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

[^{11}C]ITDM

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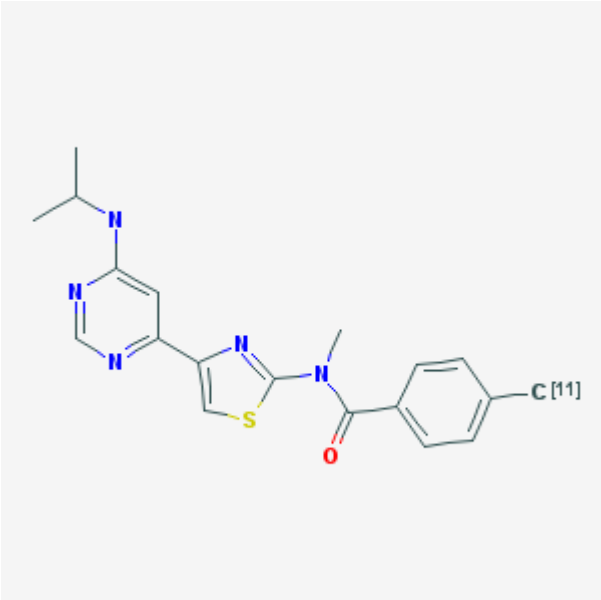
Chemical name:	*N*-(4-(6-(Isopropylamino)pyrimidin-4-yl)-1,3-thiazol-2-yl)-*N*-methyl-4-[^{11}C]methylbenzamide
Abbreviated name:	[^{11}C]ITDM, [^{11}C]4
Synonym:	
Agent category:	Compound
Target:	Metabotropic glutamate receptor subtype 1 (mGluR1)
Target category:	Receptor
Method of detection:	Positron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



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)-*N*-methyl-4-methylbenzamide (ITDM) was shown to be a selective mGluR1 antagonist with nanomolar affinity (K_i = 13.6 nM), with little inhibition of mGluR5 (9). Fujinaga et al. (9) labeled ITDM with ^{11}C to prepare *N*-(4-(6-(isopropylamino)pyrimidin-4-yl)-1,3-thiazol-2-yl)-*N*-methyl-4-[^{11}C]methylbenzamide ([^{11}C]ITDM) for use with *in vivo* PET imaging of mGluR1 distribution in rat and monkey brains.

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]ITDM by methylation of the arylstannane precursor with [^{11}C]MeI (prepared with [^{11}C]CO_2) using an automated synthesizer for 5 min at 80°C. Subsequent separation with high-performance liquid chromatography produced a radiochemical purity >99%. Average radiochemical yield was 19 ± 9% (n = 11) based on

[^{11}C]CO_2. The specific activity of [^{11}C]ITDM was 70–170 GBq/μmol (1.89–4.59 Ci/μmol) at the end of synthesis. The total synthesis time was <31 min from the end of bombardment.

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 13.6 ± 3.4 nM and 5.4 ± 1.2 nM for ITDM and FITM, respectively. Both agents showed IC_{50} values >10,000 nM for mGluR5. ITDM (LogD 1.74) was found to be slightly more lipophilic than FITM (LogD 1.45).

In vitro [^{11}C]ITDM autoradiographic imaging studies were performed on rat brain sections (9). [^{11}C]ITDM bound heterogeneously to the brain sections, with the highest accumulation of radioactivity in the mGluR1-rich cerebellum, followed by the thalamus, hippocampus, striatum, and cerebral cortex, with the lowest radioactivity in the pons. ITDM and JNJ-16259685 (1,000 nM), both mGluR1 antagonists, blocked radioactivity to homogeneity in the brain sections.

Animal Studies

Rodents

[PubMed]

