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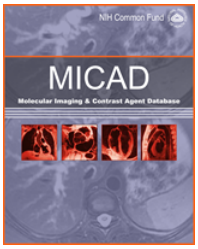

N-(4-[^{18}F]Fluorobenzyl)-4-(3-(piperidin-1-yl)indole-1-sulfonyl)benzamide

[^{18}F]PipISB

Kam Leung, PhD[1] and Sean Donohue, PhD[2]

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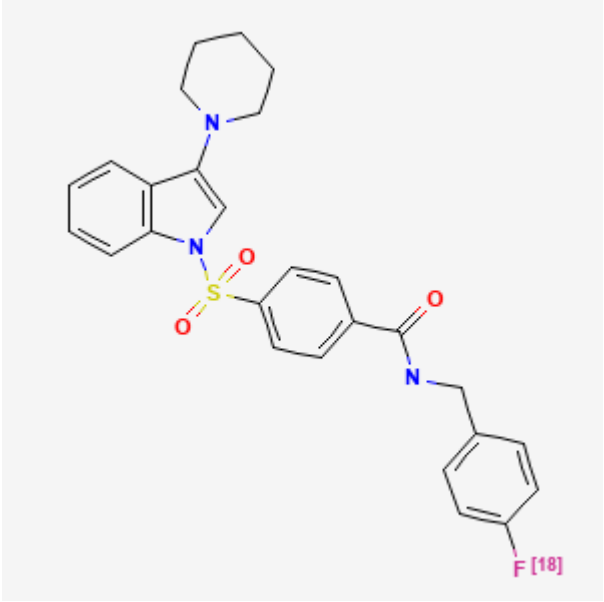
Chemical name:	*N*-(4-[^{18}F]Fluorobenzyl)-4-(3-(piperidin-1-yl)indole-1-sulfonyl)benzamide
Abbreviated name:	[^{18}F]PipISB
Synonym:	
Agent category:	Compound
Target:	Cannabinoid CB1 receptors
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Non-human primates



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Background

[PubMed]

There are two subtypes of cannabinoid receptors in mammalian tissues: CB1 and CB2 (1, 2). CB1 receptors are expressed abundantly in neuronal terminals in the central nervous system and in some peripheral tissues to inhibit neurotransmitter release. CB1 receptors are found predominantly in the striatum, hippocampus,

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substantia nigra, globus pallidus, and cerebellum. CB2 receptors are present mainly on immune cells to modulate cytokine release. Both receptor subtypes are coupled through $G_{i/o}$ proteins to inhibit adenylate cyclase and to modulate potassium and calcium channels. CB1 receptors have been demonstrated to be involved in analgesia, regulation of food intake, and control of movement in normal subjects (3). Alteration of CB1 receptor function has been implicated in a number of human diseases such as depression, schizophrenia, and obesity (4-6).

Δ9-Tetrahydrocannabinol (THC) is a major active cannabinoid that is found in marijuana and activates CB1 receptors (7). THC has a very high lipophilicity (log $D_{7.4}$ value of 7), which causes imaging studies using radiolabeled THC to be unsuccessful because of slow entry into the brain and high nonspecific binding. However, a high lipophilicity is essential for binding to CB1 receptors, and an optimal lipophilicity (log $D_{7.4}$ 1–4) is required for crossing the blood–brain barrier (BBB). Existing radiolabeled ligands are mainly analogs of the inverse agonist rimonabant (SR141716A) and the agonist WIN 55,212-2, which also exhibit high nonspecific binding and lipophilicity, limiting their application in imaging (8). Therefore, there is a need to lower the lipophilicity of the CB1 radioligands with little effect on binding affinity and ability to cross the BBB. *N*-(4-[^{18}F]Fluorobenzyl)-4-(3-(piperidin-1-yl)indole-1-sulfonyl)benzamide ([^{18}F]PipISB) is being evaluated for use as a CB1 receptor tracer (9, 10).

Related Resource Links:

- Chapters in MICAD
- Gene information in NCBI (CB1 receptors)
- Articles in OMIM
- Clinical trials (CB1)

Synthesis

[PubMed]

Donohue et al. (10) reported the synthesis of [^{18}F]PipISB by reaction of the carboxamide precursor with [^{18}F]-4-fluorobenzyl bromide in dimethylformamide containing sodium hydride for 3 min at room temperature. Average radiochemical yield was 36% (n = 2) with a total synthesis time of ~115 min from the activated [^{18}F]fluorine ion. Specific radioactivity was ~270 GBq/μmol (7.4 Ci/μmol) at the end of synthesis, with a radiochemical purity of >98%. cLog $D_{7.4}$ of PipISB was calculated to be 5.1.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Donohue et al. (10) reported that PipISB inhibited functional [γ-^{35}S]GTP binding at the human recombinant CB1 receptors with high potency (K_b = 1.5 nM). PipISB was significantly less potent at the human recombinant CB2 receptors (K_b > 7,000 nM).

Animal Studies

Rodents

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Finnema et al. (9) performed positron emission tomography imaging in one cynomolgus monkey after intravenous injection of 49 MBq (1.32 mCi) [^{18}F]PipISB (0.039 nmol/kg). The radioactivity in the striatum exhibited ~130% standardized uptake value (SUV) at 30 min and increased to 170%–180% SUV at 240 min after injection. The cerebellum, thalamus, and cortex showed moderate radioactivity (~130% SUV), whereas the pons showed the lowest radioactivity (<100% SUV) at 240 min after injection. Intravenous pretreatment with the CB1-selective ligand 4-(3-(piperidin-1-yl)indole-1-sulfonyl)-*N*-(tetrahydro-pyran-4-yl-methyl)-benzamide (1.0 mg/kg) 15 min before tracer injection reduced the radioactivity of all brain regions to 25% SUV at 240 min after injection. [^{18}F]PipISB was slowly metabolized with 57% intact in the plasma at 93 min after injection. [^{18}F]PipISB was not defluorinated but metabolized to three less lipophilic radiometabolites.

Human Studies

[PubMed]

No publication is currently available.

NIH Support

Intramural research program

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