Trans-1,2,3,5,6,10b-hexahydro-6-[4-([^{18}F]fluoroethylthio)-phenyl]pyrrolo-[2,1-a]-isoquinoline

[^{18}F]FEMcN

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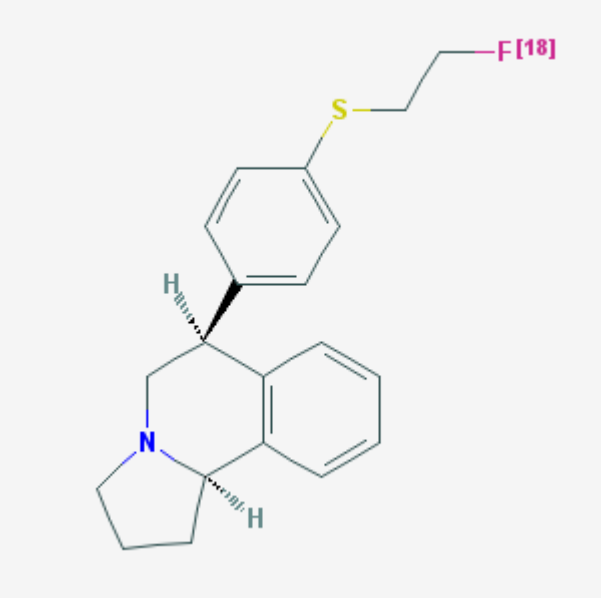
Chemical name:	Trans-1,2,3,5,6,10b-hexahydro-6-[4-([^{18}F]fluoroethylthio)-phenyl]pyrrolo-[2,1-a]-isoquinoline	
Abbreviated name:	[^{18}F]FEMcN	
Synonym:		
Agent Category:	Trans-1,2,3,5,6,10b-hexahydro-6-[4-(methylthio)-phenyl]pyrrolo-[2,1-a]-isoquinoline	
Target:	Serotonin transporter	
Target Category:	Binding	
Method of detection:	PET	
Source of signal:	^{18}F	
Activation:	Not required	
Studies:	• Rodents	Click on the above structure for additional information in PubChem.

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Background

[PubMed]

The serotonin (5-HT) system is known to serves as the gastrointestinal signaling molecule (1) and plays an important role in the development of alcohol dependence (2). It is also involved in a variety of physiological functions and has a function in the development of post-meal satiety, and the pathogenesis of epilepsies, Alzheimer's and Parkinson's diseases (3-5). It is also known to be involved in the development of anxiety and depression disorders (6). Thus imaging of the 5-HT system is considered important to understand a variety of neurological and psychiatric functions and disorders.

A variety of drugs have been labeled with radioactive iodine (^{123}I), carbon (^{11}C) or fluorine (^{18}F) for imaging of the 5-HT receptor or transporter using the positron emission tomography (PET) technique. Among these, trans-1,2,3,5,6,10b-hexahydro-6-[4-(methylthio)-phenyl]pyrrolo-[2,1-a]-isoquinoline ([^{11}C]McN5652-Z), a highly potent serotonin transport (SERT) blocker was developed for imaging and is still used for the evaluation of this system (7, 8). However, during the initial development of [^{11}C]McN5652-Z, because ^{11}C compounds have a very short half-life (20 min), Suehiro et al. (5) decided to synthesize and evaluate the use of an ^{18}F labeled analog of McN5652-Z, that would have a longer half-life, to investigate the SERT system. For this an S-[^{18}F]fluoroethyl analog of McN5652-Z, trans-1,2,3,5,6,10b-hexahydro-6-[4-([^{18}F]fluoroethylthio)-phenyl]pyrrolo-[2,1-a]-isoquinoline ([^{18}F]FEMcN) was generated and its biodistribution in the mouse brain was investigated by *ex vivo* autoradiography.

