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

[^{11}C]MMP (CUMI-101)

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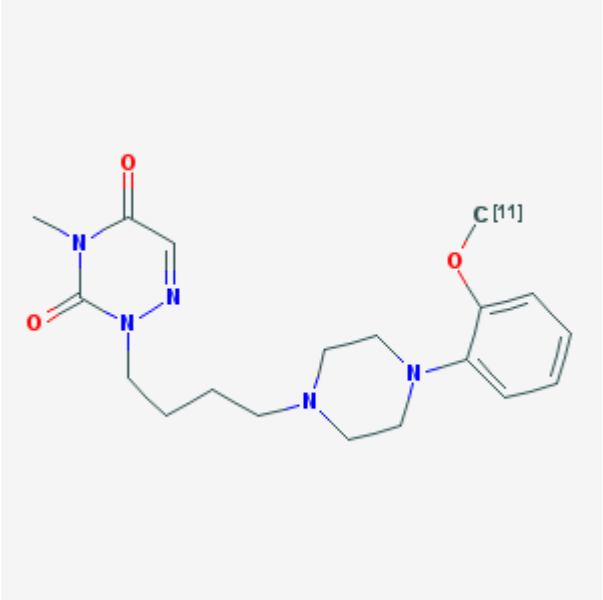
Created: September 4, 2007; Updated: June 20, 2012.

Chemical name:	[O-*methyl*-^{11}C]2-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-4-methyl-1,2,4-triazine-3,5(2*H*,4*H*)dione
Abbreviated name:	[^{11}C]MMP
Synonym:	[^{11}C]CUMI-101
Agent category:	Compound
Target:	5-HT$_{1A}$ serotonin receptor
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Non-human primates • Humans



Click on the above structure for additional information in PubChem.

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NLM Citation: Leung K. [O-*methyl*-^{11}C]2-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-4-methyl-1,2,4-triazine-3,5(2*H*,4*H*)dione. 2007 Sep 4 [Updated 2012 Jun 20]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

Background

[PubMed]

Hydroxytryptamine (5-HT), commonly known as serotonin, has diverse physiological roles as a neurotransmitter in the central nervous system (1). 5-HT is involved in regulation and modulation of sleep, affective and personality behaviors, and pain. It also is a regulator of smooth muscle function and platelet aggregation. The brain cortical 5-HT system has been implicated in several neuropsychiatric disorders, including major depression, anxiety, schizophrenia, and obsessive-compulsive disorder (2, 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 include several subtypes (4). There are five receptor subtypes within the G-protein–coupled 5-HT_1 receptor family: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F}.

5-HT_{1A} receptors are abundantly present in the hippocampus, entorhinal cortex, frontal cortex, raphe nucleus, and septum; the lowest densities are observed in the basal ganglia, substantia nigra, and cerebellum (5). Some thalamic and hypothalamic nuclei have intermediate densities. 5-HT_{1A} receptors are involved in the mediation of emotion and the function of the hypothalamus. 5-HT_{1A} receptors are implicated in anxiety, depression, hallucinogenic behavior, motion sickness, and eating disorders (6). Thus, there is a need for selective ligands to investigate the pharmacological role of 5-HT_{1A} receptors.

There have been several studies to develop specific 5-HT_{1A} radioligands [PubMed] such as [*carbonyl*-^{11}C]WAY 100635, [^{18}F]FPWAY, and [^{18}F]MPPF for positron emission tomography (PET) imaging. However, none of these antagonists distinguishes between the high- and low-affinity states of the 5-HT_{1A} receptors. The high-affinity state of the receptor is coupled to G-proteins, which mediate the functions of cells by providing intracellular signals. 2-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-4-methyl-1,2,4-triazine-3,5(2*H*,4*H*)dione (MMP) was reported to be a potent agonist of 5-HT_{1A} receptors (K_i = 0.15 nM) (7). This led to the development of [O-*methyl*-^{11}C]2-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-4-methyl-1,2,4-triazine-3,5(2*H*,4*H*)dione ([^{11}C]MMP, also known as [^{11}C]CUMI-101) as a useful tool for *in vivo* PET imaging of the 5-HT_{1A} receptor.

