N-4'-[^{18}F]Fluorobenzylpiperidin-4yl-(2-fluorophenyl)acetamide

[^{18}F]FBFPA

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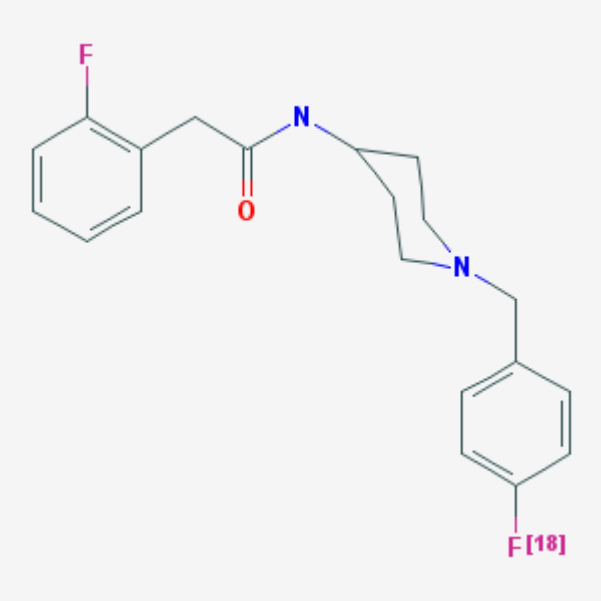
Chemical name:	*N*-4'-[^{18}F]Fluorobenzylpiperidin-4yl-(2-fluorophenyl)acetamide
Abbreviated name:	
Synonym:	[^{18}F]FBFPA
Agent Category:	Compound
Target:	σ_1 sigma receptors
Target Category:	Receptor binding
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates



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Background

[PubMed]

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Sigma receptors are functional membrane-bound proteins distributed in the central nervous system (CNS) and peripheral organs such as the liver, kidneys, and endocrine glands (1, 2). The CNS sigma receptors are unique binding sites related to higher brain function. There are at least two subtypes of sigma receptors, σ_1 and σ_2. These receptors appear to be involved in numerous pharmacologic and physiologic functions, and they also modulate a number of central neurotransmitter systems. Studies suggest that these receptors may play a role in the pathogenesis of psychiatric disorders (3, 4). The σ_1 receptors appear to play a role in CNS disorders and motor functions. The σ_2 receptors, which are linked to potassium channels and calcium release, are also implicated in malignant neoplastic diseases (5-7). The density of σ_2 receptors in tumor cells was found to be greater than that of σ_1 receptors. For example, the density of σ_2 receptors was found to be 10-fold higher in proliferating *versus* quiescent mouse mammary adenocarcinoma cells. Furthermore, it has been observed that σ_2 receptor ligands can induce apoptosis in tumor cells. Because of these effects, sigma receptor ligands may be useful for detection and treatment in neurology and oncology.

Matsuno et al. (8) have developed a potent σ_1 agonist, 1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)-piperazine dihydrochloride (SA4503), which exhibits a 14-fold selectivity for σ_1 receptors over σ_2 receptors.SA4503 has been labeled with ^{11}C and ^{18}F for positron emission tomography (PET) studies of sigma receptors in monkeys and humans (3, 9-11). Huang et al. (12) have reported a series of *N*-benzylpiperidin-4yl-phenylacetamide analogs with high affinity for σ_1 receptors and relatively low affinity for σ_2 receptors. One of these analogs has been radiolabeled as *N*-4'-[^{18}F]fluorobenzylpiperidin-4yl-(2-fluorophenyl)acetamide ([^{18}F]FBFPA) for PET imaging of CNS σ_1 receptors (13).

Synthesis

[PubMed]

[^{18}F]FBFPA was synthesized by N-alkylation of the desbenzyl compound piperidin-4yl-(2-fluorophenyl)acetamide with [^{18}F]4'-fluorobenzyliodide in dimethyformamide at 90°C for 10 min (13). After chromatographic separation, the overall yield of [^{18}F]FBFPA was 20% based on [^{18}F]CsF. The specific activity was 37–74 GBq/μmol (1–2 Ci/μmol) at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

FBFPA has been reported by Huang et al. (12) to have selective binding affinity to σ_1 receptor sites in homogenates of guinea pig brain membranes *versus* σ_2 binding sites in rat liver membranes. The inhibition constant (K_i) values for σ_1 and σ_2 were 3.15 ± 0.05 and 139.51 ± 21.89 nM, respectively. Therefore, FBFPA exhibited a 44-fold selectivity for σ_1 receptors over σ_2 receptors.

