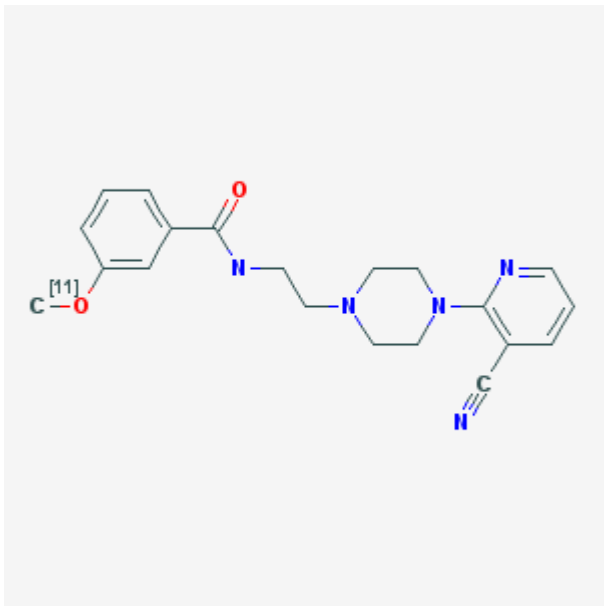


N-[2-[4-(3-Cyanopyridin-2-yl)piperazin-1-yl]ethyl]-3-[¹¹C]methoxybenzamide [¹¹C]7

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Chemical name:	N-[2-[4-(3-Cyanopyridin-2-yl)piperazin-1-yl]ethyl]-3-[¹¹ C]methoxybenzamide	
Abbreviated name:	[¹¹ C]7	
Synonym:		
Agent category:	Compound	
Target:	Dopamine D ₄ receptor	
Target category:	Receptor	
Method of detection:	Positron emission tomography (PET)	
Source of signal:	¹¹ C	
Activation:	No	
Studies:	<ul style="list-style-type: none">• <i>In vitro</i>• 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, D₁₋₅, have been well characterized pharmacologically and biochemically (4). These five subtypes have been classified into two subfamilies of D₁-like (D₁, D₅) and D₂-like (D₂, D₃, D₄) dopamine receptors. D₁-Like and D₂-like receptors exert synergistic as well as opposite effects at the biochemical and overall system levels. A great majority of striatal D₁ and D_{2/3} receptors are localized postsynaptically on the caudate-putamen neurons, and to a lesser extent presynaptically on nigrostriatal axons. On the other hand, D₄ receptors are mostly found in the extrastriatal regions of the brain, such as the cortex, hippocampus, thalamus, and medulla. These areas are believed to control emotion and cognition.

In addition to D₂ receptors, D₄ receptors may play an important role in the pathophysiology of schizophrenia, as suggested by clinical studies of the atypical neuroleptic clozapine in patients (5, 6). Clozapine is not only effective against positive symptoms of schizophrenia, but it is also efficacious against the negative symptoms. Clozapine has a 10-fold greater affinity for D₄ receptors than for D₂ receptors (7). However, it also has high affinities for 5-HT_{1A,1B,2A,2C,6,7}, α_{1A,2A,2C}, muscarinic M₁, and histamine H₁ receptors. The neurophysiological role of D₄ receptors remains to be defined. Thus, there is a need for selective ligands to investigate the pharmacological role of D₄ receptors. There have been several attempts to develop specific D₄ radioligands for use with positron emission tomography (PET) imaging of D₄ receptors (8-10). However, none has proved suitable because of a lack of selectivity, extremely low D₄ receptor density in the brain, and other pharmacological issues. Lacivita et al. (11) reported that *N*-[2-[4-(3-cyanopyridin-2-yl)piperazin-1-yl]ethyl]-3-methoxybenzamide (compound 7) is a potent inhibitor (agonist) of D₄ receptors, with >100-fold selectivity over D₂ and D₃ receptors. This led to the development of *N*-[2-[4-(3-cyanopyridin-2-yl)piperazin-1-yl]ethyl]-3-[¹¹C]methoxybenzamide ([¹¹C]7) as a potential D₄ receptor radioligand for use with PET imaging of D₄ receptors in the brain.

Related Resource Links:

- Chapters in MICAD ([dopamine receptors](#))
- Gene information in NCBI ([D₂ receptor](#), [D₃ receptor](#), [D₄ receptor](#))
- Articles in Online Mendelian Inheritance in Man (OMIM) ([D₂ receptor](#), [D₃ receptor](#), [D₄ receptor](#))
- Clinical trials ([dopamine receptors](#))

Synthesis

[PubMed]

Lacivita et al. (11) synthesized [¹¹C]7 by reaction of [¹¹C]CH₃I with *N*-[2-[4-(3-cyanopyridin-2-yl)piperazin-1-yl]ethyl]-3-hydroxybenzamide for 3 min at 70°C. [¹¹C]7 was purified with high-performance liquid chromatography (HPLC), with >99% radiochemical purity. The specific activity of [¹¹C]7 was 2,770–3,890 GBq/μmol (74.9–105.1 Ci/μmol) at the end of synthesis. The radiochemical yield was 40.5 ± 10.8% (*n* = 4), with a total synthesis time of 28 min from the end of bombardment. The Log*D*_{7.4} value of compound 7 was 2.47.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Compound 7 was reported to have high binding affinities to D₄ receptor sites but not to D_{2/3} receptors in recombinant HEK293 cell lines (11). The *K*_i value for D₄ receptors using [³H]methylspiperone was 1.52 ± 0.20 nM. Compound 7 exhibited >100-fold selectivity over D₂, D₃, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, cannabinoid CB₁, and sigma-1 receptors. Compound 7 exhibited D₄ agonist activity by a decrease in forskolin-stimulated levels of cAMP accumulation in HEK293 cells expressing human recombinant D₄ receptors.

Animal Studies

Rodents

[PubMed]

Lacivita et al. (11) performed *ex vivo* biodistribution studies in normal mice (*n* = 3) at 15, 30, 60, 120, and 240 min after intraperitoneal injection of 10 mg/kg unlabeled compound 7. Concentrations of compound 7 in the brain tissue and plasma were determined with HPLC. There was a rapid accumulation in the plasma, followed by a fast washout. The peak concentration in the plasma was 0.37 ± 0.21 μg/g at 30 min and became undetectable after 60 min. The concentration of an *N*-dealkylation metabolite, 1-(6-cyano-2-pyridyl)piperazine, was determined to be 0.22 ± 0.12 μg/g. The plasma concentrations of compound 7 and its metabolite at 30 min were 0.14 ± 0.02 μg/g and <0.1 μg/g, respectively.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Lacivita et al. (11) performed dynamic PET brain scans on a male rhesus monkey for 90 min after injection of 38.5 MBq (1.04 mCi) [¹¹C]7. The radioactivity accumulation in the hippocampus, striatum, cingulate cortex, entorhinal cortex, occipital cortex, and cerebellum peaked at 45 s and then declined. Little difference was observed between their time-radioactivity curves, suggesting no specific binding in these regions. About 3.1% injected dose reached the brain at 45 s. On the other hand, there was a gradual increase in radioactivity accumulation in the retina (reported to be rich in D₄ receptors in rats), which reached a plateau at 20–60 min. The retina/brain ratio was 6 at 90 min. No blocking studies were performed. The investigators concluded that a selective D₄ ligand with higher affinity than compound 7 is needed for further studies.

Human Studies

[PubMed]

No publication is currently available.

NIH Support

R01 MH063162, R01 MH063162-06S1

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