2-((2-Amino-4-chloro-5-[^{18}F]fluorophenyl)thio)-*N,N*-dimethylbenzenmethanamine

[^{18}F]ACF

The MICAD Research Team

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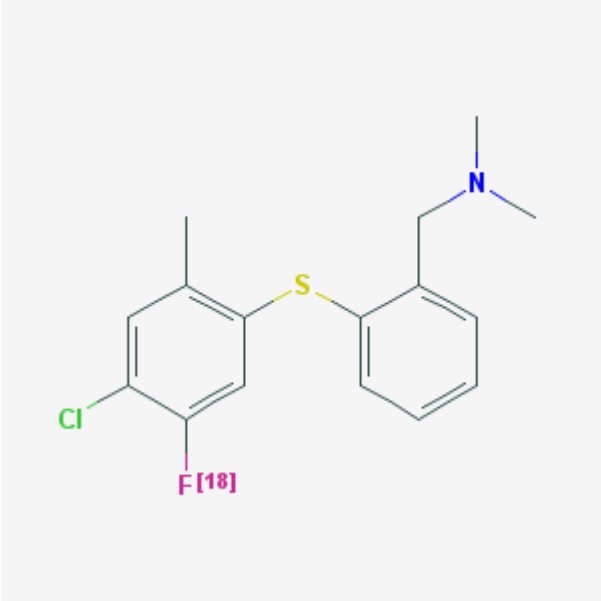
Chemical name:	2-((2-Amino-4-chloro-5-[^{18}F]fluorophenyl)thio)-*N,N*-dimethylbenzenmethanamine
Abbreviated name:	[^{18}F]ACF
Synonym:	
Agent Category:	Compound
Target:	Serotonin transporter (SERT)
Target Category:	Ligand binding
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

The neurotransmitter serotonin (5-hydroxytryptamine (5-HT)) plays a major role in a variety of brain functions (e.g., appetite, sleep, and mood). Neuropsychiatric disorders such as major depression, schizophrenia, Alzheimer's disease, and Parkinson's disease (1-3) involve a dysfunction of the brain's serotonin system. The serotonergic neurons –

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present in wide areas of the brain, including the hypothalamus, thalamus, and cerebral cortex – bear a protein called ”serotonin transporter” (SERT) (4).

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, and their effect is obtained through interaction with (and inhibition of) SERT (5). For that reason, *in vivo* imaging of the regional brain distribution of SERT is an important tool for study of 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 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 because of its high nonspecific binding, it 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, the C-11-labeled tracers *N*,*N*-dimethyl-2-(2-amino-4-cyanophenylthio)benzylamine ([^{11}C]DASB), 2-(2-(dimethylaminomethyl)phenylthio)-5-fluoromethylphenylamine ([^{11}C]AFM) (8), 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) (9) are based on a diaryl sulfide motif (4). F-18-labeled radioligands have also been synthesized and investigated (10). Compared with C-11 tracers, they offer better opportunities for data collection and full kinetic analysis. 2-((2-Amino-4-chloro-5-[^{18}F]fluorophenyl)thio)-*N*,*N*-dimethylbenzenmethanamine ([^{18}F]ACF) is a radioligand with the fluorine attached directly to the phenyl ring (for increased stability). It has been proposed as a potential PET tracer for imaging SERT.

Synthesis

[PubMed]

ACF and its F-18 radiolabeling precursor can be prepared according to a multistep procedure described by Oya et al. (11). Briefly, 2,5-dichloro-4-nitrophenylamine is coupled with thiobenzamide to give 2-(5-amino-4-chloro-2-nitrophenylthio)-*N*,*N*-dimethylbenzamide. The amino group of this compound is then converted to the fluoride 2-(4-chloro-5-fluoro-2-nitrophenylthio)-*N*,*N*-dimethylbenzamide by quenching the diazo intermediate with HPF_6 followed by thermal decomposition. Finally, the nitro and amide groups of 2-(4-chloro-5-fluoro-2-nitrophenylthio)-*N*,*N*-dimethylbenzamide are simultaneously reduced to amines with borane-tetrahydrofuran (THF) to produce ACF.

[^{18}F]ACF is obtained via [^{18}F]fluoride displacement of its precursor 2-chloro-5-(2-dimethylaminocarbonyl-phenylthio)-4-nitrophenyl)trimethylammonium. This radiolabeling procedure involves mixing the precursor with [^{18}F]fluoride in dimethyl sulfoxide at 55 °C for 10 min. This produces the intermediate compound 2-(4-chloro-5-[^{18}F]fluoro-2-nitrophenylthio)-*N,N*-dimethylbenzamide, which is then purified (by Sep-Pak) and reduced via a sequential borane and stannous reduction reaction (BH_3-THF and $SnCl_2$) to produce [^{18}F]ACF.

The reported radiochemical purity of [^{18}F]ACF produced by this method was >99% (as determined by high-performance liquid chromatography) (11). The reported radiochemical yield at the end of the synthesis was 10-15% (decay corrected), and the specific activity of the radiotracer produced was 37 GBq/mmol (1 Ci/mmol) (11). The total synthesis time, as reported by Oya et al. (11), is about 3 h.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Oya et al. (11) performed *in vitro* binding studies of ACF, using LLC-PK1 cells that over-expressed SERT, dopamine transporter (DAT), or norepinephrine transporter (NET), and showed that ACF had high affinity and good selectivity for SERT. The authors reported inhibition coefficients (K_is) of 0.05 ± 0.01, 3020 ± 110 and 650 ± 80 nM for SERT, DAT, and NET, respectively.

Animal Studies

Rodents

[PubMed]

Biodistribution studies in rats were performed by Oya et al. (11). The experimental procedure involved injecting 0.2 ml of saline solution containing 1.1 MBq (30 μCi) of [^{18}F]ACF per animal (through the femoral vein) and measuring the uptake of the radiotracer at different time points post injection, after sacrifice.

Results showed excellent uptake of [^{18}F]ACF into the brain, with accumulation in regions rich in SERT, such as the striatum, hippocampus, and hypothalamus. Uptake in the hypothalamus reached a peak between 60 and 120 min after injection, a much shorter time compared with the radiotracer [^{125}I]ADAM, for which a peak uptake is reached at ~4 h.

The total brain uptakes of [^{18}F]ACF at 2, 30, 60, 120, and 240 min post injection reported by Oya et al. (11) were 3.27, 1.28, 0.69, 0.21, and 0.06% of injected dose/organ, respectively. The thalamus/cerebellum activity ratio was 2.37 at 240 min post injection, and the hypothalamus/cerebellum activity ratio was 3.55 at 60 min post injection.

When rats were pretreated with (+)McN5652 (2 mg/kg of tissue) at 5 min before injection of [^{18}F]ACF, a significant decrease in specific retention was observed in the striatum, hippocampus, and hypothalamus (at 60 min post injection), suggesting possible competition between [^{18}F]ACF and (+)McN5652 for SERT binding sites. On the other hand, no significant difference was observed with pretreatment by nisoxetine or methylphenidate (which do not bind to SERT).

Metabolism studies at 60 post injection showed that almost all of the activity (95 ± 0.40%) extracted from the brain originated from [^{18}F]ACF and that metabolites in the peripheral tissues were not likely to play a major role on uptake and retention of the radiotracer (i.e., they are not likely to cross the blood-brain barrier).

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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