(1*R*,2*S*,3*S*,5*S*)-Methyl-8-{[(1*S*,2*S*)-2-([^{18}F]fluoromethyl)cyclopropyl]methyl}-3-phenyl-8-azabicyclo[3.2.1]octane-2-carboxylate

[^{18}F]PR17.MZ

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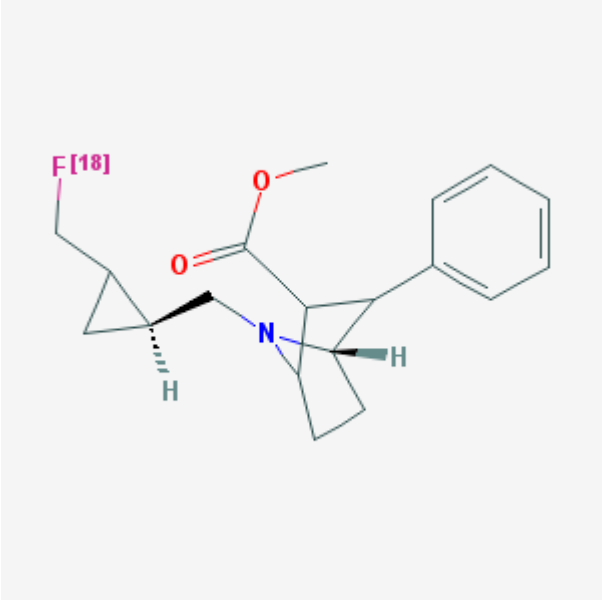
Created: July 12, 2011; Updated: December 8, 2011.

Chemical name:	(1*R*,2*S*,3*S*,5*S*)-Methyl-8-{[(1S, 2S)-2-([^{18}F]fluoromethyl)cyclopropyl]methyl}-3-phenyl-8-azabicyclo[3.2.1]octane-2-carboxylate
Abbreviated name:	[^{18}F]PR17.MZ
Synonym:	
Agent category:	Compound
Target:	Dopamine transporter (DAT)
Target category:	Transporter
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

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NLM Citation: Leung K. (1*R*,2*S*,3*S*,5*S*)-Methyl-8-{[(1*S*,2*S*)-2-([^{18}F]fluoromethyl)cyclopropyl]methyl}-3-phenyl-8-azabicyclo[3.2.1]octane-2-carboxylate. 2011 Jul 12 [Updated 2011 Dec 8]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

Background

[PubMed]

Dopamine, a neurotransmitter, plays an important role in the mediation of movement, cognition, and emotion. Parkinson's disease (PD) is associated with a loss of dopamine-containing neurons in the striatum, resulting in a loss of dopamine transporter (DAT) in the presynaptic nerve terminals (1, 2). Reduction of DAT density is inversely correlated with the severity of motor dysfunction in PD patients. Several (-)-cocaine analogs were developed for the evaluation of DAT density in neurons of PD patients. Radiolabeled 2β-carboxymethoxy-3β-(4-iodophenyl)tropane (β-CIT) and *N*-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (FP-CIT) have been used for brain imaging (3-6). Because of the short physical half-life of ^{11}C-labeled analogs, equilibrium conditions are difficult to achieve in positron emission tomography (PET) measurements. [^{123}I]β-CIT was studied in single-photon emission computed tomography (SPECT) and showed slow tracer uptake kinetics (7, 8). A tropane derivative, [^{11}C]-(*E*)-*N*-(4-fluorobut-2-enyl)-2β-carbomethoxy-3β-(4'-tolyl)nortropane ([^{11}C]LBT-999), was evaluated as a radioligand for studies of DAT with PET imaging (9-11). [1*R*,2*S*,3*S*,5*S*]-Methyl-8-{[(1S, 2S)-2-([^{18}F]fluoromethyl)cyclopropyl]methyl}-3-phenyl-8-azabicyclo[3.2.1]octane-2-carboxylate ([^{18}F]PR17.MZ) was developed through the use of a conformational restriction approach based on (-)-cocaine. PR17.MZ exhibited a 29-fold higher potency than (-)-cocaine in inhibition of human DAT and better selectivity over the human noradrenalin transporter (hNET) and human serotonin transporter (hSERT) (12). [^{18}F]PR17.MZ has been evaluated as a radioligand for studies of DAT with PET imaging.

Related Resource Links:

- Chapters in MICAD (DAT)
- Gene information in NCBI (DAT)
- Articles in Online Mendelian Inheritance in Man (OMIM) (DAT)
- Clinical trials (DAT)

Synthesis

[PubMed]

[^{18}F]PR17.MZ was readily synthesized by standard ^{18}F-fluorination of the bromo-derivative with [^{18}F]KF/Kryptofix 2.2.2 for 50 s in a focused microwave reactor (250 W, 180°C) (12). [^{18}F]PR17.MZ was purified with high-performance liquid chromatography. Overall radiochemical yield (decay-corrected) was 86%, with a specific activity of 180 GBq/μmol (4.9 Ci/μmol) at the end of synthesis and a radiochemical purity of >98%. Total synthesis time was not reported.

In Vitro studies: Testing in Cells and Tissues

[PubMed]

PR17.MZ binding affinity for hDAT, hSERT, and hNET was determined using stably transfected HEK293 cells (12). [^{3}H]β-CFT, [^{3}H]citalopram, and [^{3}H]nisoxetine were used as radioligands, respectively. The 50% inhibition concentration values for hDAT, hSERT, and hNET were 11 nM, 1,400 nM, and 175 nM, respectively. *In vitro* autoradiography studies with [^{18}F]PR17.MZ in rat brain sections showed a high radioactivity level in the striatum, with low binding in the cortical regions and cerebellum. Binding in the brain was totally blocked in the presence of 1 μM β-CFT.

Animal Studies

Rodents

[PubMed]

Riss et al. (12) performed dynamic PR17.MZ PET brain scans of normal rats (n = 3). Striatal peak accumulation of 0.92 ± 0.06% injected dose/ml (ID/ml) was reached at 70 s after injection, followed by a gradual washout to 0.49 ± 0.06% ID/ml and 0.23 ± 0.03% ID/ml at 20 min and 45 min, respectively. The accumulation in the cerebellum was 0.32 ± 0.08% ID/ml and 0.12 ± 0.06% ID/ml at 10 s and 20 min, respectively. Co-injection of β-CFT (1.5 mg/kg) with the tracer displaced the radioactivity in the striatum to the background level at 90 min after injection. The equilibrium state between the striatum and cerebellum was reached as soon as 20 min. Logan graphical analysis provided a distribution volume ratio of ~3 for the striatum.

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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