[^{11}C]2-(2-(Dimethylaminomethyl)phenylthio)-5-fluoromethylphenylamine

[^{11}C]AFM

The MICAD Research Team

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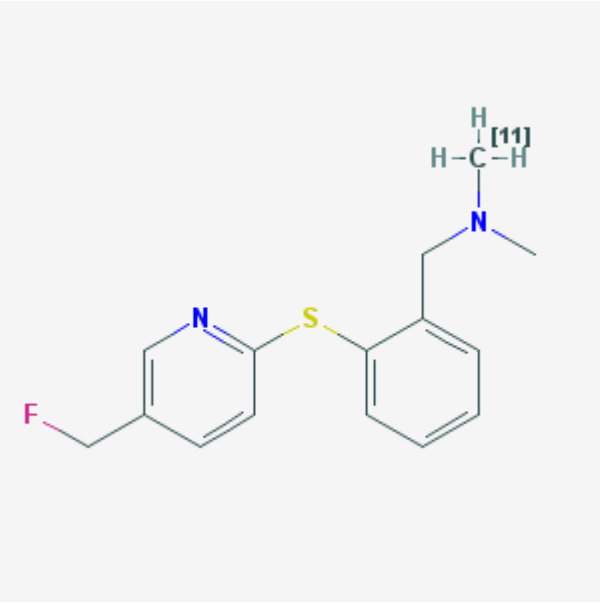
Chemical name:	[^{11}C]2-(2-(Dimethylaminomethyl)phenylthio)-5-fluoromethylphenylamine
Abbreviated name:	[^{11}C]AFM
Synonym:	
Agent Category:	Compound
Target:	Serotonin transporter (SERT)
Target Category:	Ligand binding
Method of detection:	PET
Source of signal:	^{11}C
Activation:	No
Studies:	• *In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



Background

[PubMed]

The neurotransmitter serotonin (5-HT) plays a major role in a variety of brain functions such as appetite, sleep, and mood. Neuropsychiatric disorders, including major depression, schizophrenia, and Alzheimer's and Parkinson's diseases (1-3), involve a

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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).

The SERT, located on the cell bodies and terminals of 5-HT neurons, 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 (SSRIs), and their effects are obtained through interaction with (and inhibition of) the SERT (5). For that reason, *in vivo* imaging of the regional brain distribution of the SERT is an important tool to study the 5-HT system and the treatment of neuropsychiatric disorders.

A variety of *in vivo* radioligands for positron emission tomography (PET) have been evaluated for imaging the SERT. [^{11}C]McN5652 was the first successful and widely used agent (6, 7). However, it does have some limitations; for example, its kinetics in the brain are slow and its binding ratios in humans show low or nonspecificity. It 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) because of its high nonspecific binding.

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-labeled *N,N*-dimethyl-2-(2-amino-4-cyanophenylthio)benzylamine ([^{11}C]DASB), 2-(2-(dimethylaminomethyl)phenylthio)-5-fluoromethylphenylamine ([^{11}C]AFM), 5-bromo-2-[2-(dimethylaminomethylphenylthio)]phenylamine ([^{11}C]DAPA), 2-[2-(dimethylaminomethylphenylthio)]-5-iodophenylamine ([^{11}C]ADAM), and *N,N*-dimethyl-2-(2′-amino-4′-hydroxymethylphenylthio)benzylamine ([^{11}C]HOMADAM) (8) are based on a diaryl sulfide motif (4). [^{11}C]AFM has shown high binding affinity and good selectivity for the SERT, and displays signal/noise ratios that may enable more reliable mapping of brain regions with a low density of SERT.

Synthesis

[PubMed]

AFM and its C-11 radiolabeling precursor can be prepared in a five-step procedure, as described by Huang et al. (9). Briefly, 4-chloro-3-nitrobenzyl acetate is coupled with thiosalicylic acid to give 2-(4-acetyloxymethyl-2-nitrophenylthio)benzoic acid, which is then converted to 2-(4-acetyloxymethyl-2-nitrophenylthio)-*N,N*-dimethylbenzamide. Reduction of the amide functionality to the tertiary amine and cleavage of the acetyl group with borane/tetrahydrofuran complex produce 2-(4-hydroxymethyl-2-nitrophenylthio)-*N,N*-dimethylbenzylamine. Fluorination of this compound with bis(2-methoxyethyl)aminosulfur trifluoride is then performed to produce the benzyl fluoride 2-(4-fluoromethyl-2-nitrophenylthio)-*N,N*-dimethylbenzylamine. Finally, reduction of the nitro group produces AFM.

