[*O*-methyl-^{11}C]2-{4-[4-(7-Methoxynaphthalen-1-yl)piperazin-1-yl]butyl}-4-methyl-2*H*-[1,2,4]triazine-3,5-dione

[^{11}C]MPT

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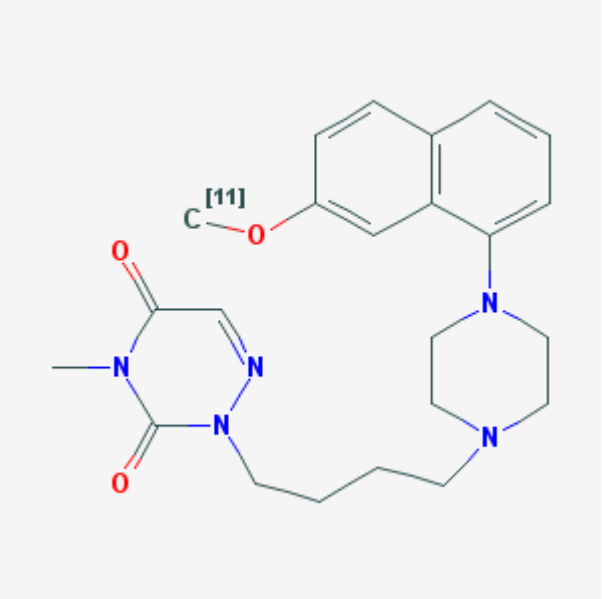
Chemical name:	[*O*-methyl-^{11}C]2-{4-[4-(7-Methoxynaphthalen-1-yl)piperazin-1-yl]butyl}-4-methyl-2*H*-[1,2,4]triazine-3,5-dione
Abbreviated name:	[^{11}C]MPT
Synonym:	[^{11}C]F1146
Agent Category:	Compound
Target:	5-HT$_{1A}$ serotonin receptors
Target Category:	Receptor binding
Method of detection:	Positron Emission Tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Non-human primates



Click on the above structure for additional information in PubChem.

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Background

[PubMed]

[*O*-methyl-^{11}C]2-{4-[4-(7-Methoxynaphthalen-1-yl)piperazin-1-yl]butyl}-4-methyl-2*H*-[1,2,4]triazine-3,5-dione ([^{11}C]MPT) is a radioligand developed for positron emission tomography (PET) imaging of serotonin-1A (5-hydroxytryptamine 1A (5-HT$_{1A}$)) receptors in the central nervous system (1). It is a selective 5-HT$_{1A}$ agonist labeled with ^{11}C, a positron emitter with a physical half-life ($t_{½}$) of 20.4 min (1, 2).

The 5-HT neurotransmission system comprises mainly neurons in the brainstem, with nerve tracts extending from these neurons to many areas of the brain and spinal cord (3). 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 (4). There are five receptor subtypes within the G-protein–coupled 5-HT$_1$ receptor family, with the 5-HT$_{1A}$ subtype located primarily in the limbic forebrain (the hippocampus, entorhinal cortex ,septum, and raphe) (4, 5). 5-HT$_{1A}$ receptors appear to function both as presynaptic (somatodendritic) autoreceptors in the raphe nuclei and as postsynaptic receptors in the terminal fields. This receptor subtype is involved in the modulation of emotion and the function of the hypothalamus, and it is implicated in the pathogenesis of anxiety, depression, hallucinogenic behavior, motion sickness, dementia, schizophrenia, and eating disorders (6). A radioligand that can be used to assess the *in vivo* densities of 5-HT$_{1A}$ receptors and their changes may facilitate investigation of the relationship of these receptors to various neuropsychiatric diseases and aid in the design of novel drugs for their treatment.

Many psychiatric drugs modulate serotonergic transmission or specifically target the 5-HT$_{1A}$ receptors (2). Various compounds have been radiolabeled for visualization and quantification of these receptors (7). 5-HT$_{1A}$ receptors appear to exist in the high (HA) and low (LA) agonist affinity states. Antagonist ligands bind to both the HA and LA conformations, whereas agonist ligands bind to the HA state, which is coupled to G-protein. WAY 100635 was developed as a highly selective, silent antagonist (possessing no intrinsic agonist activity) of 5-HT$_{1A}$ receptors at both pre- and postsynaptic sites. WAY 100635 radiolabeled with ^{11}C at the carbonyl position is an effective radioligand but it is rapidly cleared and metabolized. Analogs of WAY 100635 that bear bulkier cycloalkylcarbonyl groups appear to be more resistant to amide hydrolysis. However, the added lipophilicity also reduces receptor affinity (8). Although 5-HT$_{1A}$ receptor agonist ligands can elicit pharmacologic effects, there are some distinct potential applications of

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radiolabeled 5-HT$_{1A}$ receptor agonist ligands because they behave like serotonin, which binds preferentially to the HA sites (1, 9). Kumar et al. (1) selected MPT for development as a radiolabeled 5-HT$_{1A}$ receptor agonist probe because of its high affinity (pK_i = 10.49) and favorable calculated lipophilicity (clog$P$ = 1.8) (10, 11)

