4-Acetoxy-7-chloro-3-(3-(-4-[^{11}C]methoxybenzyl)phenyl)-2(1*H*)-quinolone

[^{11}C]AcL703,717

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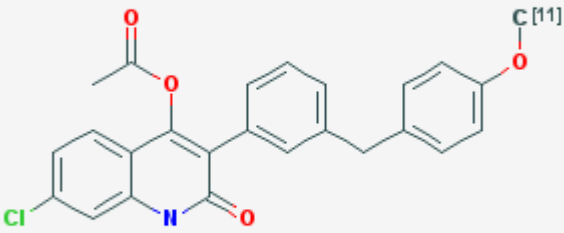
Chemical name:	4-Acetoxy-7-chloro-3-(3-(-4-[^{11}C]methoxybenzyl)phenyl)-2(1*H*)-quinolone
Abbreviated name:	[^{11}C]AcL703,717, [^{11}C]AcL703
Synonym:	
Agent category:	Compound
Target:	*N*-Methyl *D*-aspartate (NMDA) receptor
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Humans



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Background

[PubMed]

N-Methyl *D*-aspartate (NMDA) receptor is an ionotropic receptor for glutamate playing an important role in synaptic plasticity, which is a cellular mechanism for learning and memory (1). The NMDA receptor forms a heterotetramer between two NR1 and two NR2 subunits with multiple regulatory binding sites for glutamate, glycine, Mg^{2+}, polyamine, and drugs such as phencyclidine (PCP) (2). Overactivation of NMDA receptor has been suggested to be involved in a variety of neurological diseases such as ischemia, schizophrenia, Parkinson's disease, Huntington's disease, and epilepsy.

4-Hydroxy-7-chloro-3-(3-(-4-methoxybenzyl)phenyl)-2(1*H*)-quinolone (L703,717), a 4-hydroxyquinolone, is a potent antagonist for the glycine-binding site of the NMDA receptor, but it is poorly taken up by the brain because of its tight binding to serum albumin (3). Haradahira et al. (4) introduced an ester to the 4-hydroxyquinolone moiety to improve its penetration through the blood–brain barrier. 4-Acetoxy-7-chloro-3-(3-(-4-methoxybenzyl)phenyl)-2(1*H*)-quinolone (AcL703,717) taken up by the brain can be expected to be hydrolyzed to L703,717 by esterase in the brain. [^{11}C]AcL703,717 is being evaluated as a positron emission tomography (PET) radioligand to study NMDA receptor in the brain.

Synthesis

[PubMed]

[^{11}C]AcL703,717 was prepared in two-step reactions (4). The desmethyl precursor of L703,717 was reacted with [^{11}C]methyl iodide in the presence of NaH in dimethylformamide for 3 min at 30°C. Subsequently, the acetylation was performed by addition of acetic anhydride/2,6-lutidine to the mixture, which was heated for 3 min at 80°C. [^{11}C]AcL703,717 was obtained with a radiochemical purity of >99% and a specific radioactivity of 51–73 GBq/μmol (1.38–1.97 Ci/μmol) at the end of synthesis. The total synthesis time was 33 min from the end of bombardment. [^{11}C]AcL703,717 exhibited a Log *P* value of 3.9, whereas [^{11}C]L703,717 had a Log *P* value of 3.0.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Haradahira et al. (4) reported that 80% of [^{11}C]AcL703,717 was converted to [^{11}C]L703,717 by incubation with the rat brain homogenates for 20 min. No other metabolites were detected. [^{11}C]AcL703,717 was stable in saline buffer under the experimental conditions used. However, [^{11}C]AcL703,717 was readily converted to [^{11}C]L703,717 by incubation with the rat and mouse plasma (4) as well as in human blood (5) with a half-life of <1 min.

Animal Studies

Rodents

[PubMed]

[^{11}C]AcL703,717 (8 MBq (216 μCi)) was injected intravenously into normal mice to study its accumulation in the brain at 1 min after injection (4). [^{11}C]AcL703,717 showed an initial penetration into the brain with 0.71 ± 0.10% injected dose (ID)/g in the cerebellum and 0.58 ± 0.05% ID/g in cerebrum. The initial radioactivity levels in the brain were one-fold higher than those of [^{11}C]L703,717. There was <10% of intact [^{11}C]AcL703,717 in the brain at 5 min after injection with [^{11}C]L703,717 as the only metabolite. *Ex vivo* brain autoradiography at 20 min after injection of [^{11}C]AcL703,717 showed that the main radioactivity in the cerebellum was similar to that of [^{11}C]L703,717. This cerebellar radioactivity was completely blocked with co-injection of L703,717 (1 mg/kg). *Ex vivo* brain autoradiography studies of the rat brain showed that pretreatment with cyclosporine, a P-gp inhibitor, increased the cerebellar radioactivity of [^{11}C]AcL703,717 one-fold. The authors mentioned that it is not clear whether most of the [^{11}C]L703,717 is formed in the brain or formed in the blood and then cross the BBB as the [^{11}C]L703,717 to account for the increase brain accumulation of [^{11}C]AcL703,717 over [^{11}C]L703. No blocking experiment with L703,717 was presented.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

Matsumoto et al. (5) performed dynamic PET scans in six healthy male volunteers (23.3 ± 2.9 years old) for 90 min after injection of 624–851 MBq (17–23 mCi) [^{11}C]AcL703,717. The maximum whole-brain accumulation was 1.3% at 1.5 min after injection. The brain region with the highest radioactivity accumulation at 40–90 min after injection was the cerebellar cortex, followed by the frontal-temporal-parietal cortex, thalamus, striatum, and white matter. The binding potential (BP) values (white matter as reference region) for the cerebellar cortex and frontal-temporal-parietal cortex were calculated to be 2.2 ± 0.71 and 1.05 ± 0.45, respectively. The BP values for thalamus and striatum were almost zero.

References

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