(+/-)-2-(*N*-Phenethyl-*N*-1'-[^{11}C]propyl)amino-5-hydroxytetralin

[^{11}C]PPHT

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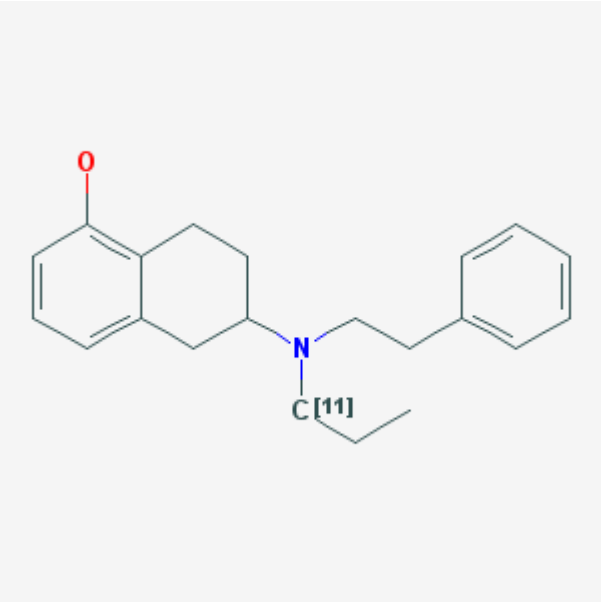
Chemical name:	(+/-)-2-(*N*-Phenethyl-*N*-1'-[^{11}C]propyl)amino-5-hydroxytetralin
Abbreviated name:	[^{11}C]PPHT
Synonym:	
Agent Category:	Compound
Target:	D_2 dopamine receptors
Target Category:	Receptor binding
Method of detection:	PET
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates



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Background

[PubMed]

Dopamine, a neurotransmitter, plays an important role in the mediation of movement, cognition, and emotion (1, 2). Dopamine receptors are involved in the pathophysiology of neuropsychiatric diseases, such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and schizophrenia (3). Five subtypes of dopamine receptors, D_1 through D_5, have been well characterized pharmacologically and biochemically (4). These five dopamine receptor subtypes are classified into two subfamilies: D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4). D_1-like and D_2-like receptors exert synergistic as well as opposite effects at both the biochemical and overall system levels. Most striatal D_1 and D_2 receptors are localized postsynaptically on caudate-putamen neurons and to a lesser extent presynaptically on nigrostriatal axons.

Dopamine receptors are G-protein–coupled receptors that exist in high- and low-affinity states with respect to agonist binding. The two states are inter-convertible. In the high-affinity state, dopamine receptors are coupled to G-proteins, whereas in the low-affinity state they are not. Dopamine has a dissociation constant (K_d) of 7 nM for the high-affinity state (K_{high}) and a K_d of 1,720 nM for the low-affinity state (K_{low}) (5). Under physiologic conditions, dopamine binds predominately to receptors in the high-affinity state. The high-affinity state was suggested to be the functional form of the dopamine receptors (6).

Substituted benzamides, such as sulpiride, raclopride, and iodobenzamide, are specific ligands with only moderate affinity for the D_2 receptors, making study of extrastriatal D_2 receptors difficult (7-9). In binding studies, [^{123}I]epidepride, an analog of isoremoxipride, was found to have high potency and low nonspecific binding, and to be selective for striatal and extrastriatal D_2 receptors (10). Epidepride exhibits marginal binding to D_4 receptors, with little affinity for other known neurotransmitter receptors. (S)-*N*-((1-Allyl-2-pyrrolidinyl)methyl)-5-(3-[^{18}F]fluoropropyl)-2,3-dimethoxybenzamide ([^{18}F]fallypride), an analog of epidepride, was found to be a selective high-affinity antagonist of $D_{2/3}$ receptors (11), and in positron emission tomography (PET) *in vivo* studies (12-14) it identified extrastriatal $D_{2/3}$ receptors. However, none of these antagonists distinguishes between the high- and low-affinity states of the D_2 receptors. (–)-*N*-[^{11}C]Propyl-norapomorphine ([^{11}C]NPA) and [^{11}C](+)-4-*N*-propyl-,3,4a,5,6,10b-hexahydro-2*H*-naphth[1,2-*b*][1,4]oxazin-9-ol ([^{11}C](+)-PHNO) have been developed as radiolabeled dopamine agonists for the non-invasive study of the high-affinity state of the $D_{2/3}$ receptors in the brain.

Various hydroxytetralin analogs with different binding affinities for the D_2 receptors have been developed as agonist radiotracers (15). (+/-)-2-(*N*-Phenethyl-*N*-1'-[^{11}C]propyl)amino-5-hydroxytetralin ([^{11}C]PPHT) is being evaluated as a PET agent for the high-affinity state of $D_{2/3}$ receptors.

Synthesis

[PubMed]

Shi et al. (15) reported a two-step synthesis of [^{11}C]PPHT in which [^{11}C]propionyl chloride was reacted with 5-hydroxy-2-[*N*-(2-phenethyl)amino]tetralin and followed by $LiAlH_4$ reduction, with a radiochemical yield of 5–10% (based on [^{11}C]CO_2 at the end of bombardment) and an average specific activity of 9–37 GBq/μmol (250–1,000 mCi/μmol) at end of synthesis after purification by high-performance liquid chromatography. [^{11}C]Propionyl chloride was prepared by reacting [^{11}C]CO_2 with ethylmagnesium bromide, followed by reaction with phthaloyl chloride. Total synthesis time was 60–75 min.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In a binding study of dopamine receptors in membranes of the rat striatum with [^{3}H]spiperone, PPHT had an IC_{50} of 0.65 nM (15). *In vitro* autoradiography studies of rat brain slices indicated selective binding of [^{11}C]PPHT to the striata, which was completely inhibited by co-incubation with 10 μM sulpiride. Gpp(NH)p decreased the striatum/cerebellum ratio from 2.0 to 1.1 by converting the high-affinity state to the low-affinity state. There was significant nonspecific binding in the cortex.

Animal Studies

Rodents

[PubMed]

Biodistribution studies in rats showed a marked accumulation of the tracer in the striata within the first 2 min [1.2% injected dose per gram (ID/g)], followed by a decrease of radioactivity to 0.5% ID/g at 30 min and 0.2% ID/g at 60 min (16). The striatum/cerebellum ratios were 1.27 at 2 min, 1.52 at 30 min, and 1.42 at 60 min after injection. Haloperidol pretreatment (1 mg/kg, 15 min before radiotracer injection) effectively reduced specific binding of [^{11}C]PPHT to the striatum with some residual binding relative to the cerebellum at 30 min. Little inhibition was seen in the cerebellum. [^{11}C]PPHT thus displays uptake and washout kinetics characteristic of reversible radiotracers.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Mukherjee et al. (16) showed selective accumulation (0.03% ID/ml) in the striata of two rhesus monkeys with striatum/cerebellum ratios of 1.5 at 30 min and 1.4 at 60 min after injection of 26–93 MBq (0.7–2.5 mCi) of [^{11}C]PPHT. Thalamus/cerebellum ratios were 1.3 at 30 min and 1.2 at 60 min. However, there was a substantial nonspecific binding in the cortex and cerebellum. The authors suggested that the use of the more active *S*-isomer may provide higher striatum/cerebellum and thalamus/cerebellum ratios.

Human Studies

[PubMed]

No relevant publication is currently available.

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