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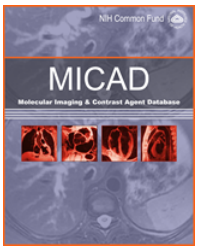


# [$^{11}$C]5-Hydroxy-2-(4-methyaminophenyl)benzofuran

The MICAD Research Team

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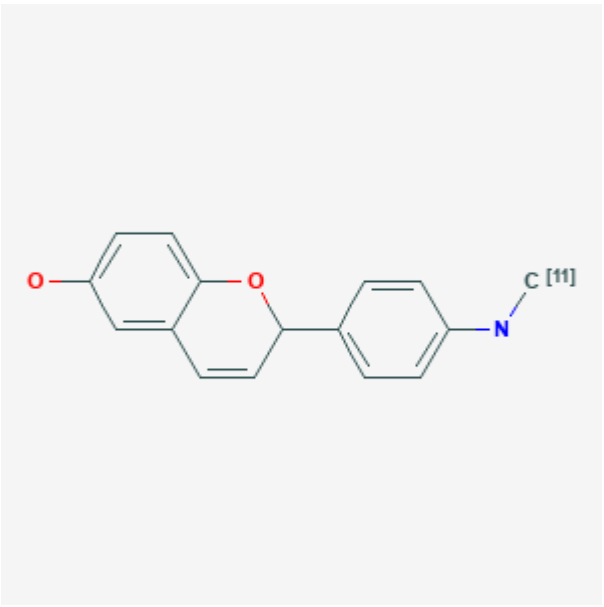
| **Chemical name:** | [$^{11}$C]5-Hydroxy-2-(4-methyaminophenyl)benzofuran |
| **Abbreviated name:** | |
| **Synonym:** | |
| **Agent Category:** | Compound |
| **Target:** | Aggregates of ß-amyloid (Aß) peptides |
| **Target Category:** | Acceptor binding |
| **Method of detection:** | Positron emission tomography (PET) |
| **Source of signal:** | $^{11}$C |
| **Activation:** | No |
| **Studies:** | • *In vitro*<br>• Rodents |




Click on the above structure for additional information in PubChem.

## Background

[PubMed]

Alzheimer's disease (AD) is a major neurodegenerative disease associated with cognitive impairment and an irreversible decline of mental functions (1, 2). It is characterized by presence in the brain of senile plaques of β-amyloid (Aβ) peptides with intracellular neurofibrillary tangles of filaments that contain the hyperphosphorylated protein tau (3, 4). Accelerated deposition of Aβ deposits seems to be a key risk factor associated with AD, and although the mechanisms of the disease are still not fully understood, reducing the deposition of amyloid plaques seems to benefit patients.

Several radioligands for positron emission tomography (PET) have been developed (5-7) and tested in humans as *in vivo* diagnostic tools for imaging and measuring the formation and Aβ deposits (5-7) The first successful agent used in human studies was [$^{18}$F]FDDNP (8), a malonitrile derivative found to bind to both neurofibrillary tangles and Aβ plaques. The second successful attempt was made with [$^{11}$C]PIB (9), also known as Pittsburgh

Compound B or [$^{11}$C]6-OH-BTA-1. [$^{11}$C]PIB showed marked retention in areas of the association cortex known to contain substantial amounts of Aβ deposits. The third PET radioligand tested in humans was [$^{11}$C]4-*N*-methylamino-4′-hydroxystilbene, a stilbene derivative commonly named [$^{11}$C]SB-13.

A series of benzofuran derivatives have recently been synthesized and are being evaluated as Aβ probes with PET. Probes that use radioactive iodine have shown very good binding affinities for Aβ aggregates and good brain penetration (10). Unfortunately, their level of nonspecific binding was found to be very high, which makes them unsuitable for *in vivo* plaque imaging. Other imaging agents that use benzofuran derivatives labeled with $^{11}$C are currently being evaluated. One of them, [$^{11}$C]5-hydroxy-2-(4-methyaminophenyl)benzofuran , is currently being tested in small animals.

## Synthesis

[PubMed]

An experimental procedure for synthesizing 5-hydroxy-2-(4-methyaminophenyl)benzofuran was reported by Ono et al. (11) in 2006. The main step of the procedure involved the formation of the benzofuran backbone, 5-methoxy-2-(4-nitrophenyl)benzofuran, by an intramolecular Wittig reaction between triphenylphosphonium salt and 4-nitrobenzoyl chloride at a 33% yield. The Wittig reagent used in the procedure was prepared from 2-methoxy-5-hydroxybenzyl alcohol and triphenylphosphine hydrobromide at 84% yield.

