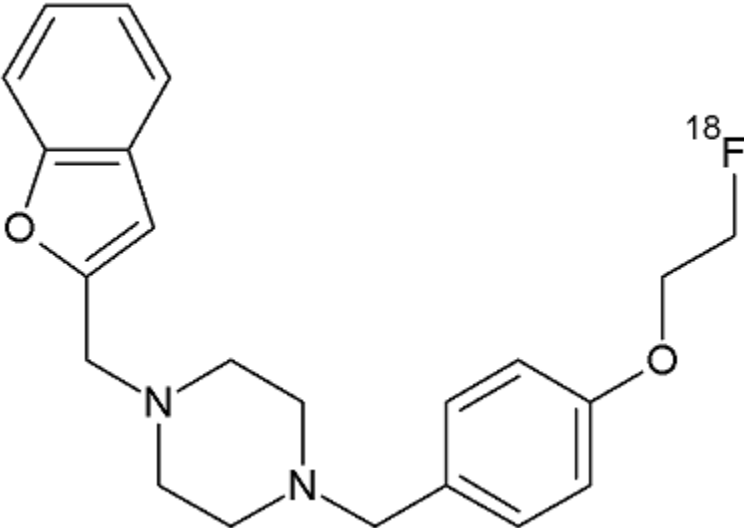


[¹⁸F]N-(2-benzofuranylmethyl)-N'-[4-(2-fluoroethoxy)benzyl]piperazine

[¹⁸F]6

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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:	<ul style="list-style-type: none">• <i>In vitro</i>• Rodents	

Structure of [¹⁸F]6

Background

[PubMed]

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

σ 1 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, σ 1 and σ 2 receptors. Although the functions of σ 2 receptor are poorly understood, σ 1 receptor is believed to act as a modulator of the signal transduction in neurotransmitter systems (2, 3). σ 1 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 inositol-1,4,5-triphosphate receptors. σ 1 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 σ 1 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 σ 1 receptor decreased in patients with schizophrenia and Alzheimer's disease (5). Discovery of specific ligands for σ 1 receptor has further prompted investigations in the imaging and treatment of neuropsychiatric diseases by targeting σ 1 receptor (3, 4).

Noninvasive imaging of σ 1 receptor *in vivo* would enable better understanding of the pathogenesis of neuropsychiatric diseases as well as how the expression and function of σ 1 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 σ 1 receptor ligands (1, 4, 8). Two compounds in this series, N-(2-benzofuranylmethyl)-N'-[4-(2-fluoroethoxy)benzyl]piperazine (compound **6**) and N-(2-benzofuranylmethyl)-N'-(4'-methoxybenzyl)piperazine (compound **13**), were further radiolabeled and tested for their feasibilities as imaging probes for σ 1 receptors.

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

Related Resource Links:

The [nucleotide](#) and [protein](#) sequences of sigma-1 (σ 1) receptors

[Sigma-1 \(\$\sigma\$ 1\) 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 [¹⁸F]**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 FFX-N module. The overall synthesis time for [¹⁸F]**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. [¹⁸F]**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 [³H](+)-pentazocine in a rat brain homogenate preparation (to determine σ₁ receptor affinity) and with competitive displacement of [³H]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 D₂ 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 [¹⁸F]6 after intravenous administration of 100 MBq (2.7 mCi) [¹⁸F]6 (1). The microPET images confirmed the ability of [¹⁸F]6 to penetrate the blood–brain barrier with accumulation in the baboon brain. The time-activity curve showed that [¹⁸F]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 [¹⁸F]6 was observed in the cortex, striatum, thalamus, and cerebellum, which are known to express σ receptors.

The *in vivo* specificity of [¹⁸F]6 uptake was evaluated in a single blocking study in the same baboon (1). Pretreatment with haloperidol (1 mg/kg) 5 min before [¹⁸F]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 [¹⁸F]6 administration alone, indicating the *in vivo* specificity of [¹⁸F]6 for σ receptors. Haloperidol is a high-affinity ligand for σ receptors.

Human Studies

[PubMed]

No references are currently available.

References

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