trans-(+)-1,2,3,5,6,10b-Hexahydro-6-(4-([^{11}C]methylthio)-phenyl)pyrrolo-(2,1-a)-isoquinoline

[^{11}C](+)McN5652

The MICAD Research Team

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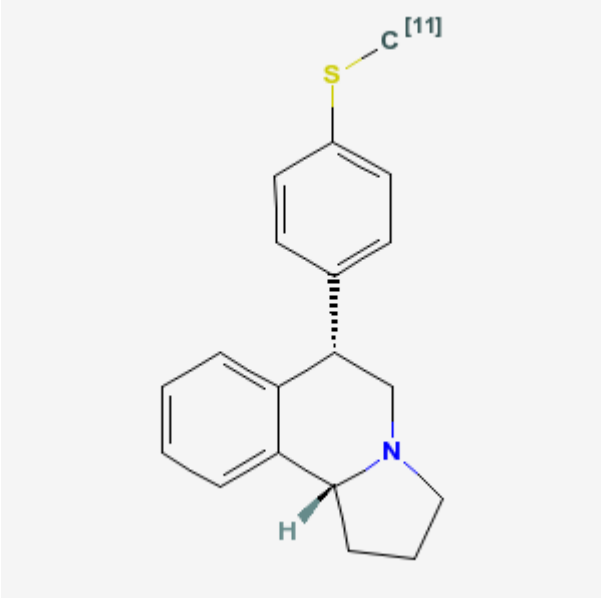
Chemical name:	*trans*-(+)1,2,3,5,6,10b-Hexahydro-6-(4-([^{11}C]methylthio)-phenyl)pyrrolo-(2,1-a)-isoquinoline
Abbreviated name:	[^{11}C](+)McN5652; [^{11}C]McN5652
Synonym:	
Agent Category:	Compound
Target:	Serotonin transporter (SERT); 5-HT
Target Category:	Ligand binding
Method of detection:	PET
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Other non-primate mammals • Non-human primates • Humans



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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, Alzheimer's disease, and Parkinson's disease (1-3), involve a dysfunction of the brain's 5-HT system.

The serotonergic neurons – present in wide areas of the brain, including the raphe nuclei, 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 5-HT 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 (and inhibition of) the SERT (5). For that reason, *in vivo* imaging of the regional brain distribution of the SERT is an important tool for studying 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. *trans*-(+)1,2,3,5,6,10b-Hexahydro-6-(4-([^{11}C]methylthio)-phenyl)pyrrolo-(2,1-a)-isoquinoline ([^{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 although adequate for regions with high SERT density, it 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 (e.g [^{11}C]DASB, [^{11}C]AFM, [^{11}C]ADAM, [^{11}C]HOMADAM).

[^{11}C]McN5652 has two optical isomeric forms. The ability of its geometric *trans* (+), pharmacologically active enantiomer, [^{11}C](+)McN5652, to block the SERT is at least two orders of magnitude higher than that of its inactive enantiomer, [^{11}C](-)McN5652 (8, 9) (inhibition constant (K_i) ~ 0.7 nM for [^{11}C](+)McN5652 *versus* 0.4 nM for [^{11}C](-)McN5652) (also see the *In Vitro* Studies section). Brain uptake and retention of [^{11}C](+)McN5652 correspond to the distribution of the SERT in rodents, non-human primates, and humans. Several methods have been used to quantify [^{11}C](+)McN5652-specific binding, but the high level of nonspecific binding, the differences in nonspecific binding among regions, and the slow equilibration between specific and nonspecific binding populations have made such a quantification difficult (10).

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Synthesis

[PubMed]

In 1995, Suehiro et al. (11) reported details of a synthetic procedure for [11C]McN5652 that addressed the instability issue of the thiol precursor used in previous established synthesis methods (12). This improved procedure involved the saponification of thioesters and enabled reaction of the precursor of McN5652 in a one-pot radiolabeling sequence. After hydrolysis of the thioester functionality (via tetrabutylammonium hydroxide for 10 min), the free thiol was reacted *in situ* with [11C]iodomethane (in dimethyl formamide, at 40-45 °C, for 1 min) without purification. The radiolabeled material produced was stable and could be used for multiple experiments.

The radiochemical yield obtained for [11C]McN5652 was ~26% (decay-corrected at end of bombardment), and the total synthesis time, as reported by Suehiro et al. (11), was about 18 min. The specific activity of the radiotracer produced was ~84,730 MBq/μmol (2,290 mCi/μmol).

