# 4-[$^{18}$F]Fluoro-*N*-[4-[6-(isopropylamino)pyrimidin-4-yl]-1,3-thiazol-2-yl]-*N*-methylbenzamide

## [$^{18}$F]FITM

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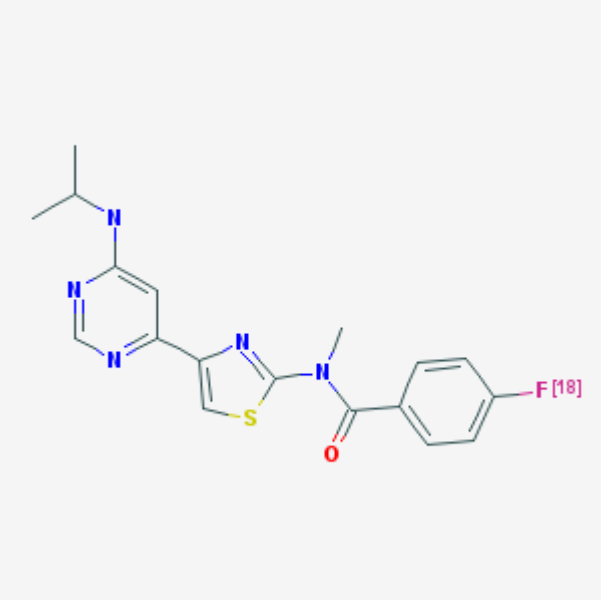
| **Chemical name:** | 4-[$^{18}$F]Fluoro-*N*-[4-[6-(isopropylamino)pyrimidin-4-yl]-1,3-thiazol-2-yl]-*N*-methylbenzamide |
| **Abbreviated name:** | [$^{18}$F]FITM, [$^{18}$F]4 |
| **Synonym:** | |
| **Agent category:** | Compound |
| **Target:** | Metabotropic glutamate receptor subtype 1 (mGluR1) |
| **Target category:** | Receptor |
| **Method of detection:** | Positron emission tomography (PET) |
| **Source of signal:** | $^{18}$F |
| **Activation:** | No |
| **Studies:** | • *In vitro*<br>• Rodents<br>• Non-human primates |

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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) radioligands targeting mGluR1 can visualize and analyze mGluR1 expression in normal physiological and pathological conditions (5-8). Several radioligands have been studied for *in vivo* imaging of mGluR1 in the brain. 4-Fluoro-*N*-[4-[6-(isopropylamino)pyrimidin-4-yl]-1,3-thiazol-2-yl]-*N*-methylbenzamide (FITM) was shown to be a selective mGluR1 antagonist with nanomolar affinity ($K_i$ = 5.4 nM), with little inhibition to mGluR2, mGluR5, and mGluR8 (9). Yamasaki and colleagues (10-12) prepared and evaluated 4-[$^{18}$F]Fluoro-*N*-[4-[6-(isopropylamino)pyrimidin-4-yl]-1,3-thiazol-2-yl]-*N*-methylbenzamide ([$^{18}$F]FITM) for use with *in vivo* PET imaging of mGluR1 distribution in the brains of small animals and monkeys.

## 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]

Yamasaki et al. (12) reported a one-step automated synthesis of [$^{18}$F]FITM. The nitro-precursor was subjected to nucleophilic fluorination with K[$^{18}$F]F/Kryptofix2.2.2 for 10 min at 180°C, with a radiochemical yield of 14 ± 3% ($n$ = 8) and a specific activity of 204–

559 GBq/μmol (5.5–15.1 Ci/μmol) after purification with high-performance liquid chromatography. The radiochemical purity of [$^{18}$F]FITM was >99%. The total synthesis time was not reported. [$^{18}$F]FITM exhibited a log $D_{7.4}$ value of 1.46 ± 0.01.

## *In Vitro* Studies: Testing in Cells and Tissues

[PubMed]

*In vitro* [$^{18}$F]FITM autoradiographic imaging studies were performed on rat brain sections ($n$ = 3/group) (12). [$^{18}$F]FITM bound heterogeneously to the brain sections, with the highest accumulation of radioactivity in the mGluR1-rich thalamus (739 ± 67 PSL/mm$^2$) and cerebellum (719 ± 209 PSL/mm$^2$), followed by the hippocampus (681 ± 16 PSL/mm$^2$), striatum (568 ± 15 PSL/mm$^2$), cerebral cortex (375 ± 50 PSL/mm$^2$), and pons (222 ± 77 PSL/mm$^2$). FITM and JNJ-16259685 (1,000 nM, mGluR1 antagonists) completely blocked radioactive signals to background levels in these brain regions. On the other hand, the mGluR5 antagonist MPEP (1,000 nM) demonstrated only marginal inhibition (5%–18%) of the signals. *In vitro* autoradiographic studies were also performed on monkey brain sections ($n$ = 6) with results similar to those found with the rat brain sections.

