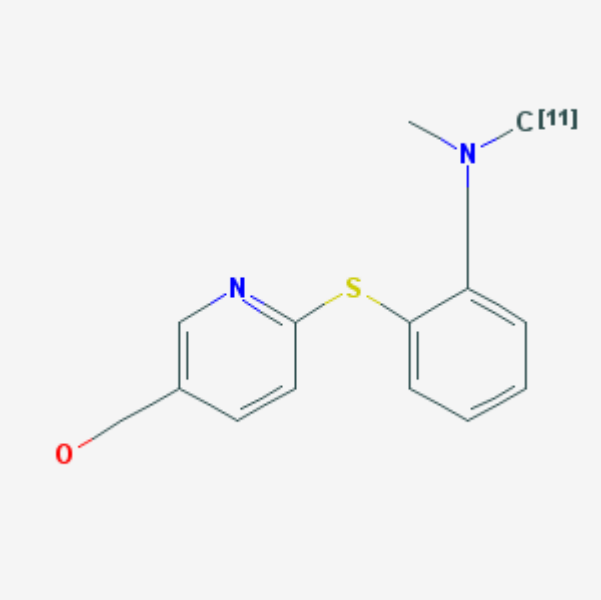
[^{11}C]*N,N*-Dimethyl-2-(2′-amino-4′-hydroxymethylphenylthio)benzylamine

[^{11}C]HOMADAM

The MICAD Research Team

Created: January 10, 2005; Updated: February 27, 2005.

Chemical name:	[^{11}C]*N,N*-Dimethyl-2-(2′-amino-4′-hydroxymethylphenylthio)benzylamine
Abbreviated name:	[^{11}C]HOMADAM
Synonym:	Carbon-11 HOMADAM
Agent Category:	Compound
Target:	Serotonin transporter (SERT)
Target Category:	Ligand binding
Method of detection:	PET
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Non-human primates



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Background

[PubMed]

A number of neuropsychiatric disorders, including major depression, schizophrenia, and Alzheimer's and Parkinson's diseases (1-3), involve a dysfunction of the brain's serotonin system. The serotonergic neurons – present in wide areas of the brain, including the hypothalamus, thalamus and cerebral cortex – bear a protein called "serotonin transporter" (SERT) (4).

NLM Citation: The MICAD Research Team. [^{11}C]*N,N*-Dimethyl-2-(2′-amino-4′-hydroxymethylphenylthio)benzylamine. 2005 Jan 10 [Updated 2005 Feb 27]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

SERT is a specific marker for the number and integrity of presynaptic terminals of serotonin-producing neurons. It regulates neurotransmission by removing released serotonin from the extracellular space back into the presynaptic neuron. A variety of radioligands for positron emission tomography (PET) have been evaluated for imaging SERT. The most recent include [^{11}C]*N,N*-dimethyl-2-(2-amino-4-cyanophenylthio)benzylamine ([^{11}C]DASB), [^{11}C]2-(2-(dimethylaminomethyl)phenylthio)-5-fluoromethylphenylamine ([^{11}C]AFM), [^{11}C]5-bromo-2-[2-(dimethylaminomethylphenylthio)]phenylamine ([^{11}C]DAPA), and [^{11}C]2-[2-(dimethylaminomethylphenylthio)]-5-iodophenylamine ([^{11}C]ADAM), which are PET radiotracers based on a diaryl sulfide motif (5).

A variety of *in vivo* radioligands for PET have been evaluated for imaging SERT. [^{11}C]McN5652 was the first successful and widely used agent (6, 7) However, it does have some limitations related to its slow brain kinetics and low to nonspecific binding ratios in humans. [^{11}C]McN5652 is adequate for regions with high SERT density but often provides insufficient signal-to-noise differentials for imaging brain regions with intermediate to low SERT densities (e.g., limbic and neocortical regions).

Over recent years, new PET radioligands have been synthesized and evaluated as SERT imaging agents and alternatives to [^{11}C]McN5652. Among them, [^{11}C]DASB, [^{11}C]AFM, [^{11}C]DAPA, and [^{11}C]ADAM are based on a diaryl sulfide motif (4). [^{11}C]*N,N*-Dimethyl-2-(2′-amino-4′-hydroxymethylphenylthio)benzylamine ([^{11}C]HOMADAM), a new benzylamine derivate, is a new PET radiotracer currently being investigated for its SERT imaging properties. It was synthesized as part of an effort to develop a radiotracer with both favorable SERT-specific binding properties and the ability to reach a quasi-equilibrium for SERT binding relatively shortly after injection.