Starting with 2-(4-acetyloxymethyl-2-nitrophenylthio)benzoic acid and replacing *N,N*-dimethylamine hydrochloride with *N*-methylamine hydrochloride (in the amide formation step) leads to the formation of the C-11 labeling precursor 5-fluoromethyl-2-(2-methylaminomethylphenylthio)phenylamine. [^{11}C]AFM is prepared from this precursor by reaction with [^{11}C]iodomethane (in dimethyl formamide, at 80-85 °C).

The chemical and radiochemical purities of [^{11}C]AFM produced by this method are ≥97% (as determined by high-performance liquid chromatography). The radiochemical yield at the end of the synthesis is 12.3 ± 8.1% (decay-corrected, based on [^{11}C]iodomethane; n = 14). The specific activity of the radiotracer produced is 64,121 ± 15,836 GBq/mmol (1,733 ± 428 Ci/mmol). The total synthesis time, as reported by Huang et al. (9), is about 30-37 min.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Huang et al. (9) assayed the affinity of AFM for the SERT, norepinephrine transporter (NET), and dopamine transporter (DAT), using cloned human receptors expressed on HEK-293 cells and the radioligands [^{3}H]paroxetine (for SERT), [^{3}H]nisoxetine (for NET), and [^{3}H]GBR12935 (for DAT). Experiments were performed according to previously published procedures (10, 11). Results showed that AFM had a high affinity and a good selectivity for SERT over NET and DAT. The authors reported the following inhibition coefficients (K_is): 1.04 ± 0.13, 663.8 ± 79.5, and >10,000 nM for SERT, NET, and DAT, respectively.

In comparative studies between various SERT radiotracers, Huang et al. (12) found no significant difference between the K_is of McN5652, ADAM, DASB, and AFM. Temperature had no significant effect on the inhibition coefficients for AFM, McN5652, and ADAM, but significantly decreased the affinity of DASB for SERT.

Animal Studies

Rodents

[PubMed]

Biodistribution studies in Sprague-Dawley rats were performed by Huang et al. (9). The experimental procedure involved injecting 3.7 MBq (100 μCi) of [^{11}C]AFM per animal (via the tail vein) and measuring the uptake of the radiotracer at 10, 30, and 60 min post injection, after sacrifice.

Results showed rapid uptake of [^{11}C]AFM into the brain, with accumulation in regions rich in SERTs, such as the thalamus, hypothalamus, and cortex. The reported total brain uptakes of [^{11}C]AFM at 10, 30, and 60 min post injection were 0.70, 1.06, and 1.00% of injected dose (ID)/g of tissue, respectively. The thalamus/cerebellum and hypothalamus/cerebellum activity ratios were 6.06 ± 0.17 and 6.05 ± 1.01, respectively, at 60 min post

injection. When pretreated with either cold AFM (2mg/kg of tissue) or citalopram (a SSRI), the brain uptake was significantly reduced.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

PET brain imaging studies of three adult male baboons were performed by Huang et al. (9), for time periods ranging from 0 to 90 min after administration of [^{11}C]AFM. Results showed rapid distribution of the radiotracer in the brain, consistent with the regional concentrations of SERT. High uptakes were observed in the midbrain and thalamus, moderate uptakes were seen in the hippocampus and striatum, and low levels of radioactivity were detected in the cortical regions.

In all brain regions, the measured activity reached a peak followed by a substantial wash-out (e.g., maximum activity obtained at 41 ± 12 min with a wash-out of 21 ± 14% for the hippocampus). At 45 min post injection, the measured total brain uptake was 0.015 ± 0.001% ID/g of tissue, a result consistent with values obtained in rats. The reported thalamus/cerebellum, striatum/cerebellum, and hippocampus/cerebellum activity ratios were 3.3 ± 0.4, 2.4 ± 0.4, and 1.7 ± 0.3, respectively, at 90 min post injection. Significant differences in clearance were observed between the several baboons used in the study.

When the baboons were pretreated with citalopram (a SSRI; 4 and 6 mg/kg of tissue) 10 min before injection of [^{11}C]AFM, a significant reduction in the brain distribution volumes was observed (30.8 ± 6.4 mL/g reduced to 15.2 mL/g (baboon A) and 29.4 ± 3.2 mL/g reduced to 21.3 mL/g (baboon B), under control conditions).

In comparative studies between the SERT radiotracers [^{11}C]ADAM, [^{11}C]AFM, [^{11}C]DASB, [^{11}C]DAPA, and [^{11}C]McN5652, Huang et al. (12) showed that the regional-specific-to-nonspecific equilibrium partition coefficient was the highest for [^{11}C]AFM, followed by [^{11}C]DASB, [^{11}C]DAPA, [^{11}C]ADAM, and [^{11}C]McN5652. [^{11}C]AFM was shown to provide higher signal/noise ratios, which might enable more reliable measurement of SERT availability in regions of low SERT density.

Human Studies

[PubMed]

No publication is currently available.

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