N-4-Fluorobut-2-yn-1-yl-2β-carbo-[^{11}C]methoxy-3β-phenyltropane

[^{11}C]PR04.MZ

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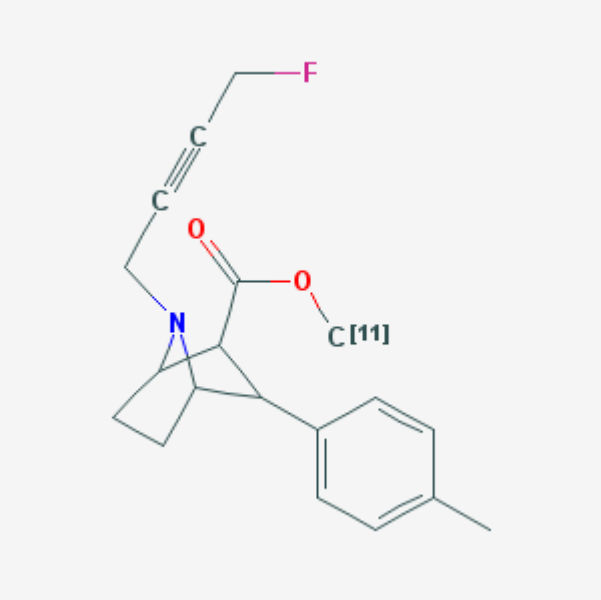
Chemical name:	*N*-4-Fluorobut-2-yn-1-yl-2β-carbo-[^{11}C]methoxy-3β-phenyltropane
Abbreviated name:	[^{11}C]PR04.MZ
Synonym:	
Agent category:	Compound
Target:	Dopamine transporter (DAT)
Target category:	Transporter
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

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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). *N*-4-Fluorobut-2-yn-1-yl-2β-carbo-[^{11}C]methoxy-3β-phenyltropane ([^{11}C]PR04.MZ) was developed through the use of a conformational restriction approach based on (-)-cocaine (12). PR04.MZ exhibited a 100-fold higher potency than (-)-cocaine in inhibition of human DAT and better selectivity over the human noradrenalin transporter (hNET) and human serotonin transporter (hSERT). [^{11}C]PR04.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]

[^{11}C]PR04.MZ was synthesized with a standard methylation reaction of its corresponding *O*-desmethyl trifluoroacetic acid salt precursor with [^{11}C]methyl iodide and rubidium carbonate in *N,N*-dimethylformamide (75°C, 5 min) (12). The radiochemical yields (non-decay corrected) were >20% (n = 3). The radiochemical purity was >98%, with a specific activity of 67 GBq/μmol (1.8 Ci/μmol) at the end of synthesis. The total synthesis time was 45 min.

In Vitro studies: Testing in Cells and Tissues

[PubMed]

PR04.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 1.9 ± 0.2 nM, 108.4 ± 1.3 nM, and 22.5 ± 0.8 nM, respectively.

Animal Studies

Rodents

[PubMed]

Riss et al. (12) performed dynamic PET brain scans in one normal rat for 60 min as a preliminary study after injection of 37 MBq (1 mCi) [^{11}C]PR04.MZ. The peak striatal accumulation of 2.22% injected dose per cm^3 of tissue was reached at 4 min after injection, and this accumulation decreased only slightly for the duration of the scans. The striatum/cerebellum ratios were 2.4, 3.6, and 5.0 at 15, 30, and 60 min after injection. Pretreatment (45 min before [^{11}C]PR04.MZ injection) with GBR12909, a structurally unrelated DAT inhibitor, decreased the striatum/cerebellum ratio to 1.6 at 60 min after injection.

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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