N-(4-(6-(Isopropylamino)pyrimidin-4-yl)-1,3-thiazol-2-yl)-4-[^{11}C]methoxy-*N*-methylbenzamide

[^{11}C]ITMM

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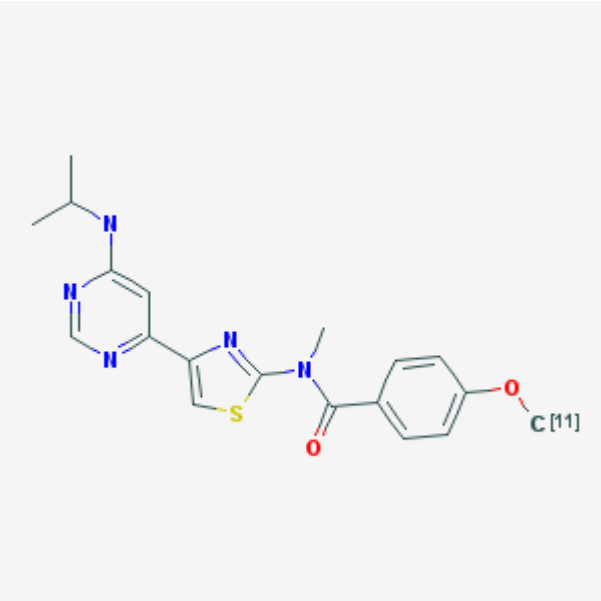
Chemical name:	*N*-(4-(6-(Isopropylamino)pyrimidin-4-yl)-1,3-thiazol-2-yl)-4-[^{11}C]methoxy-*N*-methylbenzamide
Abbreviated name:	[^{11}C]ITMM, [^{11}C]6
Synonym:	
Agent category:	Compound
Target:	Metabotropic glutamate receptor subtype 1 (mGluR1)
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Humans



Click on the above structure for additional information in PubChem.

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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 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. mGluR1 is found in moderate to high density in the cerebellum, caudate, putamen, thalamus, cingulate cortex, and hippocampus, with low density in the pons. mGluR5 is usually found in moderate to high density in the frontal cortex, caudate, putamen, nucleus accumbens, olfactory tubercle, and hippocampus, with low density in the cerebellum. 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) radioligands targeting mGluR5 can visualize and analyze mGluR5 expression in normal physiological and pathological conditions (4-8). However, only a few mGluR1 ligands have been studied. *N*-(4-(6-(Isopropylamino)pyrimidin-4-yl)-1,3-thiazol-2-yl)-4-methoxy-*N*-methylbenzamide (ITMM) was shown to be a selective mGluR1 antagonist with nanomolar affinity (K_i = 12.6 nM), with little inhibition of mGluR5. Fujinaga et al. (9) labeled ITMM with ^{11}C to prepare *N*-(4-(6-(isopropylamino)pyrimidin-4-yl)-1,3-thiazol-2-yl)-4-[^{11}C]methoxy-*N*-methylbenzamide ([^{11}C]ITMM) for use with *in vivo* PET imaging of mGluR1 distribution in rat brains. Toyohara et al. (10) evaluated [^{11}C]ITMM in mouse and human brains. [^{11}C]ITMM was shown to be a suitable PET radioligand for mapping mGluR1 in the human brain.

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]

Fujinaga et al. (9) synthesized [^{11}C]ITMM by methylation of the hydroxyl precursor with [^{11}C]MeI (prepared with [^{11}C]CO_2) for 5 min at 70°C. Subsequent separation with high-

performance liquid chromatography (HPLC) produced a radiochemical purity >99%. Average radiochemical yield was 22 ± 5% (n = 21) based on [^{11}C]CO_2. The specific activity of [^{11}C]ITMM was 95–140 GBq/μmol (2.56–3.78 Ci/μmol) at the end of synthesis (EOS). The total synthesis time was 25 ± 3 min from the end of bombardment (EOB). For higher specific activity, [^{11}C]ITMM was prepared *via* methylation of the hydroxyl precursor with [^{11}C]MeI (prepared with [^{11}C]CH_4) for 5 min at 70°C. Average radiochemical yield was 6 ± 1% (n = 3) based on [^{11}C]CH_4. The specific activity of [^{11}C]ITMM was 4,370–7,840 GBq/μmol (118–212 Ci/μmol) at EOS. The total synthesis time was 29 ± 1 min.

