4-(2′-Methoxyphenyl)-1-[2′-(*N*-2′′-pyridinyl)-*p*-[^{18}F]fluorobenzamido]ethylpiperazine

p-[^{18}F]MPPF

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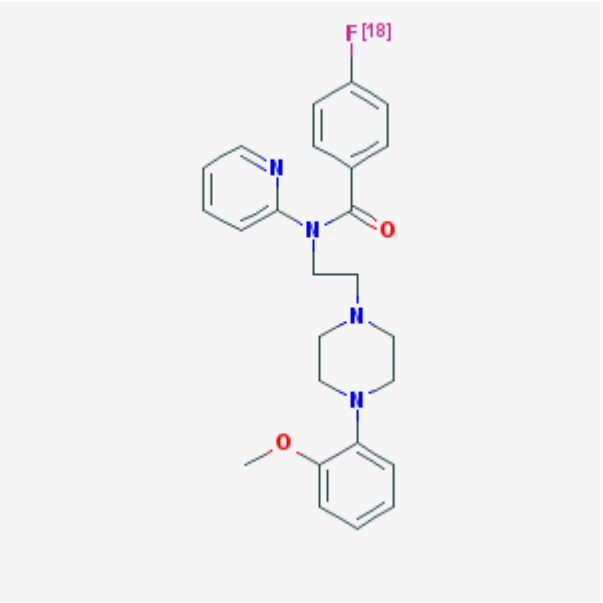
Chemical name:	4-(2′-Methoxyphenyl)-1-[2′-(*N*-2′′-pyridinyl)-*p*-[^{18}F]fluorobenzamido]ethylpiperazine
Abbreviated name:	*p*-[^{18}F]MPPF
Synonym:	[^{18}F]FBWAY, [^{18}F]MPPF
Agent Category:	Compound
Target:	5-HT$_{1A}$ receptors
Target Category:	Receptor-ligand binding
Method of detection:	Positron Emission Tomography (PET)
Source of signal / contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Non-human primates • Humans



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Background

[PubMed]

4-(2′-Methoxyphenyl)-1-[2′-(*N*-2′′-pyridinyl)-*p*-[^{18}F]fluorobenzamido]ethylpiperazine (*p*-[^{18}F]MPPF) is a radioligand developed for positron emission tomography (PET) imaging of serotonin-1A (5-HT$_{1A}$) receptors in the central nervous system (1). It is a selective 5-HT$_{1A}$ radiotracer labeled with ^{18}F, a positron emitter with a physical $t_{½}$ of 110 min (2).

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 (3). 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, and the 5-HT$_{1A}$ subtype is located primarily in the limbic forebrain (the hippocampus, entorhinal cortex, and septum). 5-HT$_{1A}$ appears to function both as a presynaptic (somatodendritic) autoreceptor in the raphe nuclei and as a postsynaptic receptor 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.

Many psychiatric drugs modulate serotonergic transmission or specifically target the 5-HT$_{1A}$ receptors. Many compounds have been radiolabeled and studied for visualization and quantification of these receptors by PET or single-photon emission computed tomography (SPECT). WAY 100635 has been developed as a highly selective, silent antagonist (possessing no intrinsic agonist activity) of 5HT$_{1A}$ receptors at both pre- and postsynaptic sites. Zhuang et al. (4, 5) first developed a series of arylpiperazine-benzamido derivatives and 4-(2′-methoxyphenyl)-1-[2′-[*N*-(2′′-pyridinyl)-*p*-iodobenzamido]ethyl]piperazine ([^{125}I]MPPI), which appeared to selectively bind to the 5-HT$_{1A}$ receptors *in vitro* and *in vivo*. Their studies showed that various benzoyl substituents affected the inhibition constant (K_i) of the compound. Zhuang et al. (4) also synthesized a fluoro analog, *p*-MPPF, that displayed a high binding affinity for 5-HT$_{1A}$ receptors and acted as a receptor antagonist *in vivo*. In 1994, Shiue et al. (6) synthesized *p*-[^{18}F]MPPF for PET studies of 5-HT$_{1A}$ receptors in humans.

