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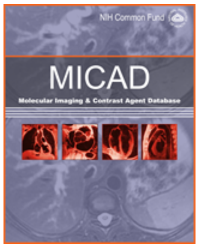
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/



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

[^{11}C]7

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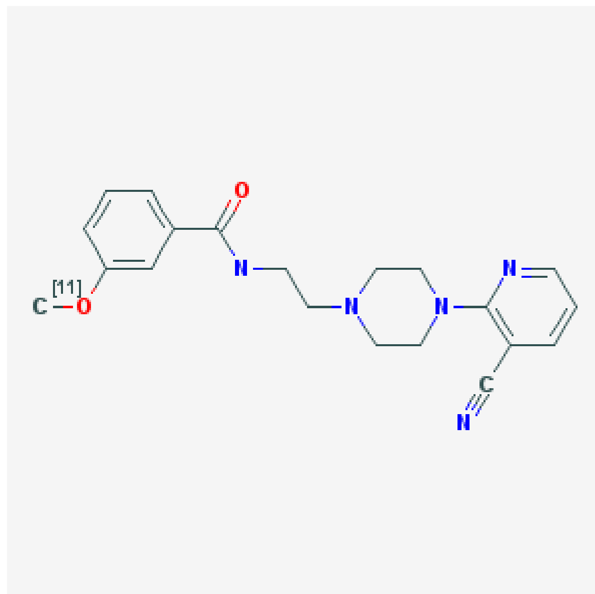
Chemical name:	*N*-[2-[4-(3-Cyanopyridin-2-yl)piperazin-1-yl]ethyl]-3-[^{11}C]methoxybenzamide	
Abbreviated name:	[^{11}C]7	
Synonym:		
Agent category:	Compound	
Target:	Dopamine D_4 receptor	
Target category:	Receptor	
Method of detection:	Positron emission tomography (PET)	
Source of signal:	^{11}C	
Activation:	No	
Studies:	• *In vitro* • Rodents • Non-human primates	Click on the above structure for additional information in PubChem.

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_{1-5}, have been well characterized pharmacologically and biochemically (4). These five subtypes have been classified into two subfamilies of D_1-like (D_1, D_5) and D_2-like (D_2, D_3, D_4) dopamine receptors. D_1-Like and D_2-like receptors exert synergistic as well as opposite effects at the biochemical and overall system levels. A great

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majority of striatal D_1 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, D_4 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 D_2 receptors, D_4 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 D_4 receptors than for D_2 receptors (7). However, it also has high affinities for 5-$HT_{1A,1B,2A,2C,6,7}$, $\alpha_{1A,2A,2C}$, muscarinic M_1, and histamine H_1 receptors. The neurophysiological role of D_4 receptors remains to be defined. Thus, there is a need for selective ligands to investigate the pharmacological role of D_4 receptors. There have been several attempts to develop specific D_4 radioligands for use with positron emission tomography (PET) imaging of D_4 receptors (8-10). However, none has proved suitable because of a lack of selectivity, extremely low D_4 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 D_4 receptors, with >100-fold selectivity over D_2 and D_3 receptors. This led to the development of *N*-[2-[4-(3-cyanopyridin-2-yl)piperazin-1-yl]ethyl]-3-[^{11}C]methoxybenzamide ([^{11}C]7) as a potential D_4 receptor radioligand for use with PET imaging of D_4 receptors in the brain.

Related Resource Links:

- Chapters in MICAD (dopamine receptors)
- Gene information in NCBI (D_2 receptor,D_3 receptor, D_4 receptor)
- Articles in Online Mendelian Inheritance in Man (OMIM) (D_2 receptor, D_3 receptor, D_4 receptor)
- Clinical trials (dopamine receptors)

Synthesis

[PubMed]

Lacivita et al. (11) synthesized [^{11}C]7 by reaction of [^{11}C]CH_3I with *N*-[2-[4-(3-cyanopyridin-2-yl)piperazin-1-yl]ethyl]-3-hydroxybenzamide for 3 min at 70°C. [^{11}C]7 was purified with high-performance liquid chromatography (HPLC), with >99% radiochemical purity. The specific activity of [^{11}C]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 D_4 receptor sites but not to $D_{2/3}$ receptors in recombinant HEK293 cell lines (11). The K_i value for D_4 receptors using [^{3}H]methylspiperone was 1.52 ± 0.20 nM. Compound 7 exhibited >100-fold selectivity over D_2, D_3, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, cannabinoid CB_1, and sigma-1 receptors. Compound 7 exhibited D_4 agonist activity by a decrease in forskolin-stimulated levels of cAMP accumulation in HEK293 cells expressing human recombinant D_4 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) [^{11}C]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 D_4 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 D_4 ligand with higher affinity than compound 7 is needed for further studies.

Human Studies

[PubMed]

No publication is currently available.

NIH Support

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