# [$^{11}$C]2-2-(Dimethylaminomethyl)phenylthio)-5-fluorophenylamine

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

The MICAD Research Team

Created: January 25, 2006; Updated: February 14, 2006.

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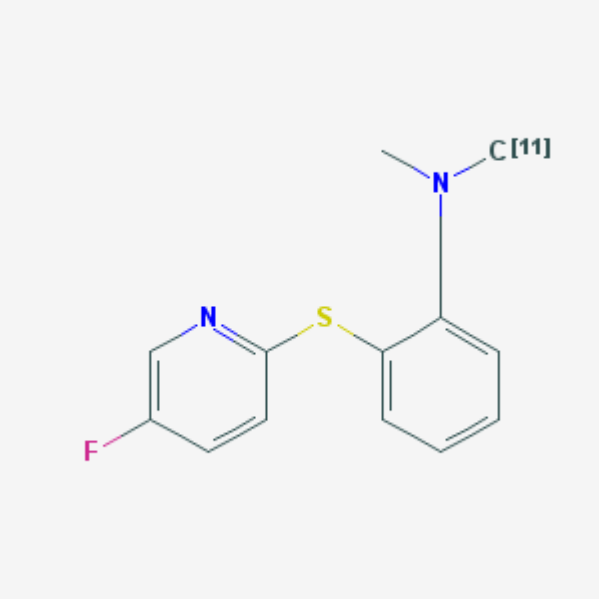
| **Chemical name:** | [$^{11}$C]2-(2-(Dimethylaminomethyl)phenylthio)-5-fluorophenylamine |
| **Abbreviated name:** | [$^{11}$C]AFA |
| **Synonym:** | |
| **Agent Category:** | Compound |
| **Target:** | Serotonin transporter (SERT) |
| **Target Category:** | Ligand binding |
| **Method of detection:** | PET |
| **Source of signal:** | $^{11}$C |
| **Activation:** | No |
| **Studies:** | • *In vitro*<br>• Rodents<br>• Non-human primates |




Click on the above structure for additional information in PubChem.

## Background

[PubMed]

A number of neuropsychiatric disorders, including major depression, schizophrenia, Alzheimer's disease, and Parkinson's disease (1-3), involve a dysfunction of the brain's serotonin system. The serotonergic neurons – present in large areas of the brain, including

NLM Citation: The MICAD Research Team. [$^{11}$C]2-2-(Dimethylaminomethyl)phenylthio)-5-fluorophenylamine. 2006 Jan 25 [Updated 2006 Feb 14]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

the hypothalamus, thalamus, and cerebral cortex – bear a protein called 'serotonin transporter' (SERT) (4).

The 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. Commonly prescribed antidepressants are selective serotonin reuptake inhibitors, and their effects are obtained through interaction with the SERT (5).

A variety of radioligands for positron emission tomography (PET) have been evaluated for imaging the SERT. The most recent include [$^{11}$C]DASB, [$^{11}$C]AFM, [$^{11}$C]AFE, [$^{11}$C]ADAM, [$^{11}$C]HOMADAM. 2-(2-(Dimethylaminomethyl)phenylthio)-5-fluorophenylamine (AFA), a novel PET radioligand, can be labeled with either $^{11}$C or $^{18}$F. *In vitro*, it has shown rapid brain uptake kinetics as well as a high affinity for SERT, with lower affinities for the norepinephrine transporter (NET) and dopamine transporter (DAT).

## Synthesis

[PubMed]

[$^{11}$C]AFA can be prepared from its monomethylamino precursor, (5-fluoro-2[2-(methylaminomethylphenylthio)]phenylamine, by reaction with [$^{11}$C]methyl iodide ([$^{11}$C]MeI). The precursor is obtained following a protocol described in details by Huang et al. (6). The radiolabeling method involves dissolving the precursor in *N, N*-dimethylformamide (DMF), and bubbling [$^{11}$C]MeI through the solution at -10 °C. After the maximum radioactivity is obtained, the solution is heated at 85 °C for 5 min in a water bath. After a multi-step purification (by HPLC), dilution with water (100mL) and passage through a Waters $C_{18}$ Sep-Pak, the solution is then eluted in ethanol. The eluted [$^{11}$C]AFA is mixed with sterile saline (0.9% NaCl), filtered through a 0.22 μm membrane filter, and collected in a sterile vial.

The chemical and radiochemical purity of [$^{11}$C]AFA produced by this method is >95%, and the radiochemical yield is 43 ± 20% (decay-corrected, based on [$^{11}$C]MeI; $n$ = 10) (6). The specific activity of the radiotracer at the end of the synthesis is 2.13 ± 1.37 Ci/mmol (7.88 ± 5.07 GBq/mmol). The total synthesis time is about 35 min.