## Animal Studies

### Rodents

[PubMed]

Yamasaki et al. (12) performed *ex vivo* autoradiographic studies in rat brain sections ($n$ = 10) that received intravenous injection of [$^{18}$F]FITM with or without co-administration of JNJ-16259685 (1 mg/kg). [$^{18}$F]FITM bound heterogeneously to the brain sections, with the highest accumulation of radioactivity in the mGluR1-rich thalamus (673 ± 38 PSL/mm$^2$) and cerebellum (636 ± 26 PSL/mm$^2$), followed by the striatum (479 ± 33 PSL/mm$^2$), hippocampus (428 ± 17 PSL/mm$^2$), cerebral cortex (342 ± 24 PSL/mm$^2$), and pons (69 ± 5 PSL/mm$^2$). JNJ-16259685 (mGluR1 antagonist) blocked radioactive signals by 86%–91% in the thalamus, cerebellum, striatum, hippocampus, and cerebral cortex, whereas the signal was reduced only 15% in the pons.

Yamasaki et al. (10) performed dynamic PET imaging studies for 90 min in rats ($n$ = 4/group) after intravenous injection of 17.5 MBq (0.5 mCi) [$^{18}$F]FITM. Blocking studies were performed by pretreatment (0.5 min) with 1 mg/kg FITM. Baseline tissue time-activity curves revealed a high accumulation of radioactivity in the cerebellum, followed by the thalamus, striatum, hippocampus, and cingulate cortex, whereas little radioactivity was detected in the pons. Pretreatment with FITM reduced the radioactivity signals to background level with no effect on the blood level of radioactivity. Logan graphic analysis showed baseline volume of distribution ($V_T$) values of 114, 59, 48, 50, 42, and 6 ml/mm$^3$ for the cerebellum, thalamus, striatum, hippocampus, cingulate cortex, and pons, respectively. Blocking with FITM reduced these $V_T$ values to 2.4–2.7 ml/mm$^3$. Non-

displaceable binding potential ($BP_{ND}$) values were estimated to be 43.9, 22.3, 17.9, 18.6, 15.5, and 1.5, respectively. Pretreatment with various doses of FITM estimated the $K_d$ values to be 1.5–2.1 nM for the thalamus, hippocampus, striatum, and cingulate cortex, with $B_{max}$ values of 36.3, 27.5, 22.2, and 20.5 pM, respectively. [$^{18}$F]FITM remained ~25% intact in the plasma at 120 min with two polar metabolites, **1** (69%) and **2** (5%). On the other hand, [$^{18}$F]FITM remained ~96% intact in the brain at 120 min with only metabolite **2** (4%).

*Ex vivo* biodistribution studies were performed in mice ($n$ = 3/group) at 1–180 min after intravenous injection of [$^{18}$F]FITM (11). The liver and kidney (>7.5% injected dose/gram (ID/g)) exhibited high initial accumulation of radioactivity at 1 min. Radioactivity increased with time in the brain (7.7% ID/g at 15 min) and small intestine (10% ID/g at 60 min), whereas radioactivity decreased with time in the other tissues, such as the lung, spleen, heart, bone, and blood (<2% ID/g at 60 min).

## Other Non-Primate Mammals

[PubMed]

No publication is currently available.

## Non-Human Primates

[PubMed]

Yamasaki et al. (11) performed dynamic PET imaging studies for 90 min in one male rhesus monkey after intravenous injection of 175 MBq (5 mCi, 0.8 nmol) [$^{18}$F]FITM. Blocking studies were performed by pretreatment (0.5 min) with 3 mg/kg JNJ-16259685. Baseline tissue time-activity curves revealed a high accumulation of radioactivity in the cerebellum, followed by the thalamus, striatum, hippocampus, and cingulate cortex, whereas little radioactivity was detected in the pons. The maximum standard uptake values (SUVs) were 3.3, 2.3, 2.0, 1.9, 1.5, and 1.7 for the cerebellum, cingulate cortex, thalamus, hippocampus, striatum, and putamen, respectively. Pretreatment with JNJ-16259685 reduced the radioactivity signals of all regions to 0.1–0.2 at 90 min after injection. Logan graphic analyses showed baseline $V_T$ values of 10.2, 5.9, 5.0, 4.4, 3.4, 3.3, and 2.4 ml/mm$^3$ for the cerebellum, cingulate cortex, thalamus, hippocampus, putamen, caudate, and pons, respectively. Similar $V_T$ values for these brain regions were obtained with two-tissue compartment model analyses.

# Human Studies

[PubMed]

No publication is currently available.

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