Related Resource Links:

- Chapters in MICAD (5-HT_{1A})
- Gene information in NCBI (5-HT_{1A})
- Articles in Online Mendelian Inheritance in Man (OMIM) (5-HT_{1A})
- Clinical trials (5-HT_{1A})
- Drug information in Food and Drug Administration (5-HT_{1A})

Synthesis

[PubMed]

The radiosynthesis of [^{11}C]MMP, reported by Kumar et al. (7), involved standard ^{11}C-methylation of the corresponding desmethyl precursor 2-(4-(4-(2-hydroxyphenyl)piperazin-1-yl)butyl)-4-methyl-1,2,4-triazine-3,5-(2*H*,4*H*)-dione with [^{11}C]CH_3OTf in acetone in the presence of NaOH. The reported overall radiochemical yield of the radiosynthesis was 30 ± 5% at the end of synthesis (EOS), the specific radioactivity was 96 ± 19 TBq/mmol (2,600 ± 500 Ci/mmol), and the radiochemical purity was >98%. The total synthesis time was 30 min at EOS.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Kumar et al. (7) performed *in vitro* competition binding studies with [^{3}H]8-OH-DPAT in bovine hippocampus membranes. MMP had a K_i of 0.15 ± 0.05 nM. The affinity of MMP for various biogenic amines, brain receptors, and transporters was determined to be >45 times lower than that of MMP. Agonist properties of MMP on 5-HT_{1A} receptors were evaluated using [^{35}S]-labeled guanosine gamma thio-phosphate ([^{35}S]GTPγS) binding in membranes of Chinese hamster ovary (CHO) cells stably expressing the human 5-HT_{1A} receptors. MMP produced a dose-dependent increase in [^{35}S]GTPγS binding. Maximal MMP-stimulated [^{35}S]GTPγS binding was 80% of that seen with 5-HT. The maximum binding fraction for MMP (0.10 nM) was comparable to that for 5-HT (0.56 nM). There was a measurable free fraction of [^{11}C]MMP in baboon (59%) and human (37%) plasma.

Animal Studies

Rodents

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

PET imaging was used to study radioactivity accumulation in baboon brains after intravenous injection of 185 MBq (5 mCi) of [^{11}C]MMP (7). Various brain regions exhibited rapid accumulation in 3–13 min with gradual decreases thereafter. [^{11}C]MMP PET images (up to 120 min after injection) displayed radioactivity concentrations (tissue/cerebellum ratio) that followed a rank order: the hippocampus (6.25), insular cortex (5.25) cingulate gyrus (4.75), prefrontal cortex (4.0), amygdala (3.75), raphe nucleus (3.0),

thalamus (2.0), and cerebellum (1.0) at 105 min. Pretreatment with the antagonist WAY 100635 (0.25 mg/kg) or the agonist 8-OH-DPAT (2 mg/kg) 30 min prior to the injection of [^{11}C]MMP markedly reduced the radioactivity by ~70% in the hippocampus, cingulate gyrus and prefrontal cortex. There was a minor blockade effect in the cerebellum. After injection of [^{11}C]MMP, 84%, 43%, 32%, and 24% of the total plasma radioactivity was intact at 4, 30, 60, and 90 min, respectively. Only hydrophilic metabolites were detected.

Milak et al. (8) performed [^{11}C]CUMI-101PET scans in the brain of two male baboons. Scanning time of 100 min was adequate and that for the region-of-interest analysis, the likelihood estimation in graphical analysis (LEGA) model provided the best results. The median test–retest percentage difference for binding potential (BP_F) was 11.15% ± 4.82% across all regions. Pre-administration of WAY100635 and 8-OH-DPAT resulted in 87% and 76% average reductions in BP_F values across all regions of interests, respectively. All metabolites were more polar than ^{11}C-CUMI-101, and no significant change in metabolites was observed in the blocking studies. The free fraction in the plasma was 59% ± 3%.

Human Studies

[PubMed]

Milak et al. (9) performed [^{11}C]CUMI-101 PET brain scans of seven human volunteers. Scanning time of 120 min was found to be adequate for the region-of-interest analysis. The LEGA model provided the best results with the median test–retest percentage difference for BP_F values was 9.9% ± 5.6% across all regions. The free fraction in the plasma was 30% ± 3%. The BP_F values for entorhinal cortex, hippocampus, temporal lobe, amygdala, insular cortex, cingulate, prefrontal cortex, raphe, and occipital lobe were 32.62, 31.66, 28.61, 25.50, 21.20, 18.48, 13.69, 12.42, and 9.70 mL/cm^3, respectively.

Hines et al. (10) performed PET imaging studies to determine biodistribution and dosimetry of 428 ± 84 MBq (11.56 ± 2.27 mCi, 5.0 ± 1.0 nmol) [^{11}C]CUMI-101 in nine healthy volunteers. The brain had high accumulation (~11% of injected dose (ID)) at 10 min. Although liver had the highest uptake (~35% ID at 120 min), excretion of radioactivity was not visible in gall bladder or intestine during the scanning session. Organs with the highest radiation doses were the pancreas (32.0 μSv/MBq, 118.4 mrem/mCi), liver (18.4 μSv/MBq, 68.1 mrem/mCi), and spleen (14.5 μSv/MBq, 53.7 mrem/mCi). The effective dose for ^{11}C-CUMI-101 was 5.3 ± 0.5 μSv/MBq (19.5 ± 2.2 mrem/mCi).

NIH Support

P50 MH62185, R21 MH077161, K08 MH76258, MH62185,

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