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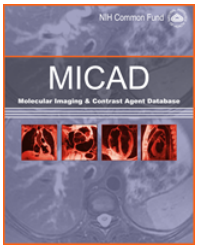

(3-Ethyl-2-[^{11}C]methyl-6-quinolinyl)(cis-4-methoxycyclohexyl)methanone

[^{11}C]JNJ-16567083

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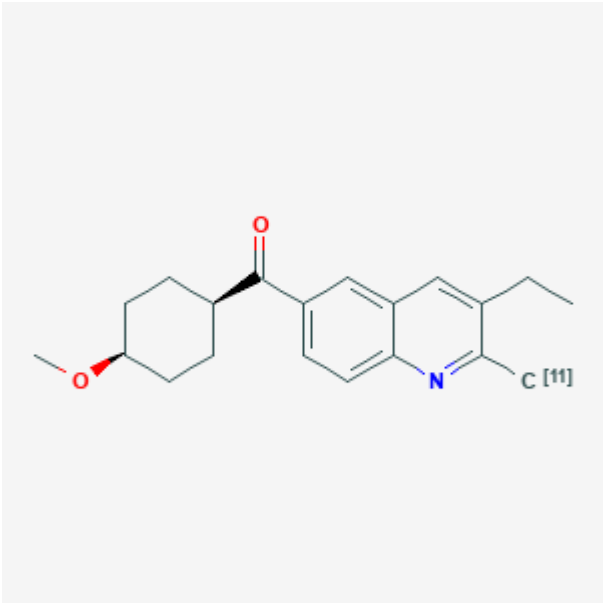
Chemical name:	(3-Ethyl-2-[^{11}C]methyl-6-quinolinyl) (cis-4-methoxycyclohexyl)methanone
Abbreviated name:	[^{11}C]JNJ-16567083
Synonym:	[^{11}C]2
Agent category:	Compound
Target:	Metabotropic glutamate receptor subtype 1 (mGluR1)
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

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,

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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. However, only a few mGluR1 ligands have been studied. (3-Ethyl-2-methyl-6-quinolinyl)(cis-4-methoxycyclohexyl)methanone (JNJ-16567083) was shown to be a selective mGluR1 antagonist with nanomolar affinity (K_i = 0.87 nM) with little inhibition of mGluR5 (5). Huang et al. (5) prepared and evaluated (3-Ethyl-2-[^{11}C]methyl-6-quinolinyl)(cis-4-methoxycyclohexyl)methanone ([^{11}C]JNJ-16567083) for use with *in vivo* PET imaging of mGluR1 distribution in rat 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]

Huang et al. (5) synthesized [^{11}C]JNJ-16567083 by methylation of the trimethyltin precursor with [^{11}C]methyl iodide ([^{11}C]MeI) at 120°C for 5 min. Subsequent separation with high-performance liquid chromatography produced a radiochemical purity >99%. An average radiochemical yield was 47 ± 17% (n = 10) based on [^{11}C]MeI. The specific activity of [^{11}C]JNJ-16567083 was 22.5 ± 8.4 GBq/μmol (607 ± 228 mCi/μmol) at the end of synthesis. The total synthesis time was 40 min.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

JNJ-16567083 exhibited K_i values of 0.87 ± 0.43 nM and 2.4 ± 0.6 μM for rat mGluR1 and mGluR5 (5), respectively.

Animal Studies

Rodents

[PubMed]

Huang et al. (5) performed *ex vivo* biodistribution studies in the brain of rats (n = 3/group) at 10, 30, and 60 min after intravenous injections of [^{11}C]JNJ-16567083. The initial accumulation of radioactivity was high in the brain and thereafter decreased. The cerebellum exhibited the highest accumulation of radioactivity at 10 min with 1.24 ± 0.06% injected dose/gram (ID/g), followed by the striatum (0.73 ± 0.04% ID/g), hippocampus (0.58 ± 0.05% ID/g), frontal cortex (0.52 ± 0.06% ID/g), medulla (0.47 ± 0.01% ID/g), and blood (0.42 ± 0.02% ID/g). The cerebellum/medulla ratios were 2.63, 4.72, and 4.06 at 10, 30, and 60 min, respectively. Pretreatment with JNJ-16567083 (2 mg/kg, 10 min) reduced the radioactivity in the cerebellum by 81% and in the striatum, hippocampus and frontal cortex by 50% at 30 min after injection.

Huang et al. (5) performed dynamic PET imaging studies in one rat after intravenous injection of 4.4 MBq (0.12 mCi) [^{11}C]JNJ-16567083 for 90 min. Blocking studies were performed by co-injection of excess JNJ-16567083. Baseline tissue time-activity curves revealed a high accumulation of radioactivity peaked at 10 min in the cerebellum, with a moderate radioactivity levels in the striatum, hippocampus and cerebral cortex. Co-injection of JNJ-16567083 reduced the radioactivity in the all brain regions to homogeneous level.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

References

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