5-Methoxy-2-(4-aminophenyl)benzofuran was converted to the monomethylamino derivative 5-methoxy-2-(4-methylaminophenyl)benzofuran by reducing the nitro group to an amino group with $SnCl_2$ and subsequently monomethylating the amino group. 5-Methoxy-2-(4-aminophenyl)benzofuran was also converted to the dimethylamino derivative 5-methoxy-2-(4-dimethylaminophenyl)benzofuran at a 39% yield by a previously described method that uses paraformaldehyde, sodium cyanoborohydride, and acetic acid (11). The removal of the *O*-methyl groups (using $BBr_3$) led to the formation of 5-hydroxy-2-(4-aminophenyl)benzofuran, the precursor used in the radiolabelling procedure of -hydroxy-2-(4-methyaminophenyl)benzofuran with $^{11}$C-labeled methyl triflate.

The final product, [$^{11}$C]5-hydroxy-2-(4-methyaminophenyl)benzofuran, was obtained at a 21% yield (decay-corrected to end of bombardment) and with a radiochemical purity >99% . Its specific activity at the end of synthesis was ≈37 GBq/μmol (1 Ci/μmol).

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

[PubMed]

*In vitro* binding assays using AD brain gray matter homogenates showed that [$^{11}$C]5-hydroxy-2-(4-methyaminophenyl)benzofuran had a high binding affinity to amyloid plaques with an inhibition constant of 0.7 ± 0.2 nM. Measurements of the partition coefficient (P) in 1-octanol/phosphate buffer (pH 7.4) led to a log P value of 2.36 (11), which is considered within the optimal lipophilicity range for crossing the blood-brain barrier.

*In vitro* fluorescent labeling of AD sections was performed by Ono et al. (11) to investigate the neuropathological staining of senile plaques by 5-hydroxy-2-(4-methyaminophenyl)benzofuran. Results showed staining of neuritic plaques and cerebrovascular amyloids. In addition, [$^{11}$C]5-hydroxy-2-(4-methyaminophenyl)benzofuran also displayed high binding affinity for neurofibrillary tangles in the AD sections. It was shown in a previous study that a marked increase in the amount of neurofibrillary tangles in the hippocampus and entorhinal cortex occurred in the preclinical AD stage (12).

Overall, the results from neuropathological staining of human AD obtained for sections showed that 5-hydroxy-2-(4-methyaminophenyl)benzofuran could bind to amyloid plaques and neurofibrillary tangles with almost the same pattern of [$^{18}$F]FDDNP or X-34 (13).

# Animal Studies

## Rodents

[PubMed]

Ono et al. (11) performed biodistribution studies of [$^{11}$C]5-hydroxy-2-(4-methyaminophenyl)benzofuran in four 6-week-old male ddY mice (i.e., a superior strain of mice widely used in pharmacological, toxicological, and drug efficacy studies) by intravenously injecting the animals with 3.7 MBq (0.1 mCi) of the radiotracer in saline solution. The experimental protocol involved sacrificing the animals at various points in time and counting the radioactivity of excised and weighed organs.

Results showed that [$^{11}$C]5-hydroxy-2-(4-methyaminophenyl)benzofuran exhibited excellent brain uptake (4.8% of the injected dose (ID)/g of the brain at 2 min) and rapid washout (>90% of the radioactivity from the brain in 30 min or less, with values of 0.4 and 0.2% ID/g of the brain at 30 and 60 min, respectively). The precise mechanisms responsible for the rapid clearance of [$^{11}$C]5-hydroxy-2-(4-methyaminophenyl)benzofuran from the normal brain are still unknown.

*Ex vivo* plaque labeling of amyloid plaques in a living mouse brain was performed by Ono et al. (11) by intravenously injecting 22-month-old female Tg2576 mice (i.e., AD mouse strain specifically engineered to overproduce the amyloid plaques in the brain) with 200 μl of a saline solution of ascorbic acid (1 mg/ml) and 7.4–9.3 MBq (0.2–0.25 mCi) of [$^{11}$C]5-hydroxy-2-(4-methyaminophenyl)benzofuran. After sacrificing the animals, brain sections were cut and exposed to a phosphor imaging plate.

Autoradiographic images of brain sections at 30 min after injection of [$^{11}$C]5-hydroxy-2-(4-methyaminophenyl)benzofuran showed high radioactivity accumulation in the cerebral cortex and hippocampus. In contrast, wild-type mouse brain displayed no remarkable accumulation of the radiotracer in the brain. In those studies, Ono et al. (11) showed that the most intense areas of staining in the brain sections of Tg2576 mice injected with [$^{11}$C]5-hydroxy-2-(4-methyaminophenyl)benzofuran corresponded with those of *in vitro* thioflavin-S staining in the same brain sections.

## 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.

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