Animal Studies

Rodents

[PubMed]

Mach et al. (13) performed brain biodistribution studies in normal rats. Their studies showed there was 0.87% injected dose (ID)/g in the whole brain at 5 min after injection of [^{18}F]FBFPA, with gradual washout to 0.53% ID/g at 120 min. On the other hand, there was rapid washout of radioactivity from the blood, which resulted in brain/blood ratios of 15 at 5 min and 53 at 120 min. There was a high accumulation and progressive washout of radioactivity in the frontal cortex, striatum, hippocampus, and cerebellum. Co-injection of [^{18}F]FBFPA with 1 mg/kg unlabeled FBFPA inhibited uptake to all the brain regions by >80%. Pretreatment with 40 mg/kg progesterone, a putative endogenous ligand, 30 min before tracer injection reduced the brain uptake by ~50%.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Biodistribution PET studies in rhesus monkeys injected with 207.2–229.4 MBq (5.6–6.2 mCi) [^{18}F]FBFPA were performed by Mach et al. (13) and showed rapid accumulation of radioactivity in the brain. PET study showed selective maximal uptake in the regions of the cingulate cortex, followed by the temporal cortex, parietal cortex, and occipital cortex. The cerebellum showed lower binding than the other brain regions. The peak level in the brain (0.045% ID/ml) was reached in the cingulated cortex at 10 min, followed by gradual washout to ~0.025% ID/ml at 180 min. Injection of 1 mg/kg haloperidol, a σ_1/ σ_2 ligand, 40 min after injection of [^{18}F]FBFPA dramatically decreased radioactivity in the brain regions studied.

Human Studies

[PubMed]

No publication is currently available.

NIH Support

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References

1. Bowen W.D. Sigma receptors: recent advances and new clinical potentials. Pharm Acta Helv. 2000;**74**(2-3):211–8. PubMed PMID: 10812960.
2. Walker J.M., Bowen W.D., Walker F.O., Matsumoto R.R., De Costa B., Rice K.C. Sigma receptors: biology and function. Pharmacol Rev. 1990;**42**(4):355–402. PubMed PMID: 1964225.
3. Mishina M., Ishiwata K., Ishii K., Kitamura S., Kimura Y., Kawamura K., Oda K., Sasaki T., Sakayori O., Hamamoto M., Kobayashi S., Katayama Y. Function of sigma1 receptors in Parkinson's disease. Acta Neurol Scand. 2005;**112**(2):103–7. PubMed PMID: 16008536.
4. Skuza G., Wedzony K. Behavioral pharmacology of sigma-ligands. Pharmacopsychiatry. 2004;**37Suppl 3**S183–8. PubMed PMID: 15547784.
5. Colabufo N.A., Berardi F., Contino M., Ferorelli S., Niso M., Perrone R., Pagliarulo A., Saponaro P., Pagliarulo V. Correlation between sigma2 receptor protein expression and histopathologic grade in human bladder cancer. Cancer Lett. 2006;**237**(1):83–8. PubMed PMID: 16005143.
6. Vilner B.J., John C.S., Bowen W.D. Sigma-1 and sigma-2 receptors are expressed in a wide variety of human and rodent tumor cell lines. Cancer Res. 1995;**55**(2):408–13. PubMed PMID: 7812973.
7. Wheeler K.T., Wang L.M., Wallen C.A., Childers S.R., Cline J.M., Keng P.C., Mach R.H. Sigma-2 receptors as a biomarker of proliferation in solid tumours. Br J Cancer. 2000;**82**(6):1223–32. PubMed PMID: 10735510.
8. Matsuno K., Nakazawa M., Okamoto K., Kawashima Y., Mita S. Binding properties of SA4503, a novel and selective sigma 1 receptor agonist. Eur J Pharmacol. 1996;**306**(1-3):271–9. PubMed PMID: 8813641.
9. Elsinga P.H., Tsukada H., Harada N., Kakiuchi T., Kawamura K., Vaalburg W., Kimura Y., Kobayashi T., Ishiwata K. Evaluation of [18F]fluorinated sigma receptor ligands in the conscious monkey brain. Synapse. 2004;**52**(1):29–37. PubMed PMID: 14755630.
10. Ishiwata K., Tsukada H., Kawamura K., Kimura Y., Nishiyama S., Kobayashi T., Matsuno K., Senda M. Mapping of CNS sigma(1) receptors in the conscious monkey: preliminary PET study with [(11)C]SA4503. Synapse. 2001;**40**(3):235–7. PubMed PMID: 11304761.
11. van Waarde A., Buursma A.R., Hospers G.A., Kawamura K., Kobayashi T., Ishii K., Oda K., Ishiwata K., Vaalburg W., Elsinga P.H. Tumor imaging with 2 sigma-receptor ligands, 18F-FE-SA5845 and 11C-SA4503: a feasibility study. J Nucl Med. 2004;**45**(11):1939–45. PubMed PMID: 15534066.
12. Huang Y., Hammond P.S., Wu L., Mach R.H. Synthesis and structure-activity relationships of N-(1-benzylpiperidin-4-yl)arylacetamide analogues as potent sigma1 receptor ligands. J Med Chem. 2001;**44**(25):4404–15. PubMed PMID: 11728186.
13. Mach R.H., Gage H.D., Buchheimer N., Huang Y., Kuhner R., Wu L., Morton T.E., Ehrenkaufer R.L. N-[18F]4'-fluorobenzylpiperidin-4yl-(2-fluorophenyl) acetamide

([18F]FBFPA): a potential fluorine-18 labeled PET radiotracer for imaging sigma-1 receptors in the CNS. Synapse. 2005;**58**(4):267–74. PubMed PMID: 16206186.