Synthesis

[PubMed]

HOMADAM and its radiolabeling substrate, *N*-methyl-2-(2′-amino-4′-hydroxymethylphenylthio)benzylamide, can be prepared by a multistep synthetic procedure described by Jarkas et al. (8). The first step involves coupling 2-bromo-5-acetoxymethyl-nitrobenzene with thiosalicylic acid to produce 2-(4′-acetoxymethyl-2′-nitrophenylthio)benzoic acid (58% yield reported by Jarkas et al. (8)), which is subsequently converted to the corresponding acid chloride by treatment with thionyl chloride and then reacted with methylamine and dimethylamine hydrochlorides. The resulting products, *N*-methyl-2-(4′-acetoxymethyl-2′-nitrophenylthio)benzamide and *N,N*-dimethyl-2-(4′-acetoxymethyl-2′-nitrophenylthio)benzamide, are obtained, with yields of 81% and 68%, respectively, reported by Jarkas et al. (8). Under catalytic hydrogenation, these products give the amines *N*-methyl-2-(4′-acetoxymethyl-2′-aminophenylthio)benzamide and *N,N*-dimethyl-2-(4′-acetoxymethyl-2′-aminophenylthio)benzamide (50% yield (8)). After reduction with BH_3-tetrahydrofuran

complex, HOMADAM and its radiolabeling substrate are obtained (yields of 35% and 47%, respectively, reported by Jarkas et al. (8)).

[^{11}C]HOMADAM is obtained by reacting a solution of the radiolabeling substrate *N*-methyl-2-(2′-amino-4′-hydroxymethylphenylthio)benzylamide (1.0 mg in 0.2 ml of dimethyl formamide at –20 °C) with [^{11}C]CH_3I (produced from [^{11}C]CO_2, as described by Plisson et al. (9)). The chemical and radiochemical purities obtained were >99%, and the overall yield was 25 ± 2% (9). The specific activity at the end of the procedure was approximately 28,490 MBq/µmol (770 mCi/µmol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro studies on murine and human embryonic kidney cells transfected with cDNAs for the human dopamine, serotonin, and norepinephrine transporters were performed by Jarkas et al. (8). They showed that HOMADAM competed for [^{3}H]citalopram binding to SERT. The affinity of HOMADAM for [^{3}H]citalopram binding in human embryonic kidney cells expressing SERT was 44 and 1.7 times lower than the affinities for ADAM and DASB, respectively. The authors reported an inhibition coefficient of HOMADAM for SERT of 0.6 nM.

Animal Studies

Rodents

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

MicroPET brain imaging studies of male rhesus monkeys were performed by Jarkas et al. (8), for time periods ranging from 0 to 90 min after administration of [^{11}C]HOMADAM (435 MBq/µmol (11.7 Ci/mmol)). Accumulation of the tracer was found in the midbrain, thalamus, pons, medulla, and occipital cortex, with a regional distribution consistent with binding to SERT-rich sites. The highest and lowest uptakes were found in the midbrain and the cerebellum, respectively. The maximum uptake of the tracer in the midbrain was obtained between ~13 and 22 min post injection, with a slow decrease thereafter (54%/h). In comparison, maximal binding for [^{11}C]DASB in the midbrain was found at ~22-45

min post injection, with a decrease of 37%/h. The highest uptakes of [^{11}C]HOMADAM in the thalamus and pons were found at ~9 and 12 min post injection.

In vivo displacement studies of [^{11}C]HOMADAM, using *R,S*-citalopram, showed a rapid and very substantial reduction of radioactivity in the thalamus, midbrain, and other SERT-rich brain regions, reflecting the selective binding of [^{11}C]HOMADAM to SERT. Displacement was also obtained by injection of *R,S*-reboxetine, a norepinephrine transporter-selective ligand with a high nanomolar affinity for SERT (8).

An arterial metabolite analysis performed by Jarkas et al. (8) showed one major polar metabolite (non-ether extractable) of [^{11}C]HOMADAM. The abundance of this metabolite increased from 10% to 90% of the total plasma measured activity at 5 and 60 min post injection. Its identity was not pursued because of its improbable brain permeability. The remaining radioactivity appeared to be from nonmetabolized [^{11}C]HOMADAM; no formation of lipophilic radiolabeled metabolites able to enter the brain was detected.

Human Studies

[PubMed]

No publication is currently available.

References

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