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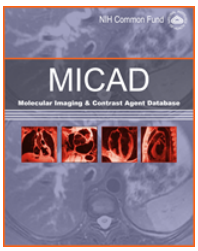


# 6-Hydroxy-[1,1'-biphenyl]-3-yl-cyclohexyl-[$^{11}$C-*carbonyl*]carbamate

## [$^{11}$C]CURB

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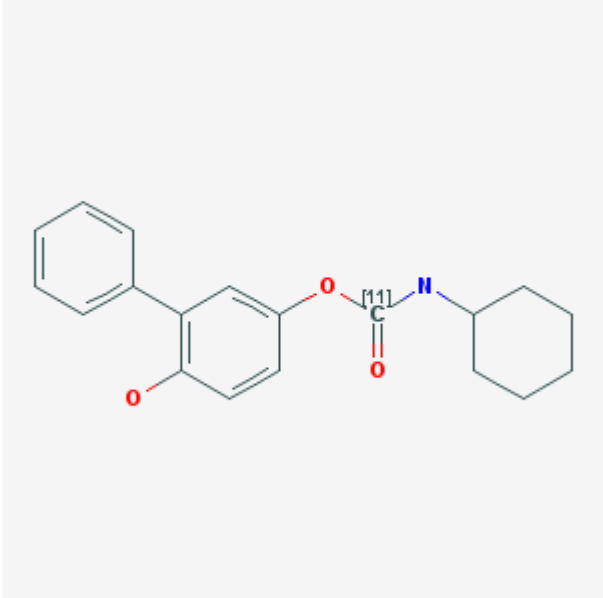
| **Chemical name:** | 6-Hydroxy-[1,1'-biphenyl]-3-yl-cyclohexyl-[$^{11}$C-*carbonyl*]carbamate |
| **Abbreviated name:** | [$^{11}$C]CURB |
| **Synonym:** | [$^{11}$C-*carbonyl*]URB694, [$^{11}$C]URB694 |
| **Agent category:** | Compound |
| **Target:** | Fatty acid amide hydrolase (FAAH) |
| **Target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

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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 $\lambda k_3$ ($\lambda=K_1/k_2$) <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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