Synthesis

[PubMed]

Zhuang et al. (5) synthesized *p*-MPPI as well as the fluoro analog of *p*-MPPF. The procedure involved the initial condensation of 2-aminopyridine with chloroacetyl

chloride and then acylation with 2-chloro-*N*-(2-pyridyl)-acetamide. The subsequent reduction to the amine as the key intermediate compound gave an 81% overall yield. Coupling of the acyl groups with this intermediate compound was accomplished with an acyl chloride in the presence of triethylamine or by the use of acids with oxalyl chloride in dimethyl formamide. Both reactions gave yields of 50-90%. Using this approach, Shiue et al. (6) synthesized *p*-[^{18}F]MPPF by first preparing the nitro compound of 4-(2′-methoxyphenyl)-1-[2′-(*N*-2"-pyridinyl)-*p*-nitrobenzamido]ethylpiperazine (*p*-MPPNO$_2$), and then used nucleophilic substitution of the nitro group with [^{18}F]fluoride. [^{18}F]Fluoride was prepared by the ^{18}O(p,n)^{18}F reaction on an enriched water target added to a solution of K_2CO_3/Kryptofix 2.2.2. The nitro compound in dimethyl sulfoxide was added to the dried K[^{18}F], and the mixture was kept at 140°C for 20 min. The final compound was purified by use of a C_{18} Sep-Pak column and then by high-performance liquid chromatography (HPLC). The synthesis time was 90 min, and the radiochemical yield was 10% at 90 min from the end of bombardment (EOB). Specific activity was 37-148 GBq (1-4 Ci)/µmol at the end of synthesis (EOS).

Le Bars et al. (7) used microwave heating at 3 min/500 W and a remotely controlled process for the radiosynthesis. They also reported better separation between the fluorinated compound and its nitro precursor with the use of a ternary solvent mixture of tetrahydrofuran, methanol, and aqueous sodium acetate for the HPLC. The synthesis time was shortened to 70 min, and the radiochemical yield was 25% at EOS. The specific activity averaged about 37-185 GBq (1-5 Ci)/µmol at EOS.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Zhuang et al. (4, 5) reported a K_i for *p*-[^{18}F]MPPF of 3.2 ± 0.8 nM with use of rat hippocampal homogenates and ^{125}I-labeled *trans*-8-hydroxy-2-(*N*-*n*-propyl-*N*-3′-iodo-2′-propenyl)aminotetralin ([^{125}I]-(*R*)-(+)-*trans*-8-OH-PIPAT). In comparison, WAY 100635 had a K_i of 0.84 ± 0.1 nM. Kung et al. (8) synthesized [^{3}H] *p*-[^{18}F]MPPF by a [^{3}H]CH_3I methylation reaction for binding studies in rat hippocampal membrane homogenates. The K_d was 0.34 ± 0.12 nM, and the B_{max} was 145 ± 35 fmol/mg protein. Autoradiographic studies of rat brain sections showed that [^{3}H] *p*-[^{18}F]MPPF localization was similar to the distribution of 5-HT_{1A} receptors. Ma et al. (9) studied the metabolites of *p*-[^{18}F]MPPF and other fluorinated WAY analogs with use of rat hepatocytes and human liver tissue. They identified the major metabolites by liquid chromatography–tandem mass spectrometry and found significant between-species differences in metabolism. In rat hepatocytes, the aromatic ring oxidation was the major metabolism pathway. For human hepatocytes, amide hydrolysis products were the major metabolites. They also reported significant differences among different fluorinated analogs.

Animal Studies

Rodents

[PubMed]

Shiue et al. (6) studied the tissue distribution of *p*-[^{18}F]MPPF in rats, using a dose of 925-1110 kBq (25-30 µCi). The brain radioactivity was 0.7% injected dose (ID)/g at 2 min and then decreased rapidly. The washout rates of radioactivity were slower in regions (e.g., hippocampus, cerebral cortex, and hypothalamus) with high concentrations of 5-HT$_{1A}$ receptors than in regions that lacked these receptors. The maximum hippocampus/cerebellum ratio was 5.6 at 30 min. Treatment with (±)8-hydroxy-2-di-*n*-propylamino-tetralin ((±)-8-OH-DPAT), a 5-HT$_{1A}$ agonist (2 mg/kg i.v.), or WAY 100635 (a 5-HT$_{1A}$ antagonist; 1 mg/kg i.v.) 5 min before radiotracer administration significantly reduced the radioactivity in the serotonergic regions. In a rat biodistribution study, Lang et al. (10) reported DUR [(%ID/g) × body weight (g)/100] values ($n \geq 4$) for *p*-[^{18}F]MPPF of 0.165 ± 0.023, 0.377 ± 0.100, and 0.066 ± 0.008 in the cortex, hippocampus, and cerebellum, respectively. The hippocampus/cerebellum DUR ratio was 4.7 and decreased to 2.1 with a 50-nmol injection of WAY 100635.