Details of a synthetic method for [11C](+)McN5652 by S-methylation of the corresponding precursor with [11C]iodomethane using an automated process were reported by Sasaki et al. (13). In this method, the desmethyl precursor was obtained by demethylation of nonradioactive McN5652 and successive stabilization by the addition of dithiothreitol (DTT), a protecting agent for the SH group, immediately after reaction. This method led to a radiochemical purity of 98.6 ± 0.4% and specific activity for [11C](+)McN5652 of 181.3 ± 7.4 GBq/μmol (4,900 ± 200 mCi/μmol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro inhibition studies performed by Shank et al. (9) showed that (+)McN5652 had the ability to prevent 5-HT uptake to a much greater extent than norepinephrine, whereas its potency for dopamine uptake was negligible. Its inhibition constant was found to be in the nanomolar range (K_i = 0.40 nM for synaptosomal 5-HT uptake), which was similar to those of paroxetine and sertraline, two high-affinity ligands for 5-HT. The optically inactive McN5652 enantiomer exhibited a much lower affinity (~150 lower) for the SERT than its optically active isomer (9).

Animal Studies

Rodents

[PubMed]

Mice studies performed by Suehiro et al. (7) showed that [11C](+)McN5652 had a higher uptake and longer retention in regions with high density of 5-HT uptake sites than the

^{11}C-labeled racemic mixture and that [^{11}C](-)McN5652 washed out rapidly. With the *trans* form [^{11}C](+) enantiomer, the hypothalamus/cerebellum ratio reached 6 at 90 min. When mice received injections of the selective 5-HT uptake blocker paroxetine (5 mg/kg of tissue) before injections of [^{11}C](+)McN5652, binding of [^{11}C](+)McN5652 was inhibited by 45 to 73% in all regions except in the cerebellum. [^{11}C](-)McN5652 showed no specific binding in any of the regions.

Other Non-Primate Mammals

[PubMed]

Brust et al. (14) performed comparative studies between [^{11}C]McN5652 and its analog *S*-([^{18}F]fluoromethyl)-(+)-McN5652 in 6-week-old female pigs. The animals received an infusion of the radiotracers (over 2 min into the jugular vein) at the following doses: 242 ± 94 GBq/μmol (6,540 ± 2,540 mCi/μmol) for [^{11}C](+)McN5652 and 274 ± 110 GBq/μmol (7,405 ± 2,973 mCi/μmol) for *S*-([^{18}F]fluoromethyl)McN5652. PET scans showed that the highest accumulation of both radiotracers was in the ventral midbrain, thalamus, olfactory lobe, and pons, consistent with the known densities of 5-HT transporters. In addition, the kinetics of *S*-([^{18}F]fluoromethyl)-(+)-McN5652 appeared to be faster. A peak of activity in the midbrain was reached at ~12 min post injection, whereas the maximum radioactivity was reached at ~22 min post injection for [^{11}C](+)McN5652. Strong inhibition of the specific binding was observed for both radiotracers after pretreatment with the selective 5-HT uptake inhibitor citalopram (5 mg/kg of tissue).

Non-Human Primates

[PubMed]

Szabo et al. (15) performed dynamic PET scans using [^{11}C]McN5652 on 3 *Papio anubis* baboons. The animals first received injections of [^{11}C](+)McN5652, followed by the pharmacologically inactive enantiomer [^{11}C](-)McN5652 (specific activities at time of injection: 64,195 ± 21,645 MBq/μmol (1,735 ± 585 mCi/μmol) for the (+) enantiomer and 93,721 ± 42,661 MBq/μmol (2,533 ± 1,153 mCi/μmol) for the (-) enantiomer); two animals received [^{11}C](+)McN5652 after pretreatment with the specific 5-HT uptake site inhibitor fluoxetine (5 mg/kg of tissue).

Results showed that the initial brain uptake into the brain was similar for both [^{11}C](+)McN5652 and [^{11}C](-)McN5652, but that at later times (45-120 min after injection), only [^{11}C](+)McN5652 exhibited a distribution pattern characteristic for 5-HT uptake sites (prominent uptake in the midbrain, hypothalamus, striatum, and pons; medium uptake in the cerebral cortex; and minimal activity in the cerebellum). On the other hand, in studies with [^{11}C](-)McN5652 and with [^{11}C](+)McN5652 after 5-HT uptake site blockade with fluoxetine, the radiotracer uptakes were significantly lower and the distribution pattern was relatively even. The differences between [^{11}C](+)McN5652 and [^{11}C](-)McN5652 were calculated for the time interval 95-125 min post injection and used to estimate specific binding. Specific binding correlated well with the known density

of 5-HT uptake sites ($r = 0.95$; $P < 0.001$) in the human brain, as determined *in vitro* by Laruelle and Maloteaux (16). There was also a high correlation ($r = 0.81$; $P < 0.002$) between specific binding obtained with [11C](+)McN5652 (or [11C](-)McN5652) and that obtained with blockade by fluoxetine. At 95-125 min post injection, the midbrain/cerebellum ratio obtained for [11C](+)McN5652 was 1.50 ± 0.38 without fluoxetine and 0.91 ± 0.16 with fluoxetine.

