2-(2-(3-[^{11}C]Methoxyphenyl)ethynyl)pyridine

[^{11}C]M-MPEP

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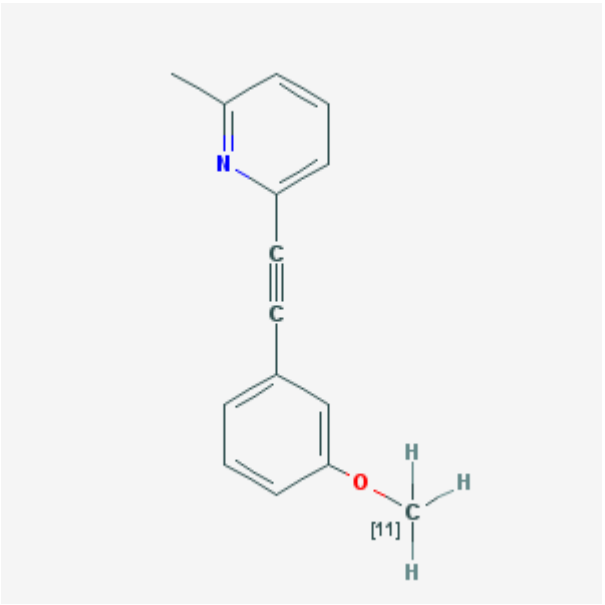
Chemical name:	2-(2-(3-[^{11}C]Methoxyphenyl)ethynyl)pyridine
Abbreviated name:	[^{11}C]M-MPEP
Synonym:	
Agent Category:	Compound
Target:	Metabotropic glutamate subtype 5 (mGlu5) receptor (mGluR5 or mGluR$_5$)
Target Category:	Receptor binding
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

Background

[PubMed]

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

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2-(2-(3-[^{11}C]Methoxyphenyl)ethynyl)pyridine ([^{11}C]M-MPEP) is a radioligand developed for positron emission tomography (PET) imaging of metabotropic glutamate (mGlu) receptor subtype 5 (mGluR5 or mGluR$_5$) in the central nervous system (CNS) (1). ^{11}C is a positron emitter with a physical half-life ($t_{½}$) of 20.3 min.

Glutamate is a major excitatory neurotransmitter at CNS synapses. Many neuroanatomical CNS projection pathways contain glutamatergic neurons (2). Glutamate produces its excitatory effects by acting on cell-surface ionotropic glutamate or mGluRs (3). The mGluRs are G-protein–coupled receptors, and the eight mGluR subtypes are further subdivided into three groups. The group I receptors include mGluR1 and mGluR5, and they are found predominantly in postsynaptic locations. The mGluR5s are found with high to moderate density in the frontal cortex, caudate, putamen, nucleus accumbens, olfactory tubercle, hippocampus, and dorsal horn of the spinal cord, whereas the density in the cerebellum is low. These receptors are coupled to phospholipase C, and they up- or downregulate neuronal excitability. They have been implicated in a variety of diseases in the CNS, including anxiety, depression, schizophrenia, Parkinson's disease, and drug addiction or withdrawal. These receptors are also involved in the modulation of various pain states, which makes them attractive targets for therapeutic drug development.

PET and single-photon emission computed tomography imaging of radioligands that target mGluR5s are used to visualize and study the CNS mGluR5s in normal and pathological states. Some mGluR5 antagonists have been successfully labeled, but their *in vivo* visualization has been hampered by high lipophilicity, unfavorable brain uptake kinetics, or high metabolism (4, 5). MPEP and its methyl analog M-MPEP have been identified as potent and highly selective noncompetitive antagonists for mGlu5 (1, 6). Yu et al. (1) synthesized [^{11}C]M-MPEP and demonstrated the feasibility of using it as an imaging ligand for *in vivo* PET imaging.

Synthesis

[PubMed]

Gasparini et al. (6) reported the synthesis of the phenolic precursor 3-(2-(6-methylpyridin-2-yl)ethynyl)-phenol of M-MPEP. Briefly, 2,6-dimethyl-pyridine and 3-hydroxy-benzaldehyde were used as starting materials. They were condensed in acetic anhydride at 165°C for 3.5 h to form a styrene derivative. This intermediate compound was dibrominated in the dark at room temperature. This dibrominated intermediate was then converted to 3-(2-(6-methylpyridin-2-yl)ethynyl)-phenol using potassium tert-butylate in potassium hydroxide (KOH), crown ether 18C6, and tetrahydrofuran at 50°C for 1.5 h.