Synthesis

[PubMed]

Kumar et al. (1) designed the synthesis of MPT in five steps from the starting material of commercially available 6-azauracil. Briefly, 6-azauracil was selectively acetylated at the 2-position by refluxing in acetic anhydride. The resulting product was methylated at the 4-position by sodium hydride in *N*,*N*-dimethylformamide (DMF) and methyl iodide followed by treatment with catalytic *p*-TsOH in refluxing ethanol. This methylated compound was alkylated with 1-bromo-4-chlorobutane in DMF and sodium hydride to produce 2-(4-chlorobutyl)-4-methyl-2*H*-[1,2,4]triazine-3,5-dione. This compound was used to prepare the precursors for MPT and [^{11}C]MPT. To prepare the radiolabeling precursor, 8-aminonaphthalen-2-ol and bis-(2-chloroethyl)amine in poly(ethylene glycol) were reacted in microwave conditions to yield 8-piperazin-1-ylnaphthalen-2-ol. This was coupled with 2-(4-chlorobutyl)-4-methyl-2*H*-[1,2,4]triazine-3,5-dione to yield the desmethyl precursor 2-{4-[4-(7-hydroxynaphthalen-1-yl)piperazin-1-yl]butyl}-4-methyl-2*H*-[1,2,4]triazine-3,5-dione, which was used for radiolabeling. This precursor was treated with [^{11}C]CH_3OTf in acetone in the presence of 10 µl of 5 M sodium hydroxide at room temperature. The radiolabeled MPT was purified by high-performance liquid chromatography (HPLC) and passed through a C-18 Sep-Pak cartridge. The radiochemical yield at the end of synthesis was 25 ± 5% (n = 15), and the chemical and radiochemical purities were >99%. The specific activity of [^{11}C]MPT was 55.5 ± 11.1 TBq/mmol (1,500 ± 300 Ci/mmol; n = 10) at the end of bombardment (EOB). The average time of labeling was 30 min from the time of EOB.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The partition coefficient (logP_{OCT}) of [^{11}C]MPT was determined to be 2.2 by the standard shake-flask method by mixing the radioligand in 1-octanol and phosphate-buffered saline (pH 7.4) (1). The inhibitory constant value (K_i) of unlabeled MPT for 5-HT$_{1A}$ was found to be 1.36 ± 0.16 nM by use of the competition binding studies with [^{3}H]8-OH-DPAT (5-HT$_{1A}$ receptor agonist) in membrane fractions from Chinese hamster ovary (CHO) cells that had a density of 8 pmol/mg 5-HT$_{1A}$ receptors. The K_i of MPT for other 5-HT receptor subtypes (5-HT$_{2A}$ to 5-HT$_7$) ranged from 9.1 (5-HT$_7$) to >10,000 nM (5-HT$_3$). In comparison, serotonin had a K_i value of 1.58 nM for the 5-HT$_{1A}$ receptors. An *in vitro* agonist-stimulated [^{35}S]GTPγS binding assay indicated that MPT was a 5-HT$_{1A}$ receptor agonist with an affinity greater than that of endogenous serotonin. The EC$_{50}$ values of MPT and serotonin were determined to be 0.05 nM and 0.5 nM,

respectively. In the inhibition assay of forskolin-stimulated cAMP accumulation, the EC_{50} values of MPT and serotonin were 0.01 nM and 1 nM, respectively.

Animal Studies

Rodents

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Kumar et al. (1) evaluated the *in vivo* properties of [^{11}C]MPT in baboons. For each study, a single male baboon received an i.v. dose of 185 ± 18.5 MBq (5 ± 0.5 mCi) for PET imaging studies. The PET imaging showed that [^{11}C]MPT rapidly penetrated the blood–brain barrier and accumulated in brain regions known to have high densities of 5-HT_{1A} receptors. The cerebellum had the lowest radioactivity level of [^{11}C]MPT. There was a high correlation between the volume of distribution (V_T) of [^{11}C]WAY 100635 and the V_T of [^{11}C]MPT. When 0.5 mg/kg unlabeled WAY 100635 or 2 mg/kg 8-OH-DPAT was given 20 min before [^{11}C]MPT administration, the radioactivity levels in all brain regions were reduced to the same level as the cerebellar reference region. Blocking studies with a 5-HT_{2A} antagonist and a dopamine antagonist showed that [^{11}C]MPT did not have significant affinity for 5-HT_{2A} or dopamine receptors.

HPLC analysis of [^{11}C]MPT metabolite in baboons indicated that [^{11}C]MPT underwent fast metabolism, and the percentages (n = 15) of unchanged [^{11}C]MPT in the total plasma radioactivity were 90 ± 2% (2 min), 87 ± 3% (4 min), 65 ± 5% (12 min), 30 ± 5% (30 min), 20 ± 3% (60 min), and 12 ± 3% (90 min) (1). Only polar metabolites were discovered in the plasma samples.

Human Studies

PubMed]

No publication is currently available.

NIH Support

NIH P50 MH62185.

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