In two *in vivo* tests of hypothermia and reciprocal forepaw treading in rats, Thielen et al. (11) confirmed that *p*-MPPF acts as a 5-HT$_{1A}$ receptor antagonist. In a similar study (11), the same research group found that *p*-MPPF behaved as a competitive antagonist of both postsynaptic 5-HT$_{1A}$ receptors and somatodendritic 5-HT$_{1A}$ autoreceptors. Lang et al. (12) studied the metabolite profile of *p*-[^{18}F]MPPF in rat brain and blood, and they reported that the radioactivity (3700 kBq (100 µCi)) was extracted with high efficiency (84-92%). In the brain distribution, radioactivity had an early rapid net efflux from the whole brain and appeared to have two components (10). The $t_{½}$ (second component) of the whole brain was 35 min. The metabolite-corrected blood $t_{½}$ was 41 min. In a blocking experiment involving injection of 50 nmol of WAY 100536, *p*-[^{18}F]MPPF showed only ~60% reduction of specific binding in the hippocampus.

Plenevaux et al. (13) studied the *in vivo* behavior of *p*-[^{18}F]MPPF in awake, freely moving rats, using a radioactivity dose of 37-185 MBq ((1-5 mCi); specific activity = 55.5 ±18.5 GBq/µmol (1.5 ± 0.5 Ci/µmol) at the EOS). After injection, plasma clearance was fast, and the plasma clearance rate was constant (k = -0.028 ± 0.007 min^{-1}) between 15 and 60 min. The highest concentrations of radioactivity were found in the liver and kidney. In the brain, the total radioactivity was cleared at a constant rate (k = -0.044 ± 0.010 min^{-1}) from 0.113 ± 0.019% ID at 15 min to 0.018 ± 0.002% ID at 60 min. At 30 min, the radioactivities in the hippocampus and frontal cortex were 1.7 and 4 times (n = 12) higher than in the cerebellum and striatum, respectively. Between 15 and 60 min, 70-90% of the radioactivity was *p*-[^{18}F]MPPF, as determined by HPLC analyses of the brain tissue. In the plasma, as much as 60% of the total radioactivity at 60 min came from metabolites. Qualitative comparisons between *ex vivop*-[^{18}F]MPPF and *in vitro* [^{3}H]-OH-DPAT autoradiographic labeling showed that the same rat brain regions were labeled.

Passchier et al. (14) showed that *p*-[^{18}F]MPPF was a substrate for P-glycoprotein in experiments using wild-type and *mdr1a*(–/–) knockout mice. Using a positron-sensitive intracerebral probe and microdialysis in rats, Zimmer et al. (15, 16) found that *p*-[^{18}F]MPPF binding could be modulated by modifications of extracellular serotonin in the rat hippocampus. The same group of researchers showed that *p*-[^{18}F]MPPF specific binding was significantly enhanced after a decrease in extracellular serotonin and that the binding was also sensitive to electrically evoked serotonin release (17, 18).

Other Non-Primate Mammals

[PubMed]

Le Bars et al. (7) injected 55.5 MBq (1.5 mCi) of *p*-[^{18}F]MPPF into adult female cats. PET imaging revealed high levels of radioactivity in the limbic cortex (including the hippocampus) and cingulate cortex. Time-activity curves showed high initial radioactivity localization in all brain regions, followed by a rapid washout. The washout rates were lower in the cingulated and limbic cortices than in the cerebellum. Pretreatment with WAY 100635 (500 μg/kg) 30 min before radiotracer injection completely blocked localization of *p*-[^{18}F]MPPF radioactivity in the serotonergic regions.