Other primate PET studies using both [11C](+)McN5652 and [11C](-)McN5652 were performed by Kakiuchi et al. (17). The aim of the studies was to investigate age-related changes in the SERT for living brains of conscious young (5.9 ± 1.8 years old) and aged (19.0 ± 3.3 years old) *Macaca mulatta* monkeys. Results showed that specific binding of the SERT was higher in the thalamus and striatum, with intermediate binding in the pons, hippocampus, cingulate gyrus, and cortical regions, and lower binding in the cerebellum (in both young and aged monkeys). Almost all regions – except the cerebellum – showed significant age-related decreases in specific binding of the SERT. When the SERT blocker fluvoxamine (1 mg/kg of tissue) was administered intravenously at 30 min after injection of the radiotracer, the specific binding of the SERT was displaced in both age groups.

Human Studies

[PubMed]

The first studies of the serotonin 5-HT transporter in the living human brain, using PET with [11C](+)McN5652, were reported by Szabo et al. (18). The experimental protocol involved injecting either [11C](+)McN5652 or [11C](-)McN5652 into three healthy subjects, and in two cases, injecting [11C](+)McN5652 after pretreatment with the 5-HT uptake site blocker fluoxetine. Results showed highest accumulation of [11C](+)McN5652, with a steady increase over 120 min after injection of the radiotracer. In contrast, with [11C](-)McN5652 and when [11C](+)McN5652 binding was inhibited with fluoxetine, radioactivity concentrations declined after reaching a peak at 20 to 30 min post injection.

Reivich et al. (19) used [11C](+)McN5652 as a PET agent to study alterations in the brain 5-HT system in patients with depression. In their experiments, four drug-free depressed patients and four healthy control subjects received intravenous injections containing 7-10 mCi of [11C](+)McN5652, and 18 sequential PET scans were obtained at increasing time periods. Distribution volume (DV) ratios of [11C](+)McN5652 (compared with the cerebellum) were calculated in selected regions of interest, using a two-compartment model (20). Results showed significantly larger DV ratios in the left frontal cortex ($P = 0.013$) and the right cingulate cortex ($P = 0.043$), compared with healthy controls. Mean region/cerebellum DV ratios were as follows: 1.941 (in patients) and 1.667 (in control subjects) for the right thalamus, 1.678 (patients) and 1.153 (controls) for the right pons, and 1.359 (patients) and 1.092 (controls) for the right cingulate.

PET studies comparing [11C](+)McN5652 and [11C]cyanoimipramine were performed by Takano et al. (21) in 15 healthy volunteers. [11C](+)McN5652 was injected at a dose of 179-759 MBq (4.8-20.5 mCi), and [11C]cyanoimipramine was injected at a dose of

360-721 MBq before PET scans were performed. The following mean thalamus/cerebellum, striatum/cerebellum, and frontal cortex/cerebellum ratios were obtained at 90 min post injection: 1.61 ± 0.15, 1.59 ± 0.10, and 1.08 ± 0.07 for [^{11}C](+)McN5652 and 1.72 ± 0.18, 1.72 ± 0.18, and 1.17 ± 0.12 for [^{11}C]cyanoimipramine. After pretreatment with 50 mg of clomipramine (injected dose, 370 MBq (100 mCi)), the DVs of [^{11}C](+)McN5652 in the cerebellum and frontal cortex were not significantly changed, but those in the thalamus and striatum were dramatically decreased. The mean thalamus/cerebellum, striatum/cerebellum, and frontal cortex/cerebellum ratios for [^{11}C](+)McN5652 obtained at 90 min post injection were 1.20 ± 0.06, 1.31 ± 0.05, and 0.98 ± 0.03, respectively.

Over recent years, a number of human PET studies using [^{11}C](+)McN5652 have been performed to evaluate the neurotoxic effects of (±)3,4-methylenedioxymethamphetamine (MDMA; "ecstasy") on human brain 5-HT system (22-24). In a study by McCann et al (23). using [^{11}C](+)McN5652 and [^{11}C]DASB, global reductions in SERT concentrations were found in MDMA users with both PET ligands. [^{11}C](+)McN5652 has also been used in PET studies for quantifying the SERT in patients with bipolar disorder (21) and social phobia (25).

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