Synthesis

[PubMed]

The synthesis of [^{18}F]FEMcN was described by Suehiro et al. (5). McN5652 was demethylated in dry dimethylforamide (DMF) with an excess of sodium thiomethoxide. The reaction mixture was then cooled and an excess of 1-bromo-2-fluoroethane was added, with stirring, at room temperature. The resulting product was extracted into dichloromethane and the solvent was evaporated under vacuum. Purification of FEMcN was performed by semipreparative high performance liquid chromatography (HPLC) followed by a dichloromethane extraction. The identity of FEMcN was confirmed by nuclear magnetic resonance and mass spectroscopy. The yield of this reaction was 41%.

The [^{18}F]fluorination of FEMcN was done with a two step procedure. To start, 1-Bromo-2-[^{18}F]fluoroethane was synthesized from 2-bromoethyl triflate in acetonitrile at room temperature (5). The [^{18}F]FEMcN was prepared by S-[^{18}F]fluoroethylation of normethyl McN5652 that was formed by hydrolysis of the butyrate thioester precursor with 1-bromo-2-[^{18}F]fluoroethane. Hydrolysis of the thioester was performed as described by Suehiro et al. (9). Tetrabutylammonium hydroxide (1 M in methanol) was added to the thioester precursor in a vial and stirred on a vortex mixer. After 10 min, 0.1 mL DMF was added, and the solution was transferred into the vial containing 1-bromo-2-

[^{18}F]fluoroethane that had been prepared as described above. The reaction mixture was warmed in a 40-45^{o} C water bath for 1 min, diluted with acetonitrile:water mixture containing 0.1 M ammonium formate and applied to a semi-preparative C-18 column. The radioactive peak with a retention time corresponding to the FEMcN standard was collected. The solvent was evaporated and the residue was dissolved in sterile normal saline. It was then filtered through a 0.22 µM filter into a sterile vial. The radioactive purity and specific activity of the compound were determined by HPLC.

The overall average yield from eleven independent synthesis reactions, based on [^{18}F]fluoride, was 13.0 ± 7.1%. The average synthesis time, including HPLC purification and analysis, was 82 ± 12.1 min. The average specific activity of [^{18}F]FEMcN was 1593 ± 625 mCi/µmole (58,941 ± 23,125 MBq/ µmole). The time at which the specific activity was measured, radiochemical purity and stability of the product was not provided by the investigators.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

No publications are currently available.

Animal Studies

Rodents

[PubMed]

Ex vivo autoradiographic studies on mice revealed that [^{18}F]FEMcN accumulated in the high density 5-HT regions of the brain such as hypothalamus, substantia nigra, and raphe nuclei (5). When nitroquipazine, a selective and highly potent 5-HT uptake blocker, was administered to the animals before [^{18}F]FEMcN, the accumulation of radioactivity was similar to that observed in regions with low 5-HT uptake (such as the cerebellum), indicating that the radiotracer bound specifically to SERT. The whole brain uptake of [^{18}F]FEMcN was 0.94% of the injected dose (%ID)/organ at 30 min. At 60 min post-injection of the label the regional distribution of radioactivity correlated with the distribution of [^{11}C]McN5652 reported earlier from the same laboratory (10). At 120 min the uptake was reduced to 0.35% ID/organ. The specific binding of this radiotracer, as determined with and without blocking by a 5-HT specific uptake blocker, showed the distribution of SERT was similar to that observed during *in vitro* studies indicating SERT could be visualized *in vivo* with [^{18}F]FEMcN. However, compared to the *invivo* behavior of [^{11}C]McN5652, it was concluded [^{18}F]FEMcN was a less favorable PET radiotracer for imaging SERT, because of its lower blood-brain barrier penetration and target-to-nontarget ratios.

Other Non-Primate Mammals

[PubMed]

No publications are currently available.

Non-Human Primates

[PubMed]

No publications are currently available.

Human Studies

[PubMed]

No publications are currently available.

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