6-Hydroxy-[1,1'-biphenyl]-3-yl-cyclohexyl-[^{11}C-*carbonyl*]carbamate

[^{11}C]CURB

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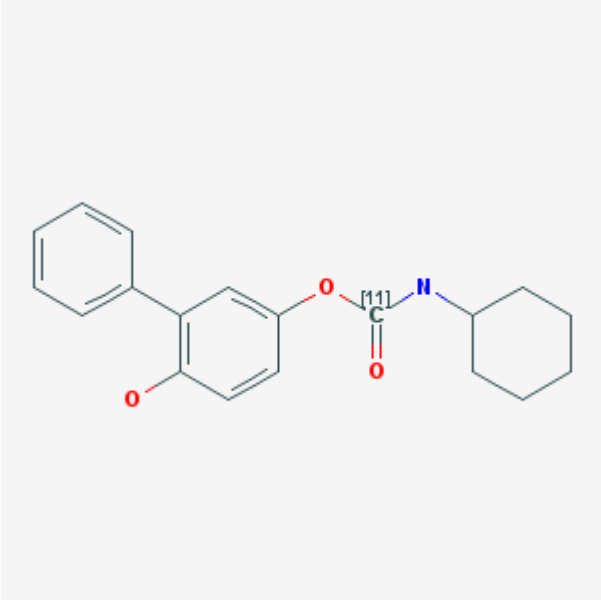
Chemical name:	6-Hydroxy-[1,1'-biphenyl]-3-yl-cyclohexyl-[^{11}C-*carbonyl*]carbamate
Abbreviated name:	[^{11}C]CURB
Synonym:	[^{11}C-*carbonyl*]URB694, [^{11}C]URB694
Agent category:	Compound
Target:	Fatty acid amide hydrolase (FAAH)
Target category:	Enzyme
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Humans



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Background

[PubMed]

Fatty acid amide hydrolase (FAAH) is an integral membrane-bound serine hydrolase and a part of the endocannabinoid system (ECS), which comprises the cannabinoid receptors (CB1 and CB2), endogenous ligands termed endocannabinoids (anandamide and oleamide), transporters, and enzymes (1, 2). FAAH plays a key role in the hydrolysis of a number of primary and secondary fatty acid amides, controlling the levels of the neuromodulatory endocannabinoids in the ECS (3, 4). FAAH is widely expressed in many tissues, with the highest levels in the liver and brain (5). Genetic or pharmacological inactivation of FAAH in the brain leads to analgesic, anti-inflammatory, anxiolytic, and anti-depression effects in animal models (6-8).

Cyclohexylcarbamic acid 3'-carbamoylbiphenyl-3-yl ester (URB597) is an irreversible, substrate-like inhibitor of FAAH involving carbamylation of the catalytic nucleophilic Ser^{241} and the *O*-biaryl group as the leaving group (9-11). On the basis of the structure of URB597, Wyffels et al. (12) prepared biphenyl-3-yl-4-[^{11}C]methoxyphenylcarbamate ([^{11}C]-1) for *in vivo* positron emission tomography (PET) imaging studies of the brain FAAH in mice. It was proposed that the carbamylation of Ser^{241} would leave the [^{11}C]-methoxyanilino group bound to the FAAH for visualization of FAAH in the brain. However, the results of *in vitro* and *ex vivo* studies indicated that [^{11}C]-1 is a reversible inhibitor of FAAH, and the rapid brain washout of the tracer limits its utility as a PET agent for *in vivo* measurements of FAAH. Wilson et al. (13) reported the ^{11}C-radiolabeling of a close analog of URB597, 6-hydroxy-[1,1'-biphenyl]-3-yl-cyclohexylcarbamate (URB694), yielding [^{11}C-*carbonyl*]URB694 ([^{11}C]CURB) for PET imaging of FAAH in the brain. [^{11}C]CURB showed good brain accumulation with regional heterogeneity, irreversibility, and specific binding to FAAH *in vivo* in rats. Rusjan et al. (14) reported [^{11}C]CURB PET studies in human brain.

