N-{2-[4-(2-Methoxyphenyl)piperazinyl]ethyl}-*N*-(2-pyridyl)-*N*-(4-[^{18}F]-fluoromethylcyclohexane)carboxamide

[^{18}F]MeFWAY

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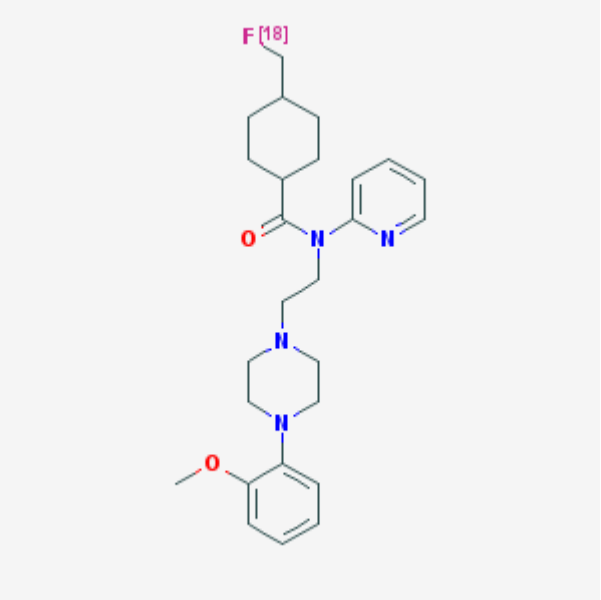
Chemical name:	*N*-{2-[4-(2-Methoxyphenyl)piperazinyl]ethyl}-*N*-(2-pyridyl)-*N*-(4-[^{18}F]-fluoromethylcyclohexane)carboxamide
Abbreviated name:	[^{18}F]MeFWAY
Synonym:	
Agent category:	Compound
Target:	5-HT$_{1A}$ serotonin receptor
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates



Click on the above structure for additional information in PubChem.

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Background

[P ubMed]

Serotonin (5-hydroxytryptamine, 5-HT) has diverse physiologic roles as a neurotransmitter in the central nervous system (1). It 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 with 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. Thus, there is a need for selective ligands to investigate the pharmacologic role of 5-HT_{1A} receptors.

There have been several studies to develop specific 5-HT_{1A} radioligands [PubMed], such as [*carbonyl*-^{11}C]WAY 100635, [^{18}F]FPWAY and [^{18}F]MPPF, for positron emission tomography imaging. However, some of these compounds lack good resistance to in vivo metabolism (6) or exhibit substantial cleavage of the ^{18}F-fluorine bond (7), causing difficulties in using the reference region method for determination of brain 5-HT_{1A} receptor densities . *N*-{2-[4-(2-Methoxyphenyl)piperazinyl]ethyl}-*N*-(2-pyridyl)-*N*-(4-fluoromethylcyclohexane)carboxamide (MeFWAY), a fluoromethyl derivative to the cyclohexyl-ring of WAY-100635, was reported to be a potent inhibitor of 5-HT_{1A} receptors and to provide more resistance towards defluorination and metabolism *in vivo*. This led to the development of *N*-{2-[4-(2-methoxyphenyl)piperazinyl]ethyl}-*N*-(2-pyridyl)-*N*-(4-[^{18}F]-fluoromethylcyclohexane)carboxamide ([^{18}F]MeFWAY) as a useful tool for 5-HT_{1A} receptor positron emission tomography (PET) imaging *in vivo* (8).

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 reported radiosynthesis of [^{18}F]MeFWAY by Saigal et al. (8) involved standard ^{18}F-nucleophilic fluorination of the corresponding tosylate precursor, *N*-{2-[4-(2-methoxyphenyl)piperazinyl]ethyl}-*N*-(2-pyridyl)-*N*-(4-tosyloxymethylcyclohexane)carboxamide, with K[^{18}F]F/Kryptofix2.2.2 in acetonitrile at 96°C for 30 min in an automated radiosynthesis unit, followed by high-performance liquid chromatography purification. The reported overall radiochemical yield of the radiosynthesis was 10-20% at the end of synthesis, the specific radioactivity was 74-111 GBq/μmol (2-3 Ci/μmol), and the radiochemical purity was >95%. Lipophilicity (log P) of [^{18}F]MeFWAY was found to be 2.62 ± 0.06.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro autoradiography studies of rat brain slices indicated the highest binding of [^{18}F]MeFWAY to the hippocampus, colliculus, cortex and the lowest in the cerebellum, consistent with 5-HT$_{1A}$ receptor distribution (8). The hippocampus/cerebellum, colliculus/cerebellum, and cortex/cerebellum ratios were 82, 46, and 40, respectively. Serotonin inhibited [^{18}F]MeFWAY binding with IC_{50} values of 169 ± 5, 218 ± 15, and 244 ± 2 nM for the hippocampus, cortex, and colliculus, respectively. MeFWAY and WAY-100635 inhibited [^{18}F]MeFWAY binding to the brain regions with IC_{50} values of 25.7 ± 2.4 and 23.2 ± 2.8 nM for the hippocampus, respectively.