Non-Human Primates

[PubMed]

Shiue et al. (6) performed PET brain imaging with *p*-[^{18}F]MPPF in a male cynomologus monkey. An i.v. bolus dose of 150 MBq (4.06 mCi) was given, and PET scans showed localization and retention of radioactivity in the monkey's hippocampus. The ratio of radioactivity in the hippocampus to that in the cerebellum was 3 at 30 min after injection. This ratio was reduced to 1 by the injection of (±)-8-OH-DPAT (2 mg/kg i.v.) 23 min after injection of *p*-[^{18}F]MPPF in the displacement experiment. Plasma metabolite analyses showed that the appearance of metabolites in the plasma was relatively rapid. Only 23% of radioactivity in the monkey plasma remained as *p*-[^{18}F]MPPF at 30 min after injection. Carson et al. (19) performed brain imaging of [^{18}F]fluorobenzoic acid, a major metabolite of *p*-[^{18}F]MPPF, in rhesus monkeys. [^{18}F]Fluorobenzoic acid was taken up by the monkey brain, but HPLC analysis of arterial blood showed no metabolites for [^{18}F]fluorobenzoic acid.

Udo De Haes et al. (20) described a *p*-[^{18}F]MPPF binding study with microdialysis and PET scanning in conscious male rhesus monkeys. The specific activity of *p*-[^{18}F]MPPF was >10 TBq/mmol (270 Ci/mmol) at the time of administration (TOA). The dose was given as a bolus–continuous infusion scheme to eliminate the possible effects of blood flow, with a mean injected activity of 420 ± 351 MBq (11.4 ± 9.5 mCi). The binding potentials (BPs) of *p*-[^{18}F]MPPF in various monkey brain regions (n = 3) were estimated to be 0.4 ± 0.1, 0.5 ± 0.2, 1.1 ± 0.2, and 1.2 ± 0.4 for the striatum, raphe nucleus, frontal cortex, and hippocampus, respectively. Administration of fenfluramine, a serotonin-releasing agent and reuptake inhibitor, at i.v. doses of 5 or 10 mg/kg (90-130 min after *p*-

[^{18}F]MPPF injection) did not show significant changes in the BPs of *p*-[^{18}F]MPPF. The authors suggested that the majority of 5-HT$_{1A}$ receptors were in the low affinity state in the living monkey brain and that, therefore, the released 5-HT affected only a small percentage of the bound *p*-[^{18}F]MPPF.

Human Studies

[PubMed]

Passchier et al. (21) studied the quantitative imaging of 5-HT$_{1A}$ receptors with *p*-[^{18}F]MPPF in 6 healthy volunteers. Each subject received 70 ± 18 MBq (1.9 ± 0.5 mCi) of *p*-[^{18}F]MPPF with a specific activity of 95 ± 31 TBq/mmol (2565 ± 837 Ci/mmol) at TOA. The injected radioactivity was rapidly cleared from plasma and rapidly metabolized. Only 1% of *p*-[^{18}F]MPPF remained in the plasma at 10 min. The authors found good correlation (r = 0.95) between the BPs and reported densities of 5-HT$_{1A}$ receptors in various brain areas. A blocking experiment with pindolol (30 mg) showed a decrease of 40% in the region/cerebellum ratios of the target areas. In a similar study, the same group of researchers (22) found that the BPs of the medial temporal cortex, lateral temporal cortex, insular cortex, cingulate cortex, frontal cortex, striatum, and thalamus (n = 5) were 1.59 ± 0.31, 0.92 ± 0.07, 0.91 ± 0.16, 0.63 ± 0.11, 0.48 ± 0.09, 0.12 ± 0.13, and 0.10 ± 0.12, respectively. The lowest amounts of radioactivity were found in the cerebellum and basal ganglia.

In a study with 5 healthy volunteers, Costes et al. (23) quantified the parameters of ligand-receptor exchanges by use of a double-injection protocol (two *p*-[^{18}F]MPPF bolus injections of 185 ± 9 MBq (5 ± 0.2 mCi) at a mean interval of 88.5 ± 4.2 min). A three-compartment ligand-receptor model was used to determine the kinetic parameters of 2 *p*-[^{18}F]MPPF. The authors found a B_{max} of 2.9 pmol/ml and a K_d of 2.8 nmol/l in hippocampal regions. They also suggested that in the absence of blood arterial sampling, the BPs estimated by the Logan method would be a good index of local receptor concentrations in healthy subjects.

