1-(2-{(2R)-1-[(2-[^{18}F]Fluorophenyl)sulfonyl]pyrrolidin-2-yl}ethyl)-4-methylpiperidine

[^{18}F]-2FP3

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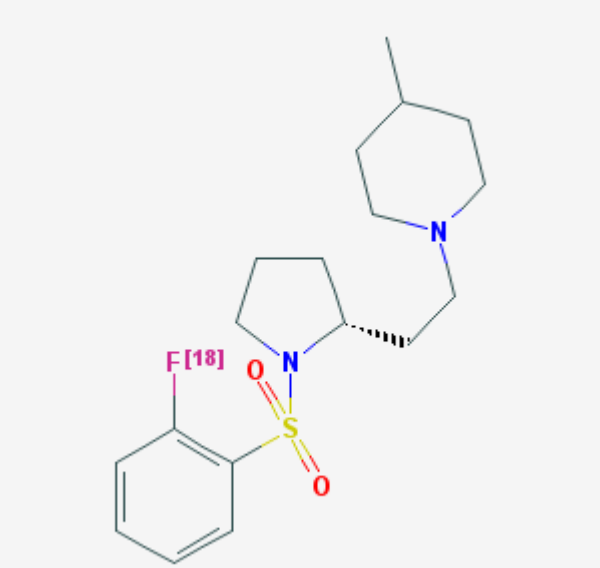
Chemical name:	1-(2-{(2R)-1-[(2-[^{18}F]Fluorophenyl)sulfonyl]pyrrolidin-2-yl}ethyl)-4-methylpiperidine
Abbreviated name:	[^{18}F]-2FP3
Synonym:	
Agent category:	Compound
Target:	5-HT$_7$ serotonin receptors
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals



Click on the above structure for additional information in PubChem.

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Background

[PubMed]

5-Hydroxytryptamine (5-HT), commonly known as serotonin, has diverse physiological roles as a neurotransmitter in the central nervous system (1). 5-HT is involved in regulation and modulation of sleep, affective and personality behaviors, and pain. It also is a regulator of smooth muscle function and platelet aggregation. The brain cortical 5-HT system has been implicated in several neuropsychiatric disorders, including major depression, anxiety, schizophrenia, and obsessive-compulsive disorder (2, 3). The effects of 5-HT are mediated by as many as seven classes of receptor populations (5-HT_1 to 5-HT_7), many of which include several subtypes (4). There are five receptor subtypes within the G-protein–coupled 5-HT_1 receptor family: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F}.

5-HT_7 receptors are abundantly present in the hippocampus, thalamus, and hypothalamus; low densities are observed in the cortex and amygdala (5-7). 5-HT_7 receptors are involved in the mediation of emotion and the function of the hypothalamus. 5-HT_7 receptors are implicated in anxiety, depression, hallucinogenic behavior, circadian rhythms and sleep, memory, epilepsy, and pain. Thus, there is a need for selective ligands to investigate the pharmacological role of 5-HT_7 receptors. 1-(2-{(2R)-1-[(2-[^{18}F]Fluorophenyl)sulfonyl]pyrrolidin-2-yl}ethyl)-4-methylpiperidine ([^{18}F]-2FP3) was evaluated as a positron emission tomography (PET) probe for 5-HT_7 receptors because the unlabeled 2FP3 was found to be a selective 5-HT_7 antagonist with nanomolar affinity for the 5-HT_7 receptor.

Related Resource Links:

- Chapters in MICAD (5-HT_7)
- Gene information in NCBI (5-HT_7)
- Articles in Online Mendelian Inheritance in Man (OMIM) (5-HT_7)
- Clinical trials (5-HT)
- Drug information in Food and Drug Administration (5-HT_7)

Synthesis

[PubMed]

The automated radiosynthesis of [^{18}F]-2FP3 involved standard fluoronucleophilic substitution of the corresponding nitro precursor with K[^{18}F]F/Kryptofix2.2.2 in dimethyl sulfoxide for 10 min at 150°C in an automated radiosynthesis unit, followed by solid-phase extraction with C18 cartridge (8, 9). The reported overall radiochemical yield of the radiosynthesis was 48% at the end of bombardment, with a specific activity of 40–130 MBq/nmol (1.1–3.5 mCi/nmol) at the end of synthesis, and a radiochemical purity of >98%. The total synthesis time was 100–120 min. The log *P* value for [^{18}F]-2FP3 was 1.2–1.4.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Lemoine et al. (8) performed *in vitro* autoradiography in rat brains with [^{18}F]-2FP3, which exhibited radioactivity in the cingulate cortex, hippocampus, cerebellum, and thalamus. The radioactivity in the cortex and hippocampus was inhibited by SB269970 (a selective 5-HT$_7$ receptor antagonist), with 43% inhibition at 10 nM and 80% inhibition at 1,000 nM. *In vitro* binding was performed with CHO cells transfected with human recombinant 5-HT receptors. The binding affinity K_d values of [^{18}F]-2FP3 for 5-HT$_7$ receptors was 1.43 nM with little affinity for 5-HT$_{1A}$ and 5-HT$_6$ receptors.

Animal Studies

Rodents

[PubMed]

Ex vivo stability studies of [^{18}F]-2FP3 in the brains of rats (n = 3/group) were performed at 10, 20, 30, and 40 min after intravenous injection of 55.5 MBq (1.5 mCi) [^{18}F]-2FP3. [^{18}F]-2FP3 remained >95% intact at these time points as determined with HPLC (8).

Rat brains were excised at 20 min after injection of 55.5 MBq (1.5 mCi) [^{18}F]-2FP3. *Ex vivo* PET imaging studies (n = 3/group) were performed at 45 min after the brains were removed (8). Higher radioactivity levels were observed in the cingulate cortex and hippocampus than in the striatum and cerebellum. Pretreatment with excess SB269970 (30 min, 5 mg/kg) decreased [^{18}F]-2FP3 binding in all brain areas.

Other Non-Primate Mammals

[PubMed]

Lemoine et al. (8) performed *in vivo* PET imaging studies in the brains of two male cats for 90 min after injection of 74 MBq (2 mCi) [^{18}F]-2FP3. High initial radioactivity levels were observed in the cingulate cortex, thalamus, hippocampus, and cerebellum. Pretreatment with excess SB269970 (30 min, 5 mg/kg) decreased [^{18}F]-2FP3 binding in these brain areas to background levels.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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