3-Chloro-4-[^{18}F]fluorophenyl-(4-fluoro-4-[[(5-methyl-pyrimidin-2-ylmethyl)-amino]-methyl]-piperidin-1-yl)methanone (F15599)

[^{18}F]F15599

Kam Leung, PhD[1]

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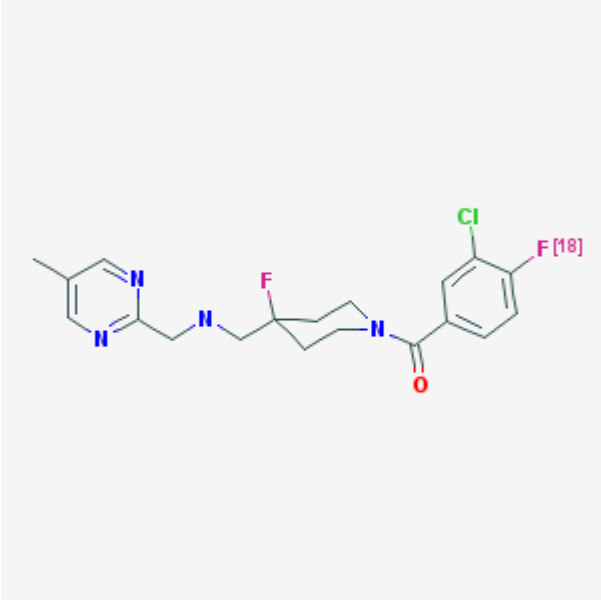
Chemical name:	3-Chloro-4-[^{18}F]fluorophenyl-(4-fluoro-4-[[(5-methyl-pyrimidin-2-ylmethyl)-amino]-methyl]-piperidin-1-yl)methanone (F15599)
Abbreviated name:	[^{18}F]F15599
Synonym:	
Agent category:	Compound
Target:	5-HT$_{1A}$ serotonin receptor
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals



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[1] National Center for Biotechnology Information, NLM, NIH; Email: MICAD@ncbi.nlm.nih.gov.

Corresponding author.

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_{1A} receptors are abundantly present in the hippocampus, entorhinal cortex, frontal cortex, raphe nucleus, and septum; the lowest densities are observed in the basal ganglia, substantia nigra, and cerebellum (5). Some thalamic and hypothalamic nuclei have intermediate densities. 5-HT_{1A} receptors are involved in the mediation of emotion and the function of the hypothalamus. 5-HT_{1A} receptors are implicated in anxiety, depression, hallucinogenic behavior, motion sickness, and eating disorders (6). Thus, there is a need for selective ligands to investigate the pharmacological role of 5-HT_{1A} receptors.

There have been several studies to develop specific 5-HT_{1A} radioligands [PubMed] for positron emission tomography (PET) imaging, such as [*carbonyl*-^{11}C]WAY 100635, [^{18}F]FPWAY, and [^{18}F]MPPF. However, none of these antagonists distinguishes between the high- and low-affinity states of the 5-HT_{1A} receptors. The high-affinity state of the receptor is coupled to G-proteins, which mediate cell functions by providing intracellular signals. 2-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-4-methyl-1,2,4-triazine-3,5(2*H*, 4*H*)dione (MMP) was reported to be a potent agonist of 5-HT_{1A} receptors (K_i = 0.15 nM) (7). This led to the development of [O-*methyl*-^{11}C]MMP([^{11}C]MMP, also known as [^{11}C]CUMI-101) as a useful tool for *in vivo* PET imaging of the 5-HT_{1A} receptor (8-10). However, [^{11}C]CUMI-101 was shown to be a partial 5-HT_{1A} agonist and therefore was less efficient in mediating cell function (11, 12). 3-Chloro-4-[^{18}F]fluorophenyl-(4-fluoro-4-[[(5-methyl-pyrimidin-2-ylmethyl)-amino]-methyl]-piperidin-1-yl)methanone ([^{18}F]F15599) was evaluated as a PET probe for the 5-HT_{1A} receptor (13) because unlabeled F15599 was found to be a selective 5-HT_{1A} agonist with nanomolar affinity for the 5-HT_{1A} receptor (14).