Sanabria-Bohorquez et al. (24) performed 60-min dynamic PET scans in 13 healthy volunteers after a single bolus injection of 3.7 MBq/kg (0.1 mCi/kg) *p*-[^{18}F]MPPF (specific activity = 37-148 MBq/pmol (1-4 mCi/pmol) at the TOA). Metabolite quantification revealed that ~25% of total plasma activity was *p*-[^{18}F]MPPF at 5 min. A plasma input function (PIF) method and a reference tissue method (RTM) were used to describe the kinetics parameters. The PIF method gave calculated BPs for the right and left hippocampus of 1.594 ± 0.274 and 1.576 ± 0.250, respectively, whereas the RTM gave corresponding BPs of 1.323 ± 0.193 and 1.301 ± 0.190, respectively.

Udo De Haes et al. (25) studied the effect of tryptophan depletion and infusion on *p*-[^{18}F]MPPF binding in 6 healthy subjects. Each subject received 110-160 MBq (3-4.3 mCi) of *p*-[^{18}F]MPPF (specific activity >10 TB/mmol (270 Ci/mmol) at the TOA), and [^{15}O]H_2O was used to assess regional cerebral blood flow. BPs were calculated with the simplified RTM. The mean changes in BPs for comparison of tryptophan depletion with

tryptophan infusion were -0.6% in the medial temporal cortex, +1.9% in the cortical regions, and -16.6% in the raphe nucleus. The authors suggested that the induced changes in serotonin levels did not produce a significant effect on *p*-[^{18}F]MPPF binding in human brains. Merlet et al. (26) found that the binding of *p*-[^{18}F]MPPF to 5-HT$_{1A}$ receptors in patients with refractory temporal lobe epilepsy (n = 9) was decreased in the epileptogenic temporal lobe. A decrease in BP was strongly correlated to the degree of epileptic activity. Praschak-Rieder et al. (27) reported that tryptophan depletion did not appear to have a significant effect on the regional brain BP of *p*-[^{18}F]MPPF in 8 patients with major depressive disorder.

In a study designed to compile a normative database that included 27 female and 26 male healthy volunteers, Costes et al. (28) studied the possible influence of age and sex on *p*-[^{18}F]MPPF BP, using a single injection of 192.7 ± 23.8 MBq (5.2 ± 0.6 mCi) of *p*-[^{18}F]MPPF. They found a negative linear correlation between age and global *p*-[^{18}F]MPPF BP values in females (a decrease of 3.6% per decade) but not in males. Male subjects in their 30s showed decreased binding in most cerebral regions compared with subjects in their 20s.

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References

1. Passchier J., van Waarde A. Visualisation of serotonin-1A (5-HT1A) receptors in the central nervous system. Eur J Nucl Med. 2001;**28**(1):113–29. PubMed PMID: 11202445.
2. Bantick R.A., Rabiner E.A., Hirani E., de Vries M.H., Hume S.P., Grasby P.M. Occupancy of agonist drugs at the 5-HT1A receptor. Neuropsychopharmacology. 2004;**29**(5):847–59. PubMed PMID: 14985704.
3. Sunderland, P.M., Structure and function of the nervous system, in Pathophysiology: The biologic basis for disease in adults and children, K.L. McCance, and S.H. Huether, Editor. 1994, Mosby-Year Book, Inc.: St. Louis, MO. p. 397-436.
4. Zhuang Z.P., Kung M.P., Chumpradit S., Mu M., Kung H.F. Derivatives of 4-(2'-methoxyphenyl)-1-[2'-(N-2"-pyridinyl-p-iodobenzamido)ethyl]pipera zine (p-MPPI) as 5-HT1A ligands. J Med Chem. 1994;**37**(26):4572–5. PubMed PMID: 7799409.
5. Zhuang Z.P., Kung M.P., Kung H.F. Synthesis and evaluation of 4-(2'-methoxyphenyl)-1-[2'-[N-(2"-pyridinyl)-p- iodobenzamido]ethyl]piperazine (p-MPPI): a new iodinated 5-HT1A ligand. J Med Chem. 1994;**37**(10):1406–7. PubMed PMID: 8182697.
6. Shiue C.Y., Shiue G.G., Mozley P.D., Kung M.P., Zhuang Z.P., Kim H.J., Kung H.F. P-[18F]-MPPF: a potential radioligand for PET studies of 5-HT1A receptors in humans. Synapse. 1997;**25**(2):147–54. PubMed PMID: 9021895.
7. Le Bars D., Lemaire C., Ginovart N., Plenevaux A., Aerts J., Brihaye C., Hassoun W., Leviel V., Mekhsian P., Weissmann D., Pujol J.F., Luxen A., Comar D. High-yield

