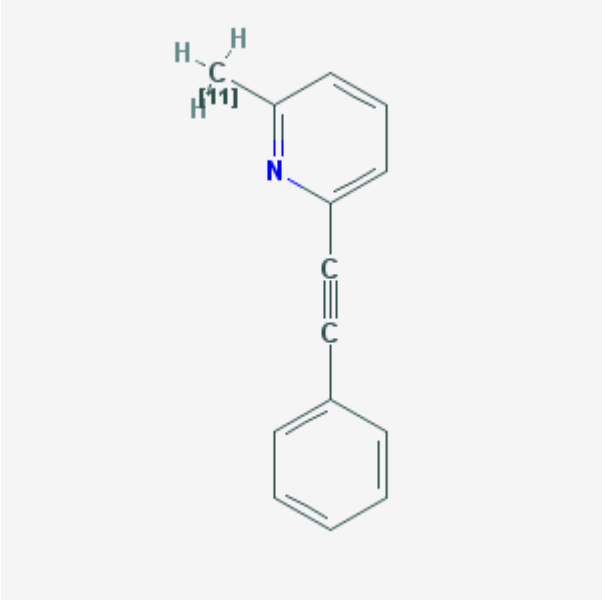
2-[^{11}C]Methyl-6-(2-phenylethynyl)pyridine

[^{11}C]MPEP

Kenneth T. Cheng, PhD[1]

Created: November 15, 2007; Updated: February 4, 2008.

Chemical name:	2-[^{11}C]Methyl-6-(2-phenylethynyl)pyridine
Abbreviated name:	[^{11}C]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:	^{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.

NLM Citation: Cheng KT. 2-[^{11}C]Methyl-6-(2-phenylethynyl)pyridine . 2007 Nov 15 [Updated 2008 Feb 4]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

2-[^{11}C]Methyl-6-(2-phenylethynyl)pyridine ([^{11}C]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 groups I, II, and III. 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 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 can be 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]MPEP and demonstrated the feasibility of using it as a PET imaging ligand for *in vivo* imaging.

Synthesis

[PubMed]

Yu et al. (1) reported the synthesis of [^{11}C]MPEP from its stannyl precursor. The precursor was prepared from 2-bromo-6-(phenylethynyl)pyridine. Briefly, phenylacetylene was added to a mixture of 2,6-dibromopyridine, CuI, $PdCl_2(PPh_3)_2$, and triethylamine. The mixture was stirred at room temperature for 27 h. The product was then filtered and purified on a silica gel column. The yield of 2-bromo-6-(phenylethynyl)pyridine was 42%. This was then reacted with tetrakis(triphenylphosphine)palladium(0) (Pd(0)) and toluene in a Chemglass cylindrical pressure vessel. A nitrogen stream was bubbled through the solution, and hexamethyldistannane was added. The pressure vessel was then capped and heated to 115–120°C for 6 h. After filtration on a silica gel column, the residue was stirred for 2 h with saturated aqueous sodium bicarbonate and 35% aqueous hydrogen peroxide to oxidize PPh_3 to PPh_3O for removal by column chromatography. The yield of the MPEP

precursor, 2-(trimethylstannyl)-6-(2-phenylethynyl)pyridine, was 51%. For the radiosynthesis, [^{11}C]carbon dioxide ([^{11}C]CO_2) was produced by the ^{14}N(p, α)^{11}C nuclear reaction in nitrogen, and [^{11}C]CO_2 was transformed to [^{11}C]methyl iodide ([^{11}C]CH_3I) for radiolabeling. The MPEP precursor was reacted with [^{11}C]CH_3I by the rapid Stille coupling reaction of aromatic stannanes. In this reaction, Pd(0) was used as the catalyst in toluene, and the reaction mixture was heated for 5 min at 100°C. The radiochemical purity was 97.4 ± 2.3% (n = 14), and the specific activity was 40.4 ± 5.0 GBq/μmol (1,093 ± 134 mCi/μmol). The radiochemical yield was 12.6 ± 10.6 mCi at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

No publication is currently available.

Animal Studies

Rodents

[PubMed]

