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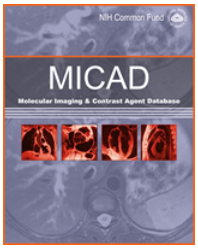

3-(6-Methyl-pyridin-2-ylethynyl)-cyclohex-2-enone-*O*-^{11}C-methyl-oxime

[^{11}C]ABP688

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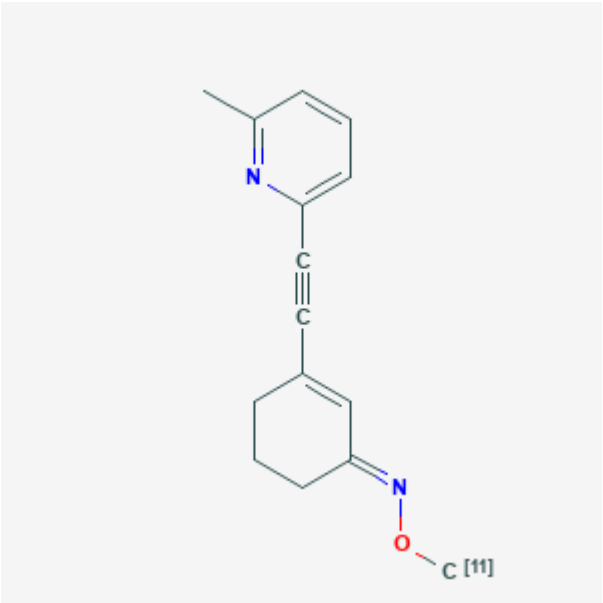
Chemical name:	3-(6-Methyl-pyridin-2-ylethynyl)-cyclohex-2-enone-*O*-^{11}C-methyl-oxime
Abbreviated name:	[^{11}C]ABP688
Synonym:	
Agent Category:	Compound
Target:	Metabotropic glutamate receptor subtype 5 (mGlu5)
Target Category:	Receptor binding
Method of detection:	Positron emission tomography (PET)
Source of signal/ contrast:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

3-(6-Methyl-pyridin-2-ylethynyl)-cyclohex-2-enone-*O*-^{11}C-methyl-oxime ([^{11}C]ABP688) is a radioligand developed for positron emission tomography (PET) imaging of metabotropic glutamate receptor subtype 5 (mGlu5) in the central nervous system (CNS) (1).

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 metabotropic glutamate (mGlu) receptors (3). The mGlu receptors are G-protein-

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coupled receptors, and there are eight mGlu receptor subtypes that are further subdivided into groups I, II, and III. The group I receptors include mGlu1 and mGlu5, and they are mostly in postsynaptic locations. The mGlu5 receptors 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 down-regulate 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. They thus are attractive targets for therapeutic drug development.

PET and single-photon emission tomography of radioligands targeting mGlu5 receptors can visualize and study the CNS mGlu5 receptors in normal and pathologic states. Some mGlu5 antagonists have been successfully labeled, but their in *vivo* visualization has been hampered by high lipophilicity, unfavorable brain uptake kinetics, or a high metabolism (1, 4). 2-Methyl-6-(phenylethynyl)-pyridine (MPEP) and its methyl analog M-MPEP have been identified as potent and highly selective noncompetitive antagonists for mGlu5. With MPEP used as a template, [^{11}C]ABP688 was synthesized and developed as a potential PET agent without shortcomings similar to those for other agents (1).

Synthesis

[PubMed]