Animal Studies

Rodents

[PubMed]

Choi et al. (9) performed dynamic PET imaging studies for 120 min in rats after intravenous injection of 15-20 MBq (0.41-0.54 mCi) [^{18}F]MeFWAY. Baseline tissue time-activity curves revealed a high accumulation of radioactivity that peaked at 5 min in the hippocampus, frontal cortex and cerebellum. However, the washout pattern was the slowest in the hippocampus, followed by the frontal cortex and cerebellum. Standard uptake values (SUVs) at 75 min were 6.41, 1.25, 0.95, and 0.4 for the skull, hippocampus, frontal cortex, and cerebellum, respectively. Binding potential (BP_{ND}) values for the hippocampus and frontal cortex were 5.5 and 2.7 at 75 min using the cerebellum as a reference, respectively. Pretreatment with fluconazole (an inhibitor of MeFWAY metabolism in rat live microsomes, 60 mg/kg, 60 min) reduced the SUV in the skull (1.1) but increased the SUVs in the hippocampus (3.2) and frontal cortex (1.8) with little change in the cerebellum (0.5) at 75 min. Pretreatment with WAY-100635 reduced the radioactivity in the brain by 88% at 20 min. Displacement studies were performed at 30 min after tracer injection. WAY-100635 produced a rapid decrease in radioactivity in the brain with 66% inhibition at 120 min.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

The brain accumulation of radioactivity was studied by PET imaging in a rhesus monkey after intravenous injection of 130 MBq (3.5 mCi) of [^{18}F]MeFWAY, with a rapid accumulation in the various brain regions of >0.03%ID/ml in <2 min (8). [^{18}F]Mefway images (up to 180 min after injection) displayed radioactivity concentrations that followed a rank order: the hippocampus and insular cortex (tissue/cerebellum ratios of 8 to 10) > temporal cortex, cingulate gyrus, frontal cortex, and occipital cortex (tissue/cerebellum ratios of 5 to 8) > striatum, thalamus, and raphe (tissue/cerebellum ratios of 2 to 3.5) > cerebellum. The tissue/cerebellum ratios peaked at ~80 min with gradual decreases thereafter. The hippocampus/cerebellum ratio is similar to that of [*carbonyl*-^{11}C]WAY 100635 (10) and better than that of [^{18}F]MPPF (11). After injection of [^{18}F]MeFWAY in the monkey, 40-50% and 30% of the total plasma radioactivity was intact [^{18}F]MeFWAY at 50 and 180 min, respectively. There was one hydrophilic metabolite representing the amide-hydrolysis product, 4-[^{18}F]fluoromethylcyclohexane carboxylic acid. Little radioactivity was detected in the skull of the monkey, indicating that there was little defluorination of [^{18}F]MeFWAY. No blocking experiment was performed.

Wooten et al. (12) compared dynamic PET brain imaging studies of [^{18}F]MeFWAY, [^{18}F]MPPF, and [^{11}C]WAY100635 in four rhesus monkeys for 120 min. High 5-HT$_{1A}$ radioactivity levels were observed in the anterior cingulate cortex (ACG), mesial temporal cortex (MTC), raphe nuclei (RN) and insula cortex (IC). The BP_{ND} in the brain regions were; MTC: 7.4 ± 0.6, 3.1 ± 0.4, 7.0 ± 1.2, ACG: 7.2 ± 1.2, 2.1 ± 0.2, 7.9 ± 1.2; RN: 3.7 ± 0.6, 1.3 ± 0.3, 3.3 ± 0.7 and IC: 4.2 ± 0.6, 1.2 ± 0.1, 4.7 ± 1.0 for [^{18}F]MeFWAY, [^{18}F]MPPF, and [^{11}C]WAY100635, respectively. These data indicate that [^{18}F]MeFWAY and [^{11}C]WAY100635 have very similar *in vivo* kinetics throughout the regions of the brain and provides the BP_{ND} values of 1-2 folds higher than [^{18}F]MPPF in the rhesus monkey.

Human Studies

[PubMed]

No publication is currently available.

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