Fujinaga et al. (9) performed *ex vivo* biodistribution studies in mice (n = 4/group) at 1–90 min after intravenous injection of 4.8 MBq (0.13 mCi) [^{11}C]ITDM (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 small intestine (66.76% injected dose/gram (ID/g)), followed by the liver (11.38% ID/g), kidney (4.41% ID/g), brain (2.58% ID/g), lung (2.56% ID/g), heart (1.28% ID/g), blood (1.27% ID/g), muscle (0.96% ID/g), and spleen (0.93% ID/g). The accumulation in the brain remained high at 1.99% ID/g and 1.59% ID/g at 15 min and 30 min, respectively. No blocking studies were performed.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Fujinaga et al. (9) performed dynamic PET imaging studies for 90 min in a male rhesus monkey after intravenous injection of 185–220 MBq (5.0–5.9 mCi) [^{11}C]ITDM (5–6 nmol). Blocking studies were performed with injection of excess ITDM (1 mg/kg) or mGluR1 antagonist JNJ-16259685 (3 mg/kg) just before injection of the tracer in the same monkey two weeks later. Baseline tissue time-activity curves revealed high accumulation of radioactivity that peaked at 15–30 min in the cerebellum, with moderate radioactivity in the cingulate cortex, thalamus, and striatum and low radioactivity in the pons. The radioactivity declined in all brain regions after the peaks. The maximum standard uptake values in the cerebellum, cingulate cortex, and thalamus were 1.2, 0.9, and 0.8 at ~20 min after injection of [^{11}C]ITDM, respectively. Pretreatment with ITDM and JNJ-16259685 reduced the levels of radioactivity to that of the whole brain. Logan graphic analysis was used to estimate the distribution volume ratio (DVR) values under the equilibrium state. The DVR values were 4.3, 2.6, 2.0, 1.8, 1.5, 1.5, and 1.0 for the cerebellum, cingulate cortex, thalamus, hippocampus, caudate, putamen, and pons, respectively.

Human Studies

[PubMed]

No publication is currently available.

References

1. Pin J.P., Duvoisin R. *The metabotropic glutamate receptors: structure and functions.* Neuropharmacology. 1995;34(1):1–26. PubMed PMID: 7623957.
2. Ferraguti F., Crepaldi L., Nicoletti F. *Metabotropic glutamate 1 receptor: current concepts and perspectives.* Pharmacol Rev. 2008;60(4):536–81. PubMed PMID: 19112153.
3. Abe T., Sugihara H., Nawa H., Shigemoto R., Mizuno N., Nakanishi S. *Molecular characterization of a novel metabotropic glutamate receptor mGluR5 coupled to inositol phosphate/Ca2+ signal transduction.* J Biol Chem. 1992;267(19):13361–8. PubMed PMID: 1320017.
4. Gasparini F., Lingenhohl K., Stoehr N., Flor P.J., Heinrich M., Vranesic I., Biollaz M., Allgeier H., Heckendorn R., Urwyler S., Varney M.A., Johnson E.C., Hess S.D., Rao S.P., Sacaan A.I., Santori E.M., Velicelebi G., Kuhn R. *2-Methyl-6-(phenylethynyl)-pyridine (MPEP), a potent, selective and systemically active mGlu5 receptor antagonist.* Neuropharmacology. 1999;38(10):1493–503. PubMed PMID: 10530811.
5. Ametamey S.M., Kessler L.J., Honer M., Wyss M.T., Buck A., Hintermann S., Auberson Y.P., Gasparini F., Schubiger P.A. *Radiosynthesis and preclinical evaluation of 11C-ABP688 as a probe for imaging the metabotropic glutamate receptor subtype 5.* J Nucl Med. 2006;47(4):698–705. PubMed PMID: 16595505.
6. Ametamey S.M., Treyer V., Streffer J., Wyss M.T., Schmidt M., Blagoev M., Hintermann S., Auberson Y., Gasparini F., Fischer U.C., Buck A. *Human PET studies of metabotropic glutamate receptor subtype 5 with 11C-ABP688.* J Nucl Med. 2007;48(2):247–52. PubMed PMID: 17268022.

7. Baumann C.A., Mu L., Johannsen S., Honer M., Schubiger P.A., Ametamey S.M. *Structure-activity relationships of fluorinated (E)-3-((6-methylpyridin-2-yl)ethynyl)cyclohex-2-enone-O-methyloxime (ABP688) derivatives and the discovery of a high affinity analogue as a potential candidate for imaging metabotropic glutamate recepors subtype 5 (mGluR5) with positron emission tomography (PET).* J Med Chem. 2010;53(10):4009–17. PubMed PMID: 20411954.
8. Honer M., Stoffel A., Kessler L.J., Schubiger P.A., Ametamey S.M. *Radiolabeling and in vitro and in vivo evaluation of [(18)F]-FE-DABP688 as a PET radioligand for the metabotropic glutamate receptor subtype 5.* Nucl Med Biol. 2007;34(8):973–80. PubMed PMID: 17998101.
9. Fujinaga M., Yamasaki T., Maeda J., Yui J., Xie L., Nagai Y., Nengaki N., Hatori A., Kumata K., Kawamura K., Zhang M.R. *Development of N-[4-[6-(Isopropylamino)pyrimidin-4-yl]-1,3-thiazol-2-yl]-N-methyl-4-[(11)C]methy lbenzamide for Positron Emission Tomography Imaging of Metabotropic Glutamate 1 Receptor in Monkey Brain.* J Med Chem. 2012;55(24):11042–51. PubMed PMID: 23194448.