radiosynthesis and preliminary in vivo evaluation of p-[18F]MPPF, a fluoro analog of WAY-100635. Nucl Med Biol. 1998;**25**(4):343–50. PubMed PMID: 9639295.

8. Kung H.F., Stevenson D.A., Zhuang Z.P., Kung M.P., Frederick D., Hurt S.D. New 5-HT1A receptor antagonist: [3H]p-MPPF. Synapse. 1996;**23**(4):344–6. PubMed PMID: 8855520.
9. Ma Y., Lang L., Kiesewetter D.O., Eckelman W.C. Liquid chromatography-tandem mass spectrometry identification of metabolites of three phenylcarboxyl derivatives of the 5-HT(1A) antagonist, N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridyl) trans-4-fluorocyclohexanecarboxamide (FCWAY), produced by human and rat hepatocytes. J Chromatogr B Analyt Technol Biomed Life Sci. 2002;**780**(1):99–110. PubMed PMID: 12383485.
10. Lang L., Jagoda E., Schmall B., Sassaman M., Ma Y., Eckelman W.C. Fluoro analogs of WAY-100635 with varying pharmacokinetics properties. Nucl Med Biol. 2000;**27**(5):457–62. PubMed PMID: 10962250.
11. Thielen R.J., Fangon N.B., Frazer A. 4-(2'-Methoxyphenyl)-1-[2'-[N-(2"-pyridinyl)-p-iodobenzamido]ethyl] piperazine and 4-(2'-methoxyphenyl)-1-[2'-[N-(2"-pyridinyl)-p- fluorobenzamido]ethyl]piperazine, two new antagonists at pre- and postsynaptic serotonin-1A receptors. J Pharmacol Exp Ther. 1996;**277**(2):661–70. PubMed PMID: 8627543.
12. Lang L., Jagoda E., Schmall B., Vuong B.K., Adams H.R., Nelson D.L., Carson R.E., Eckelman W.C. Development of fluorine-18-labeled 5-HT1A antagonists. J Med Chem. 1999;**42**(9):1576–86. PubMed PMID: 10229627.
13. Plenevaux A., Weissmann D., Aerts J., Lemaire C., Brihaye C., Degueldre C., Le Bars D., Comar D., Pujol J., Luxen A. Tissue distribution, autoradiography, and metabolism of 4-(2'-methoxyphenyl)-1-[2' -[N-2"-pyridinyl)-p-[(18)F]fluorobenzamido]ethyl]piperazine (p-[(18)F]MPPF), a new serotonin 5-HT(1A) antagonist for positron emission tomography: An In vivo study in rats. J Neurochem. 2000;**75**(2):803–11. PubMed PMID: 10899958.
14. Passchier J., van Waarde A., Doze P., Elsinga P.H., Vaalburg W. Influence of P-glycoprotein on brain uptake of [18F]MPPF in rats. Eur J Pharmacol. 2000;**407**(3):273–80. PubMed PMID: 11068023.
15. Zimmer L., Mauger G., Le Bars D., Bonmarchand G., Luxen A., Pujol J.F. Effect of endogenous serotonin on the binding of the 5-hT1A PET ligand 18F-MPPF in the rat hippocampus: kinetic beta measurements combined with microdialysis. J Neurochem. 2002;**80**(2):278–86. PubMed PMID: 11902118.
16. Zimmer L., Pain F., Mauger G., Plenevaux A., Le Bars D., Mastrippolito R., Pujol J.F., Renaud B., Laniece P. The potential of the beta-Microprobe, an intracerebral radiosensitive probe, to monitor the [(18)F]MPPF binding in the rat dorsal raphe nucleus. Eur J Nucl Med Mol Imaging. 2002;**29**(9):1237–47. PubMed PMID: 12192569.
17. Zimmer L., Rbah L., Giacomelli F., Le Bars D., Renaud B. A reduced extracellular serotonin level increases the 5-HT1A PET ligand 18F-MPPF binding in the rat hippocampus. J Nucl Med. 2003;**44**(9):1495–501. PubMed PMID: 12960198.