Toyohara et al. (10) prepared [^{11}C]ITMM by methylation of the hydroxyl precursor with [^{11}C]methyl triflate under NaOH as a base using an automated synthesizer for 1 min at room temperature. Subsequent separation with HPLC produced a radiochemical purity >98%. Average radiochemical yield was 66.0 ± 27.4% (n = 4) based on [^{11}C]methyl triflate. The specific activity of [^{11}C]ITMM was 97.9–351.1 GBq/μmol (2.64–9.49 Ci/μmol) at EOS. The total synthesis time was <25 min from the EOB.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro binding affinity of ITMM was determined with rat brain homogenates using [^{18}F]fluoro-*N*-[4-[6-(isopropylamino)pyrimidin-4-yl]-1,3-thiazol-2-yl]-*N*-methylbenzamide ([^{18}F]FITM) as the mGluR1 radioligand (9). The K_i values were 12.6 ± 1.2 nM and 5.4 ± 1.2 nM for ITMM and FITM, respectively. Both agents showed IC_{50} values >10,000 nM for mGluR5. ITMM (LogD 2.57) was found to be more lipophilic than FITM (LogD 1.45).

In vitro [^{11}C]ITMM autoradiographic imaging studies were performed on rat brain sections (9). [^{11}C]ITMM bound heterogeneously to the brain sections, with the highest accumulation of radioactivity in the mGluR1-rich cerebellum, followed by the thalamus and striatum, with the lowest radioactivity in the pons. JNJ-16259685 (1,000 nM), another mGluR1 antagonist, blocked radioactivity signals by >70% in the cerebellum, thalamus, and striatum.

Animal Studies

Rodents

[PubMed]

Fujinaga et al. (9) performed *ex vivo* biodistribution studies in mice (n = 4/group) at 1–60 min after intravenous injection of 4.8 MBq (0.13 mCi) [^{11}C]ITMM (0.04 nmol). The radioactivity levels in most tissues were highest at 1–5 min and decreased gradually thereafter. The highest accumulation at 5 min was observed in the liver (8.34% injected dose/gram (ID/g)), followed by the kidney (5.64% ID/g), small intestine (4.55% ID/g),

brain (3.21% ID/g), lung (2.90% ID/g), heart (2.09% ID/g), spleen (1.96% ID/g), blood (1.95% ID/g), and muscle (1.22% ID/g). The accumulation in the brain remained high at 2.38% ID/g and 1.85% ID/g at 30 min and 60 min, respectively.

Fujinaga et al. (9) performed dynamic PET imaging studies for 90 min in rats (n = 4) after intravenous injection of 37–55 MBq (1.0–1.5 mCi) [^{11}C]ITMM (0.3–0.5 nmol). Blocking studies were performed with injection of excess ITMM (1 mg/kg) or mGluR1 antagonist JNJ-16259685 (3 mg/kg) just before injection of the tracer. Baseline tissue time-activity curves revealed high accumulation of radioactivity that peaked at 30–45 min in the cerebellum, with moderate radioactivity in the thalamus and striatum and low radioactivity in the pons. The cerebellum/pons, thalamus/pons, and striatum/pons maximum ratios were 6.98, 5.05, and 4.32, respectively. Both ITMM and JNJ-16259685 showed >85% inhibition of radioactivity in the cerebellum, thalamus, and striatum. PET imaging studies with wild-type and mGluR1-knockout mice showed high radioactivity in the cerebellum and thalamus in the wild-type mouse brain and only a low, homogeneous distribution of radioactivity in the knockout mouse brain. Toyohara et al. (10) showed that the maximum standard uptake values in the cerebellum, cerebral cortex, and striatum were 1.7, 0.9, and 0.8, respectively, at 15 min after injection of [^{11}C]ITMM in mice (n = 4).

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

Toyohara et al. (10) performed dynamic PET imaging scans for 90 min with a normal male subject (27 years old) after injection of 565 MBq (15.3 mCi) [^{11}C]ITMM (8 nmol). Radioactivity in the cerebellum reached a plateau at 40 min. The volume of distribution (V_T) values were 2.7, 1.1, 0.9, 0.8, 0.7, 0.6, 0.5, and 0.5 for the cerebellum, thalamus, temporal cortex, parietal cortex, frontal cortex, occipital cortex, caudate, and putamen, respectively. [^{11}C]ITMM remained 84.7% intact in the blood at 10 min and declined to 60.5% intact at 60 min. Plasma radioactivity decreased rapidly and exhibited a three-phase clearance pattern with half-lives of 1, 4, and 29 min.

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