PET imaging was performed in male rats (1). Each anesthetized rat received 92.91 ± 34.15 MBq (2.51 ± 0.92 mCi) in 0.433 ± 0.163 μg ((2–3 nM)/0.1 ml or 2.3 nmol calculated from the mean specific activity of 1.09 mCi/nmol) by i.v. administration. Imaging showed high and rapid radioactivity accumulation of [^{11}C]MPEP in brain areas, including the olfactory bulb, striatum, hippocampus, frontal cortex, and cerebellum. The maximum accumulation occurred in 2–3 min except in the olfactory bulb, where the radioactivity accumulated up to 10 min. The highest accumulation was in the olfactory area, followed by the hippocampus, cortex, and striatum. The radioactivity level ratio of olfactory bulb/cerebellum reached the maximum of 7.0 at 30 min. The radioactivity levels (n = 9) of the whole brain in percentage of the injected dose per cubic centimeter (% ID/cc) obtained from volumetric region-of-interest image analysis were 0.402 ± 0.066 (5 min), 0.223 ± 0.031 (10 min), 0.159 ± 0.018 (20 min), 0.128 ± 0.012 (30 min), 0.112 ± 0.009 (40 min), 0.096 ± 0.053 (50 min), and 0.094 ± 0.048 (60 min). The radioactivity levels (% ID/cc) of the olfactory bulb were 1.060 ± 0.182 (5 min), 1.110 ± 0.040 (10 min), 0.954 ± 0.032 (20 min), 0.821 ± 0.041 (30 min), 0.724 ± 0.058 (40 min), 0.616 ± 0.036 (50 min), and 0.568 ± 0.315 (60 min). When a blocking dose of 10 mg/kg unlabeled MPEP was administered 5 min before the radioligand injection (102.601 ± 18.06 MBq (2.77 ± 0.49 mCi) or 0.490 ± 0.079 μg (2.53 nmol calculated from the mean specific activity of 1.093 mCi/nmol)), the radioactivity levels (n = 4) of the olfactory lobe were decreased by 45.1% at 5 min and 61.5% at 40 min. High radioactivity levels were also observed in the liver, pancreas, and intestine. With the blocking dose of MPEP, the radioactivity levels (%ID/cc) of the duodenum (n = 2) decreased from 0.299 ± 0.083 to 0.131 ± 0.077 at 20 min and from 0.379 ± 0.074 to 0.079 ± 0.038 at 60 min. In another study that used a higher blocking

dose at an earlier time point (MPEP 20 mg/kg at 10 s before radioligand injection) in two rats, there was decreased accumulation in all brain areas until 40 min. The radioactivity level decreases in the olfactory area were 80.2 ± 14.5% and 80.0 ± 8.2% at 5 min and 40 min, respectively. In the striatal area, the decreases were 35.8 ± 20.5% and 16.5 ± 14.0% at 5 min and 40 min, respectively.

In the *in vivo* metabolism study, [^{11}C]MPEP was shown by high-performance liquid chromatography analysis to be rapidly metabolized after administration (1). The percentage of the radioligand remaining intact in the plasma after administration (n = 2) was 26.2 ± 6.2% at 5 min and 3.5 ± 2.6% at 20 min. No any lipophilic metabolite from [^{11}C]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.

NIH Support

NIH/NIBIB grant EB01850.

References

1. Yu M., Tueckmantel W., Wang X., Zhu A., Kozikowski A.P., Brownell A.L. Methoxyphenylethynyl, methoxypyridylethynyl and phenylethynyl derivatives of pyridine: synthesis, radiolabeling and evaluation of new PET ligands for metabotropic glutamate subtype 5 receptors. Nucl Med Biol. 2005;**32**(6):631–40. PubMed PMID: 16026710.
2. Pin J.P., Duvoisin R. The metabotropic glutamate receptors: structure and functions. Neuropharmacology. 1995;**34**(1):1–26. PubMed PMID: 7623957.
3. Slassi A., Isaac M., Edwards L., Minidis A., Wensbo D., Mattsson J., Nilsson K., Raboisson P., McLeod D., Stormann T.M., Hammerland L.G., Johnson E. Recent advances in non-competitive mGlu5 receptor antagonists and their potential therapeutic applications. Curr Top Med Chem. 2005;**5**(9):897–911. PubMed PMID: 16178734.

4. Ametamey S.M., Kessler L.J., Honer M., Wyss M.T., Buck A., Hintermann S., Auberson Y.P., Gasparini F., Schubiger P.A. Radiosynthesis and Preclinical Evaluation of 11C-ABP688 as a Probe for Imaging the Metabotropic Glutamate Receptor Subtype 5. J Nucl Med. 2006;**47**(4):698–705. PubMed PMID: 16595505.
5. Patel S., Ndubizu O., Hamill T., Chaudhary A., Burns H.D., Hargreaves R., Gibson R.E. Screening cascade and development of potential Positron Emission Tomography radiotracers for mGluR5: in vitro and in vivo characterization. Mol Imaging Biol. 2005;**7**(4):314–23. PubMed PMID: 16080024.
6. Gasparini F., Andres H., Flor P.J., Heinrich M., Inderbitzin W., Lingenhohl K., Muller H., Munk V.C., Omilusik K., Stierlin C., Stoehr N., Vranesic I., Kuhn R. [(3)H]-M-MPEP, a potent, subtype-selective radioligand for the metabotropic glutamate receptor subtype 5. Bioorg Med Chem Lett. 2002;**12**(3):407–9. PubMed PMID: 11814808.