18. Rbah L., Leviel V., Zimmer L. Displacement of the PET ligand 18F-MPPF by the electrically evoked serotonin release in the rat hippocampus. Synapse. 2003;**49**(4): 239–45. PubMed PMID: 12827643.
19. Carson R.E., Wu Y., Lang L., Ma Y., Der M.G., Herscovitch P., Eckelman W.C. Brain uptake of the acid metabolites of F-18-labeled WAY 100635 analogs. J Cereb Blood Flow Metab. 2003;**23**(2):249–60. PubMed PMID: 12571456.
20. Udo de Haes J.I., Cremers T.I., Bosker F.J., Postema F., Tiemersma-Wegman T.D., den Boer J.A. Effect of increased serotonin levels on [18F]MPPF binding in rat brain: fenfluramine vs the combination of citalopram and ketanserin. Neuropsychopharmacology. 2005;**30**(9):1624–31. PubMed PMID: 15827572.
21. Passchier J., van Waarde A., Pieterman R.M., Elsinga P.H., Pruim J., Hendrikse H.N., Willemsen A.T., Vaalburg W. Quantitative imaging of 5-HT(1A) receptor binding in healthy volunteers with [(18)f]p-MPPF. Nucl Med Biol. 2000;**27**(5):473–6. PubMed PMID: 10962253.
22. Passchier J., van Waarde A., Pieterman R.M., Elsinga P.H., Pruim J., Hendrikse H.N., Willemsen A.T., Vaalburg W. In vivo delineation of 5-HT1A receptors in human brain with [18F]MPPF. J Nucl Med. 2000;**41**(11):1830–5. PubMed PMID: 11079490.
23. Costes N., Merlet I., Zimmer L., Lavenne F., Cinotti L., Delforge J., Luxen A., Pujol J.F., Le Bars D. Modeling [18 F]MPPF positron emission tomography kinetics for the determination of 5-hydroxytryptamine(1A) receptor concentration with multiinjection. J Cereb Blood Flow Metab. 2002;**22**(6):753–65. PubMed PMID: 12045674.
24. Sanabria-Bohorquez S.M., Biver F., Damhaut P., Wikler D., Veraart C., Goldman S. Quantification of 5-HT(1A) receptors in human brain using p-MPPF kinetic modelling and PET. Eur J Nucl Med Mol Imaging. 2002;**29**(1):76–81. PubMed PMID: 11807610.
25. Udo de Haes J.I., Bosker F.J., Van Waarde A., Pruim J., Willemsen A.T., Vaalburg W., Den Boer J.A. 5-HT(1A) receptor imaging in the human brain: effect of tryptophan depletion and infusion on [(18)F]MPPF binding. Synapse. 2002;**46**(2):108–15. PubMed PMID: 12211089.
26. Merlet I., Ostrowsky K., Costes N., Ryvlin P., Isnard J., Faillenot I., Lavenne F., Dufournel D., Le Bars D., Mauguiere F. 5-HT1A receptor binding and intracerebral activity in temporal lobe epilepsy: an [18F]MPPF-PET study. Brain. 2004;**127**(Pt 4): 900–13. PubMed PMID: 14985263.
27. Praschak-Rieder N., Hussey D., Wilson A.A., Carella A., Lee M., Dunn E., Willeit M., Bagby R.M., Houle S., Meyer J.H. Tryptophan depletion and serotonin loss in selective serotonin reuptake inhibitor-treated depression: an [(18)F] MPPF positron emission tomography study. Biol Psychiatry. 2004;**56**(8):587–91. PubMed PMID: 15476688.
28. Costes N., Merlet I., Ostrowsky K., Faillenot I., Lavenne F., Zimmer L., Ryvlin P., Le Bars D. A 18F-MPPF PET Normative Database of 5-HT1A Receptor Binding in Men and Women Over Aging. J Nucl Med. 2005;**46**(12):1980–1989. PubMed PMID: 16330560.