3-Chloro-4-[^{18}F]fluorophenyl-(4-fluoro-4-[[((5-methyl-4-methylamino-pyridin-2-ylmethyl)-amino]-methyl]-piperidin-1-yl)methanone (F13714)

[^{18}F]F13714

Kam Leung, PhD[1]

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Chemical name:	3-Chloro-4-[^{18}F]fluorophenyl-(4-fluoro-4-[[((5-methyl-4-methylamino-pyridin-2-ylmethyl)-amino]-methyl]-piperidin-1-yl)methanone (F13714)
Abbreviated name:	[^{18}F]F13714
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

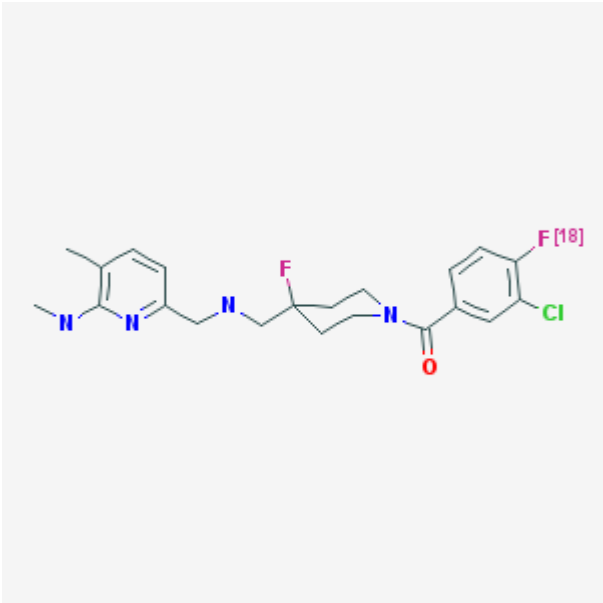

Table continues on next page...

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

Table continued from previous page.

Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals	Click on the above structure for additional information in PubChem.

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*,

Corresponding author.

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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*-11C]MMP ([11C]MMP, also known as [11C]CUMI-101) as a useful tool for *in vivo* PET imaging of the 5-HT_{1A} receptor (8-10). However, [11C]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-[18F]fluorophenyl-(4-fluoro-4-[[((5-methyl-4-methylamino-pyridin-2-ylmethyl)-amino]-methyl]-piperidin-1-yl)methanone ([18F]F13714) was evaluated as a PET probe for the 5-HT_{1A} receptor because unlabeled F13714 was found to be a selective 5-HT_{1A} agonist with subnanomolar affinity for the 5-HT_{1A} receptor (13).

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 [18F]F13714, reported by Lemoine et al. (13), involved standard fluoronucleophilic substitution of the corresponding nitro precursor with K[18F]F/Kryptofix2.2.2 in dimethyl sulfoxide for 10 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 ~10%, the specific radioactivity was 80–150 MBq/nmol (2.16–4.10 mCi/nmol) at the end of synthesis (EOS), and the radiochemical purity was >98%. The total synthesis time was 90 min. The log D (octanol-water partition coefficient) was 2.2 (lipophilic).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Lemoine et al. (13) performed *in vitro* autoradiography with [18F]F13714 in rat brains, which showed radioactivity in the cingulate, entorhinal cortex, hippocampus, raphe nucleus, and brain stem. Little radioactivity was observed in the cerebellum. The hippocampus/cerebellum and raphe/cerebellum ratios were 5.5 and 3.3, respectively. Competition binding studies of F13714, WAY100635, and 5-HT with [18F]F13714 in rat hippocampus sections were also performed. F13714 reduced the binding of [18F]F13714 by 28%, 77%, and 85% at 1, 10, and 100 nM F13714, respectively. WAY100635 inhibited the binding by 20%, 66%, and 83% at 1, 10, and 100 nM WAY100635, respectively. 5-HT inhibited the binding by 20%, 30%, and 70% at 1, 10, and 100 nM, respectively. Gpp(NH)p (10 μM, a non-hydrolysable analog of guanosine 5'-triphosphate) inhibited the [18F]F13714 binding by 70% in the cortex and 60% in the hippocampus.

Animal Studies

Rodents

[PubMed]

Ex vivo stability studies (n = 3/group) of [^{18}F]F13714 in rat brain hippocampus were performed after intravenous injection of 55.5 MBq (1.5 mCi) [^{18}F]F13714 (13). [^{18}F]F13714 remained 80%, 90%, 94%, and 91% intact in the hippocampus at 10, 20, 30, and 40 min after injection, respectively.

Other Non-Primate Mammals

[PubMed]

Lemoine et al. (13) 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]F13714. High radioactivity levels were observed in the hippocampus, cingulate cortex, and amygdala. The cingulate cortex/cerebellum, amygdala/cerebellum, and hippocampus/cerebellum ratios were 1.5, 1.4, and 1.2, respectively. Pretreatment with WAY100635 (1 mg/kg, 30 min) decreased the cingulate cortex/cerebellum, amygdala/cerebellum, and hippocampus/cerebellum ratios to 1.2, 12, and 1.0, respectively.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

References

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