N-(2-(1-(4-(2-Methoxyphenyl)piperazinyl)ethyl))-*N*-(2-(6-[^{18}F]fluoro)-pyridinyl)cyclohexanecarboxamide

[^{18}F]6FPWAY

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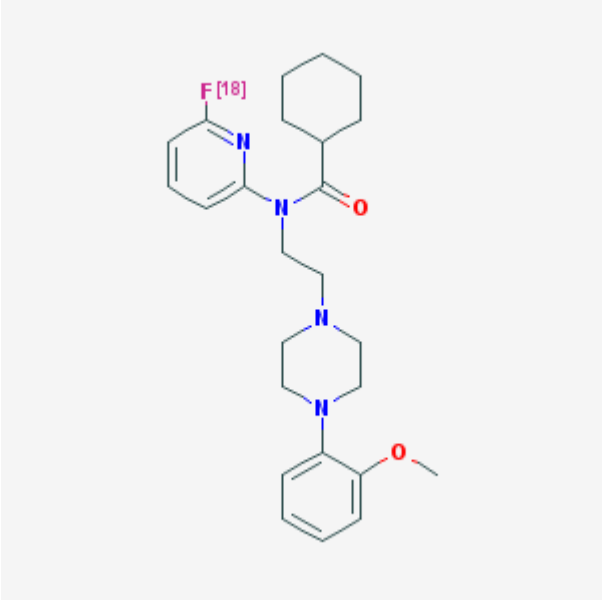
Created: December 29, 2005; Updated: June 30, 2008.

Chemical name:	*N*-(2-(1-(4-(2-Methoxyphenyl)piperazinyl)ethyl))-*N*-(2-(6-[^{18}F]fluoro)-pyridinyl)cyclohexanecarboxamide
Abbreviated name:	[^{18}F]6FPWAY
Synonym:	[6-*Pyridinyl*-^{18}F]-WAY-100635
Agent Category:	Compound
Target:	5-HT$_{1A}$ receptors
Target Category:	Receptor-ligand binding
Method of detection:	Positron emission tomography (PET)
Source of signal/ contrast:	^{18}F
Activation:	No
Studies:	• Non-human primates



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Background

[PubMed]

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NLM Citation: Cheng KT. *N*-(2-(1-(4-(2-Methoxyphenyl)piperazinyl)ethyl))-*N*-(2-(6-[^{18}F]fluoro)-pyridinyl)cyclohexanecarboxamide. 2005 Dec 29 [Updated 2008 Jun 30]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

N-(2-1-(1-(4-(2-Methoxyphenyl)piperazinyl)ethyl)-*N*-(2-(6-[^{18}F]fluoro)-pyridinyl)cyclohexanecarboxamide ([^{18}F]6FPWAY) is a radioligand developed for positron emission tomography (PET) imaging of serotonin-1A (5-HT_{1A}) receptors in the central nervous system (1, 2). It is a selective 5-HT_{1A} antagonist labeled with ^{18}F, a positron emitter with a physical $t_{½}$ of 110 min (3, 4).

The serotonin (5-hydroxytryptamine 5-HT) neurotransmission system consists mainly of neurons in the brainstem, with nerve tracts extending from these neurons to many areas of the brain and spinal cord (5). During firing, the neurons release 5-HT, a neurotransmitter that is involved in the modulation of various important physiologic functions and behavior, such as thermoregulation, cardiovascular function, aggressive and sexual behavior, mood, appetite, and the sleep–wake cycle. 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 also contain several subtypes. There are five receptor subtypes within the G protein-coupled 5-HT_1 receptor family with the 5-HT_{1A} subtype located primarily in the limbic forebrain (the hippocampus, entorhinal cortex and septum). 5-HT_{1A} receptors appear to function both as presynaptic (somatodendritic) autoreceptors in the raphe nuclei and as postsynaptic receptors in the terminal fields. This receptor subtype is involved in the modulation of emotion and the function of the hypothalamus, and is implicated in the pathogenesis of anxiety, depression, hallucinogenic behavior, motion sickness, dementia, schizophrenia, and eating disorders. A radioligand that can be used to assess the *in vivo* densities of 5-HT_{1A} receptors and their changes may facilitate investigation of the relationship of these receptors to various neuropsychiatric diseases and aid in the design of novel drugs for their treatment.

Many psychiatric drugs modulate serotonergic transmission or specifically target the 5-HT_{1A} receptors. Various compounds have been radiolabeled for visualization and quantification of these receptors. WAY 100635 was developed as a highly selective, silent antagonist (possessing no intrinsic agonist activity) of 5HT_{1A} receptors at both presynaptic and postsynaptic sites. WAY 100635 radiolabeled with ^{11}C at the carbonyl position is an effective radioligand but it is rapidly cleared and metabolized. The short $t_{½}$ of ^{11}C also presents some challenges in clinical application of the radiotracer. A radioligand with slower metabolism and labeled with a longer-lived radioisotope would be a better agent for quantitative PET studies. A number of fluorinated derivatives of WAY 100635 have been developed. Sandell et al. (6) reported the synthesis of 6FPWAY and that the presence of a halogen in the pyridine ring appeared to retard its metabolism in primates. 6FPWAY was very different from another WAY analog synthesized by Lang et al. (7) which contained a fluorine in the para position of the benzamide moiety and was abbreviated FPWAY. Recently, Jagoda et al. (8) published a full description of FPWAY, which had previously been referred to as 1,3 pyrimidine WAY.