Kessler (5) designed a four-step reaction sequence for the synthesis of desmethyl-ABP688 as a precursor of [^{11}C]ABP688 radiosynthesis. ABP688 was labeled with ^{11}C by reaction of the sodium salt of desmethyl-ABP688 in anhydrous dimethylformamide with [^{11}C]methyl iodide at 90 °C for 5 min (1). The product was purified by semipreparative high-performance liquid chromatography (HPLC). The prepared [^{11}C]ABP688 was >95% radiochemically pure, the radiochemical yield was 35 ± 8%, and the specific activity was 100-200 GBq (2.7-8.1 Ci)/μmol. The total synthesis time was reported to be 45-50 min. ^{13}C-Nuclear magnetic resonance (NMR) gave a peak signal for the O-methyl C atom at 61.5 ppm. Mass spectrometry indicated that the molecular ion peak ($[M + 1]^+$) was at *m/z* 242. NMR data showed an *E*/*Z* isomeric ratio of at least 6:1. The *E*-isomer was the most potent isomer and could be consistently obtained as the major component (>10:1) when the desmethyl-ABP688 sodium salt was preheated to 90 °C and [^{11}C]methyl iodide was then added at that temperature.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The distribution coefficient (Log D) of [^{11}C]ABP688, as determined by Ametamey et al. (1), was 2.4 ± 0.1 (n = 3). [^{11}C]ABP688 was stable in human plasma *in vitro* at 37 °C for at least 60 min. *In vitro* binding of [^{11}C]ABP688 was studied in rat brain tissue membranes. Saturation studies indicated that the receptor binding was saturable, and the Scatchard plot indicated a single high-affinity binding site with a K_D of 1.7 ± 0.2 nM (n = 3). The B_{max} was 231 ± 18 fmol/mg of protein. *Ex vivo* autoradiography of rat brain showed that the brain uptake of [^{11}C]ABP688 was highly selective, with high radioactivity concentrations in known mGlu5-rich regions and negligible radioactivity in mGlu5-poor regions. Autoradiography in wild-type (wt) mice showed a similar specific brain uptake of [^{11}C]ABP688. Studies in mGlu5-knockout (ko) mice showed homogeneous and markedly reduced accumulation of radioactivity throughout the brain.

Animal Studies

Rodents

[PubMed]

Ametamey et al. (1) performed biodistribution studies of [^{11}C]ABP688 in rats. The rats received doses of 50-450 MBq (1.4-12.2 mCi) in 0.4-3.5 nM and were decapitated 30 min after injection. The kidney and liver had the highest radioactivity localization, with 0.2 and 0.18% of injected dose normalized to body weight (% ID norm/g), respectively. The lung, blood, muscle, and bone had <0.1% ID norm/g. In the brain, relatively high amounts of radioactivity were found in mGlu5-rich regions such as the hippocampus, striatum, and cortex, whereas relatively low amounts of radioactivity were found in mGlu5-poor regions (cerebellum). The striatum/cerebellum, hippocampus/cerebellum, and cortex/cerebellum ratios (n = 3) were 6.6 ± 0.1, 5.4 ± 0.1, and 4.6 ± 0.1, respectively. In a blocking experiment in which 1.0 mg/kg M-MPEP (mGlu5 antagonist) was injected together with [^{11}C]ABP688, up to 80% of radioactivity uptake was blocked in the hippocampus and striatum. No blocking effects were found in the cerebellum. Under blocking conditions, the liver showed an increase in radioactivity uptake. No blocking effects were observed in all other peripheral organs. HPLC analysis of whole-brain extracts showed that >95% of [^{11}C]ABP688 remained unchanged 30 min after injection. About 75% of the radioactivity in the blood and 95% of the radioactivity in the urine was radiolabeled polar metabolites that could not cross the blood-brain barrier. Brain PET imaging (90 min) was performed on rats that had received doses of 18-22 MBq (0.49-0.59 mCi) in 1-3 nmol. Images showed specific radioactivity localization in mGlu5-rich regions such as the caudate putamen and hippocampus. This localization was inhibited by coadministration of M-MPEP.

Similar biodistribution studies in wt and ko mice were performed by Ametamey et al. (1). The mice received doses of 50-350 MBq (1.4-9.5 mCi) in 0.5-2.5 nM and were decapitated 20 min after administration. Brain radioactivity distribution patterns in mGlu5-rich regions in wt mice were similar to those in the rat brain, whereas localization of radioactivity in all of the brain regions was significantly less in the ko mice. Brain PET imaging was performed in mice that received doses of 18-22 MBq (0.49-0.59 mCi) in 1-3 nmol. Brain images from wt mice showed localization of radioactivity similar to that in the rats, with the highest amounts of radioactivity in the striatum and hippocampus. Radioactivity ratios for the hippocampus/cerebellum and striatum/cerebellum were >2. The ko mice showed homogeneous distribution of radioactivity throughout the brain.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Put non-human primates here.

Human Studies

[PubMed]

No publication is currently available.

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