Yu et al. (1) reported the radiosynthesis of [^{11}C]M-MPEP by radiolabeling this phenolic precursor with ^{11}C methyl iodide ([^{11}C]CH_3I) under basic conditions. [^{11}C]CH_3I was prepared from $^{11}CO_2$ with the use of the $^{14}N(p,\alpha)^{11}C$ reaction. The best yield conditions were obtained with KOH as the base. In this radiolabeling reaction, 4–10 mg of solid

KOH powder was added to 0.5–1.0 mg of the precursor dissolved in dimethyl sulfoxide before [^{11}C]CH_3I was added to the reaction mixture. The mixture was heated at 90°C for 6 min. The radioligand was purified by high-performance liquid chromatography (HPLC). The radiochemical purity was >98.4 ± 1.3% (n = 7), and the specific activity was 23.2 ± 4.7 GBq/μmol (857 ± 173 mCi/μmol). The radiochemical yield was 3.1 ± 1.5 GBq (84.7 ± 39.6 mCi) at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

No publication is currently available.

Animal Studies

Rodents

[PubMed]

Yu et al. (1) performed dynamic PET imaging of [^{11}C]M-MPEP in male rats (n = 13). Each anesthetized rat received 108.52 ± 73.70 MBq (2.93 ± 2.00 mCi) in 0.72 ± 0.49 μg [^{11}C]M-MPEP (2–3 nM in 0.1 ml or ~3.4 nmol calculated from the mean specific activity of 0.86 mCi/nmol) by intravenous administration. Imaging for 1 h showed that the radioligand was eliminated from the body through gastrointestinal pathways; no radioactivity was observed in the bladder. Maximum radioactivity accumulation occurred within 1–2 min except in the pancreas and ductus choreolus, where the radioactivity accumulated for up to 50 min. In the brain, the highest radioactivity level was in the olfactory area, followed by the hippocampus, cortex, and striatum. The authors suggested that this distribution pattern appeared to match the brain mGluR5 densities in rats (7). The olfactory bulb/cerebellum ratio of radioactivity reached a maximum of 4.2 at 40 min. The radioactivity levels (n = 13) of the whole brain in percentage of injected dose per cubic centimeter (% ID/cc) obtained from volumetric region-of-interest image analysis were 0.187 ± 0.130 (5 min), 0.106 ± 0.070 (10 min), 0.072 ± 0.046 (20 min), 0.057 ± 0.034 (30 min), 0.049 ± 0.029 (40 min), 0.044 ± 0.025 (50 min), and 0.045 ± 0.029 (60 min). The radioactivity levels (% ID/cc) of the olfactory bulb were 0.390 ± 0.316 (5 min), 0.302 ± 0.246 (10 min), 0.244 ± 0.194 (20 min), 0.192 ± 0.145 (30 min), 0.163 ± 0.120 (40 min), 0.148 ± 0.109 (50 min), and 0.122 ± 0.103 (60 min). The [^{11}C]M-MPEP radioactivity level was reversible in all areas of the body. When a blocking dose of 10 mg/kg unlabeled MPEP was administered 5 min before the radioligand injection (79.18 ± 56.98 MBq (2.14 ± 1.54 mCi) in 0.52 ± 0.38 μg (~2.49 nmol calculated from the mean specific activity of 0.86 mCi/nmol)), the radioactivity levels (n = 8) of the olfactory lobe were decreased by 59.7% at 5 min and 29.4% at 40 min. In the other parts of the brain, MPEP decreased radioactivity levels of [^{11}C]M-MPEP in the early time points. The decrease was 28.9% in the whole brain, 44.8% in the cortex, 14.0% in the hippocampus, and 28.7% in the striatum at 5 min. At the later time points, the radioactivity levels of [^{11}C]M-MPEP

increased moderately. Outside the brain, MPEP decreased the [^{11}C]M-MPEP radioactivity level in the intestine at 10 min. The authors suggested that the effect of unlabeled MPEP administration was time- and dose-dependent.

In the *in vivo* metabolism study, [^{11}C]M-MPEP was shown by HPLC analysis to be rapidly metabolized after administration (1). The percentage of the radioligand remaining intact in the plasma after administration (n = 2) was 44.5 ± 0.8% at 5 min, 32.7 ± 5.9% at 10 min, and 21.4 ± 0.5% at 20 min. No lipophilic metabolite from [^{11}C]M-MPEP was found.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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