Dimethylamino-3(4-[^{11}C]methoxyphenyl)-3*H*-pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4-one

[^{11}C]MMTP

Kam Leung, PhD[1]

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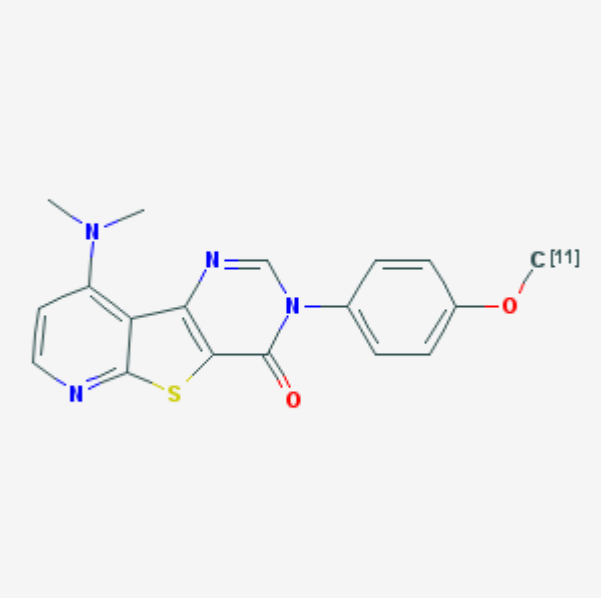
Chemical name:	Dimethylamino-3(4-[^{11}C]methoxyphenyl)-3*H*-pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4-one
Abbreviated name:	[^{11}C]MMTP, [^{11}C]1
Synonym:	
Agent category:	Compound
Target:	Metabotropic glutamate receptor subtype 1 (mGluR1)
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Non-human primates



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

Corresponding author.

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Background

[PubMed]

Glutamate is a major excitatory neurotransmitter at neuronal synapses in the central nervous system (CNS) (1, 2). Glutamate produces its excitatory effects by acting on cell-surface ionotropic glutamate or metabotropic glutamate receptors (mGluRs). The mGluRs are GTP-binding protein (G-protein)–coupled receptors that play important roles in regulating the activity of many synapses in the CNS, and many neuronal projection pathways contain mGluRs. There are eight mGluR subtypes, which 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 mGluR1 is found in moderate to high density in the cerebellum, caudate, putamen, thalamus, cingulate cortex, and hippocampus, with low density in the pons. The mGluR5 is usually found in moderate to high density in the frontal cortex, caudate, putamen, nucleus accumbens, olfactory tubercle, and hippocampus, whereas the density in the cerebellum is low. The mGluR1 and mGluR5 are positively coupled to phospholipase C in the regulation of neuronal excitability (3). Dysfunction of mGluR1 and mGluR5 is implicated in a variety of diseases in the CNS, including anxiety, depression, schizophrenia, Parkinson's disease, and drug addiction or withdrawal (2, 4).

Positron emission tomography (PET) and single-photon emission tomography of radioligands targeting the mGluR1 can visualize and analyze mGluR1 expression in normal physiological and pathological conditions. Several radioligands have been studied for *in vivo* imaging of the mGluR1 in the brain (5). Dimethylamino-3(4-methoxyphenyl)-3*H*-pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4-one (MMTP) was shown to be selective for the mGluR1, with nanomolar affinity (K_i = 7.9 nM), and exhibited little inhibition of the mGluR5. Prabhakaran et al. (6) prepared and evaluated dimethylamino-3(4-[^{11}C]methoxyphenyl)-3*H*-pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4-one ([^{11}C]MMTP) for use with *in vivo* PET imaging of mGluR1 distribution in the brain of baboons.

Related Resource Links:

- Chapters in MICAD (mGluR1, mGluR5)
- Gene information in NCBI (mGluR1, mGluR5)
- Articles in Online Mendelian Inheritance in Man (OMIM) (mGluR1, mGluR5)
- Clinical trials (mGluR1, mGluR5)

Synthesis

[PubMed]

Prabhakaran et al. (6) synthesized [^{11}C]MMTP by *O*-methylation of the desmethyl precursor dimethylamino-3(4-hydroxyphenyl)-3*H*-pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4-one with [^{11}C]methyl trifluoromethanesulfonate (MeOTf) at 25°C for 5

min. Subsequent separation with high-performance liquid chromatography produced a radiochemical purity >99%. The radiochemical yield was 30% based on [^{11}C]MeOTf, and specific activity was 111–185 GBq/μmol (3–5 Ci/μmol; $n = 6$) at the end of synthesis. The total synthesis time was not reported. [^{11}C]MMTP exhibited a log P value of 3.15.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro [^{11}C]MMTP (12 nM) autoradiographic imaging studies were performed on postmortem human brain sections ($n = 4$/group) (6). JNJ-16259685 (a selective mGluR1 antagonist, 10 μM) was used to determine non-specific binding. [^{11}C]MMTP bound heterogeneously to the brain sections, with the highest accumulation of radioactivity in the mGluR1-rich cerebellum ($B_{max} = 140 \pm 20$ fmol/cm^2), followed by the hippocampus ($B_{max} = 110 \pm 25$ fmol/cm^2), frontal cortex ($B_{max} = 85$ fmol/cm^2), and striatum ($B_{max} = 20$ fmol/cm^2). JNJ-16259685 completely blocked radioactive signals to background levels in these brain regions.

Animal Studies

Rodents

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Prabhakaran et al. (6) performed dynamic PET imaging studies for 90 min in baboons (number of animals studied not reported) after intravenous injection of 175 MBq (5 mCi, 2 nmol) [^{11}C]MMTP. Baseline tissue time-activity curves revealed a high accumulation of radioactivity in the cerebellum. However, the caudate, amygdala, putamen, hippocampus, and frontal cortex exhibited lower radioactivity levels and faster washout than the cerebellum. The radioactivity levels of these brain regions were similar. The ratios of cerebellum to most of the other brain regions were 2.0, 1.7, and 1.6 at 35, 65, and 85 min after injection, respectively. [^{11}C]MMTP remained 45% and 30% intact in the plasma at 30 min and 90 min, respectively. No blocking studies were performed.

Human Studies

[PubMed]

No publication is currently available.

NIH Support

R21 MH081801

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