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Related Resource Links:

- Chapters in MICAD (5-HT$_{1A}$)
- Gene information in NCBI (5-HT$_{1A}$)
- Articles in Online Mendelian Inheritance in Man (OMIM) (5-HT$_{1A}$)
- Clinical trials (5-HT$_{1A}$)
- Drug information in Food and Drug Administration (5-HT$_{1A}$)

Synthesis

[PubMed]

The automated radiosynthesis of [^{18}F]F15599, reported by Lemoine et al. (13), involved standard fluoronucleophilic substitution of the corresponding nitro precursor with K[^{18}F]F/Kryptofix2.2.2 in dimethyl sulfoxide for 30 min at 150°C in an automated radiosynthesis unit, followed by solid-phase extraction with a C18 cartridge. The reported overall radiochemical yield of the radiosynthesis was ~30%, the specific activity was 85–120 MBq/nmol (2.3–3.2 mCi/nmol) at the end of synthesis (EOS), and the radiochemical purity was >98%. The total synthesis time was 80 min. The log P value for [^{18}F]F15599 was 1.17 (lipophilic).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Lemoine et al. (13) performed *in vitro* autoradiography with [^{18}F]F15599 in rat and cat brains, which showed radioactivity in the cingulate, hippocampus, and raphe nucleus. Little radioactivity was observed in the cerebellum, a region poor in 5-HT$_{1A}$ receptors. In comparison with [^{18}F]MPPF (a 5-HT$_{1A}$ antagonist), the radioactivity levels of [^{18}F]F15599 were 50%–80% less than those of [^{18}F]MPPF in the hippocampus and raphe nucleus in both rats and cats. Competition binding studies of WAY100635 (a 5-HT$_{1A}$ antagonist) and 8-OH-DPAT (a 5-HT$_{1A}$ agonist) with [^{18}F]F15599 in rat hippocampus sections were also performed. WAY100635 reduced the binding of [^{18}F]F15599 by 69% and 76% with 10 nM and 100 nM WAY100635, respectively. 8-OH-DPAT inhibited the binding by 67% and 85% with 10 nM and 100 nM 8-OH-DPAT, respectively. Gpp(NH)p (10 μM, a non-hydrolysable analog of guanosine 5'-triphosphate) inhibited the [^{18}F]F15599 binding by 70% in the hippocampus ($P < 0.05$).

Animal Studies

Rodents

[PubMed]

Ex vivo stability studies ($n = 3$/group) of [^{18}F]F15599 in rat brain hippocampus were performed after intravenous injection of 55.5 MBq (1.5 mCi) [^{18}F]F15599 (13).

[^{18}F]F15599 remained 80%, 90%, 97%, and 85% intact in the brain at 10, 20, 30, and 40 min after injection, respectively.

Ex vivo PET imaging studies (n = 3/group) were performed in the excised rat brains at 30 min after injection of 74 MBq (2 mCi) [^{18}F]F15599 (13). Higher radioactivity levels were observed in the cingulate cortex and hippocampus than in the striatum and cerebellum. Pretreatment or post-treatment with excess WAY100635 decreased [^{18}F]F15599 binding in the cortical areas, whereas no reduction of radioactivity levels was observed in the cerebellum. *In vivo* PET imaging studies were also performed. High radioactivity levels were observed in the hippocampus and cingulate cortex. The cingulate cortex/cerebellum and hippocampus/cerebellum ratios were 1.6 and 1.2, respectively.

Other Non-Primate Mammals

[PubMed]

Lemoine et al. (13) performed *in vivo* PET imaging studies in the brain of one male cat for 90 min after injection of 74 MBq (2 mCi) [^{18}F]F15599. High radioactivity levels were observed in the raphe nucleus, cingulate cortex, and amygdala. The cingulate cortex/cerebellum, amygdala/cerebellum, and raphe nucleus/cerebellum ratios were 1.3, 1.3, and 1.5, respectively.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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