Synthesis

[PubMed]

The nonradioactive reference compound, 6FPWAY, was synthesized by Marchais et al. (9) by a synthesis pathway using 2-amino-6-pyridine as the precursor. In this method, the nucleophilic substitution was performed directly by heating 2,6-difluoropyridine in tetrahydrofuran with an amine nucleophile. The intermediate product was then acylated with cyclohexanecarbonyl chloride to 6FPWAY with a yield of 10%. The precursor, *N*-(2-1-(1-(4-(2-methoxyphenyl)piperazinyl)ethyl)-*N*-(2-(6-bromo)-pyridinyl)cyclohexanecarboxamide (6BPWAY) was prepared by oxidizing 2,6-dibromopyridine with hydrogen peroxide. This was then reacted with an amine nucleophile, followed by reduction with iron in acetic acid. Reaction of the product with cyclohexanecarbonyl chloride in dichloromethane gave 6BPWAY with 75% yield.

Karramkam et al. (4) reported the radiosynthesis of [^{18}F]6FPWAY. No-carrier-added aqueous [^{18}F]fluoride was produced by an [^{18}O(p,n)^{18}F] nuclear reaction initiated by irradiation of 2 ml of 95% enriched [^{18}O]water with a 17 MeV proton beam. 6BPWAY was prepared as the precursor as described by Marchais et al. (9). Introduction of ^{18}F was performed in dimethyl sulfoxide with the activated K[^{18}F]F-K_{222} complex by conventional heating at 145 °C for 10 min.

Alternatively, the nitro derivative of WAY 100635 (6NPWAY) could be prepared as the precursor and reacted with [^{18}F] fluoride by microwave heating at 100 W for 1 min. With 6-bromopyridine derivative used as the precursor, after Sep-Pak separation, the product that was purified by high performance liquid chromatography (HPLC) was pure [^{18}F]6FPWAY. The reported yield was15-25% based on the starting [^{18}F]fluoride activity. The synthesis time was 50-70 min, with 0.55-0.92 GBq (15-25 mCi) of [^{18}F]6FPWAY obtained from 3.7 GBq (100 mCi) of [^{18}F]fluoride. The specific activity was 37-72 GBq (1-2 Ci)/μmol at the end of synthesis. The chemical purity was >95%, and the radiochemical purity was >99%. The radiotracer was radiochemically stable for at least 120 min based on HPLC analysis.

McCarron et al. (2) reacted 6BPWAY with dry [^{18}F]fluoride ion at 100 °C for 20 min and reported a 2% radiochemical decay-corrected yield. The radiochemical purity was >99%.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

No publication is currently available.

Animal Studies

Rodents

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

McCarron et al. (2) studied the *in vivo* behavior of [^{18}F]6FPWAY with PET imaging in a male cynomolgus monkey. In the first (distribution) study a 28 MBq (0.78 mCi) i.v. dose of [^{18}F]6FPWAY (>99% radiochemical purity) was injected, and in the second (blocking) study, a 29 MBq (0.784 mCi) i.v. dose was injected into the same monkey 10 min after i.v. injection of WAY 100635 (0.5 mg/kg). In the distribution study, the radioactivity reached the brain and peaked at 4.33% of injected dose around 7.5 min after injection. Localization of radioactivity in the brain was rapid and was followed by a slower clearance. Radioactivity was localized in regions known to contain high densities of 5-HT_{1A} receptors (e.g., the insula, temporal, and frontal cortex). The tissue/cerebellum radioactivity ratio was highest (~2) in the insula after 30 min. The second highest ratio was in the cingulated gyrus. When WAY 100635 was administered in the blocking study, there was notably much less radioactivity in brain 5-HT_{1A} receptor-rich regions. The tissue/cerebellum ratios were also lower for these regions. HPLC analysis of blood samples obtained from the monkey showed two main peaks of radioactive metabolites. One metabolite was possibly [^{18}F]descyclohexylcarbonyl-6FPWAY (comigrated with the metabolite in HPLC), and it represented about 19% of radioactivity in the plasma at 55 min. This indicated that amide scission was likely the major route of metabolism. [^{18}F]Descyclohexylcarbonyl-6FPWAY was possibly able to cross the blood-brain barrier (BBB). The lack of radioactivity on the skull might indicate that rapid defluorination did not occur. The researchers suggested that the position 6 of the pyridinyl ring in the [^{18}F]6FPWAY was a metabolically resistant site for ^{18}F labeling. The first WAY 100635 analog was radiolabeled with ^{11}C at the methoxyphenyl position. On hydrolysis of the amide in humans, the radiolabeled metabolite crossed the BBB (10).

Human Studies

[PubMed]

No publication is currently available.

NIH Support

NIH Intramural Support.

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