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

[PubMed]

Comparative *in vitro* studies using cloned human monoamine transporters and the radioligands [$^3$H]paroxetine, [$^3$H]nisoxetine, and [$^3$H]GBR2935 were performed by Huang et al. (6) to assess the affinity of [$^{11}$C]AFA for the SERT, NET and DAT. Results showed a high affinity for the SERT ($K_i$ = 1.46 ± 0.15 nM) and much lower affinities for the NET ($K_i$ = 141.7 ± 47.4 nM) and DAT ($K_i > 10^4$ nM). [$^{11}$C]AFA showed virtually no

affinity for benzodiazepine, serotonin, and dopamine receptors such as 5-$HT_{1A}$, 5-$HT_{2c}$, 5-$HT_3$, 5-$HT_6$, 5-$HT_7$ and $D_1$ through $D_5$.

# Animal Studies

## Rodents

[PubMed]

Biodistribution studies were performed *ex-vivo* on Sprague-Dawley rats by Huang et al. The experimental procedure involved injecting 3.7 MBq (100 μCi) of [$^{11}$C]AFA into each animal (via the tail vein) and measuring the uptake of the radiotracer at 10, 30, 60, and 90 min post injection, after sacrifice.

Results showed rapid uptake of [$^{11}$C]AFA into the brain, with accumulation in regions rich in SERTs. The highest levels were found in the thalamus and hypothalamus, followed by the frontal cortex, striatum, and hippocampus. The reported hypothalamus/cerebellum activity ratios were 5.32 ± 0.49 and 6.38 ± 1.32, respectively, at 60 and 120 min post injection.

When pretreated with either cold AFA (2 mg/kg of tissue) or citalopram (a selective serotonin reuptake inhibitor), about 50 to 66% of the specific binding was found to be displaced at 45 min after injection of the tracer. In contrast, pretreatment with nisoxetine (a selective norepinephrine reuptake inhibitor) did not lead to a significant change with respect to [$^{11}$C]AFA specific binding in SERT-rich regions.

## Other Non-Primate Mammals

[PubMed]

No publication is currently available.

## Non-Human Primates

[PubMed]

Huang et al. (6) performed PET brain imaging studies of baboons for time periods ranging from 0 to 120 min after administration of [$^{11}$C]AFA (injected dose ~185 MBq (5 mCi); specific activity at time of injection, 1854 ± 1106 Ci/mmol (68.6 GBq/μmol). The highest tracer levels of the tracer were found in regions of high SERT density (e.g., thalamus, midbrain and striatum), and the lowest levels were found in the cerebellum. [$^{11}$C]AFA exhibited rapid uptake kinetics, with peak activity levels between 15 and 40 min post-injection.

When the baboons were pretreated with 4.8 ± 0.5 mCi of citalopram (a selective serotonin reuptake inhibitor) 20 min before injection of [$^{11}$C]AFA, the radiotracer uptakes in the midbrain, thalamus, striatum, hippocampus, and cortex were reduced to the level in the cerebellum, showing significant reduction in the specific binding of [$^{11}$C]AFA in all

SERT-containing brain regions. A kinetic analysis done by the authors of the study (6) showed that the regional equilibrium specific-to-nonspecific partition coefficients of [$^{11}$C]AFA were similar to those obtained for the imaging agent [$^{11}$C]McN5652, but lower than those obtained for [$^{11}$C]DASB (e.g., midbrain partition coefficients were 0.95 ± 0.07 and 1.68 ± 0.21 for [$^{11}$C]AFA and [$^{11}$C]DASB respectively).

## Human Studies

[PubMed]

No publication is currently available.

## References

1. Owens MJ, Nemeroff CB. The serotonin transporter and depression. Depress Anxiety. 1998;8Suppl 15–12. PubMed PMID: 9809208.
2. Palmer AM, Francis PT, Benton JS, Sims NR, Mann DM, Neary D, Snowden JS, Bowen DM. Presynaptic serotonergic dysfunction in patients with Alzheimer's disease. J Neurochem. 1987;48(1):8–15. PubMed PMID: 2432177.
3. Roth BL, Xia Z. Molecular and cellular mechanisms for the polarized sorting of serotonin receptors: relevance for genesis and treatment of psychosis. Crit Rev Neurobiol. 2004;16(4):229–236. PubMed PMID: 15862107.
4. Laakso A, Hietala J. PET studies of brain monoamine transporters. Curr Pharm Des. 2000;6(16):1611–1623. PubMed PMID: 10974156.
5. White KJ, Walline CC, Barker EL. Serotonin transporters: implications for antidepressant drug development. Aaps J. 2005;7(2):E421–E433. PubMed PMID: 16353921.
6. Huang Y, Narendran R, Bae SA, Erritzoe D, Guo N, Zhu Z, Hwang DR, Laruelle M. A PET imaging agent with fast kinetics: synthesis and in vivo evaluation of the serotonin transporter ligand [11C]2-[2-dimethylaminomethylphenylthio)]-5-fluorophenylamine ([11C]AFA). Nucl Med Biol. 2004;31(6):727–738. PubMed PMID: 15246363.