Related Resource Links:

- Chapters in MICAD (FAAH)
- Gene information in NCBI (FAAH)
- Articles in Online Mendelian Inheritance in Man (OMIM) (FAAH)
- Clinical trials (FAAH)

Synthesis

[PubMed]

Wilson et al. (13) synthesized [^{11}C]CURB by reaction of [^{11}C]CO_2 with cyclohexylamine for 1 min at room temperature, followed by addition of 2-phenyl-1,4-dihydroquinone. [^{11}C]CURB was purified with high-performance liquid chromatography. The specific activity of [^{11}C]CURB was 80–160 GBq/μmol (2.2–4.4 Ci/μmol) at the time of injection.

The radiochemical yield, radiochemical purity, and total synthesis time were not reported. The $LogD_{7.4}$ value of [^{11}C]CURB was 2.8 ± 0.1.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Mor et al. (11) showed that unlabeled URB694 and URB597 inhibited the hydrolysis of [^{3}H]-anandamide by FAAH with IC_{50} values of 30.0 ± 5.8 and 7.7 ± 1.5 nM, respectively. Both compounds were irreversibly bound to FAAH.

Animal Studies

Rodents

[PubMed]

Ex vivo biodistribution studies in normal rats (n = 5/group) were performed at 5, 15, 40, and 60 min after intravenous injection of 50 MBq (1.35 mCi) [^{11}C]CURB (13). The accumulation level of radioactivity was highest in the cortex, followed by the hippocampus, cerebellum, striatum, and hypothalamus, with standard uptake values of 1.5–2.5 at 5 min after injection. The distribution of radioactivity in the brain regions is in agreement with the known distribution of FAAH in the rat brain. The cortex/hypothalamus ratio was 2.8 at 60 min. Radioactivity in the blood was lower than in the brain. The brain/blood ratios increased from 5 at 5 min to 16 at 60 min after injection. Pretreatment (30 min) with various doses (10, 50, and 500 μg/kg) of URB594 inhibited the radioactivity in the brain in a dose-dependent manner at 60 min after injection of [^{11}C]CURB. At the highest dose of URB594, radioactivity levels were reduced by 62%–86%, depending on the brain regions. Pretreatment with URB597 (2 mg/kg) reduced the radioactivity levels by 72%–88%. At 2 min, 18% of radioactivity was irreversibly bound to brain tissue increasing to 80% at 60 min. Pretreatment with excess URB597 almost completely abolished the tissue-binding radioactivity. [^{11}C]CURB was 67%, 60%, 47%, and 45% intact in the plasma at 5, 15, 40, and 60 min, respectively, with two polar metabolites. On the other hand, 80% of radioactivity was bound to the brain tissue, and the soluble fraction contained 19% intact [^{11}C]CURB and 1% metabolite at 40 min. The investigators concluded that [^{11}C]CURB should be a useful tool as a PET agent for *in vivo* measurements of FAAH because of its good brain accumulation with regional heterogeneity, irreversibility, and specific binding to FAAH.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

Rusjan et al. (14) reported [^{11}C]CURB PET studies in human brain using kinetic modeling in six healthy subjects (age 19-53 yr) scanned with arterial blood sampling for 90 min. [^{11}C]CURB was 68%, 48%, and 37% intact in the plasma at 8, 20, and 90 min, respectively. High standard uptake values (SUVs) were observed in the putamen (4.3 ± 0.8), thalamus (4.2 ± 0.6), and anterior cingulate cortex (3.5 ± 0.5). Kinetic parameters were estimated regionally using a one-tissue compartment model (TCM), a 2-TCM, a 2-TCMi (with irreversible trapping), and an irreversible 3-TCM. The 2-TCMi provided the best identifiability of PET outcome measures among the models analyzed (coefficient of variation (COV) of the net influx constant K_i and the composite parameter λk_3 ($\lambda=K_1/k_2$) <5%, and COV (k_3) <10%). Binding of [^{11}C]CURB in the healthy human brain can be well identified with an irreversible two-tissue compartment kinetic model using 60 minutes of scan data.

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