1-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-4-((6-[^{18}F]fluoropyridin-3-yl)methyl)piperazine

[^{18}F]3d

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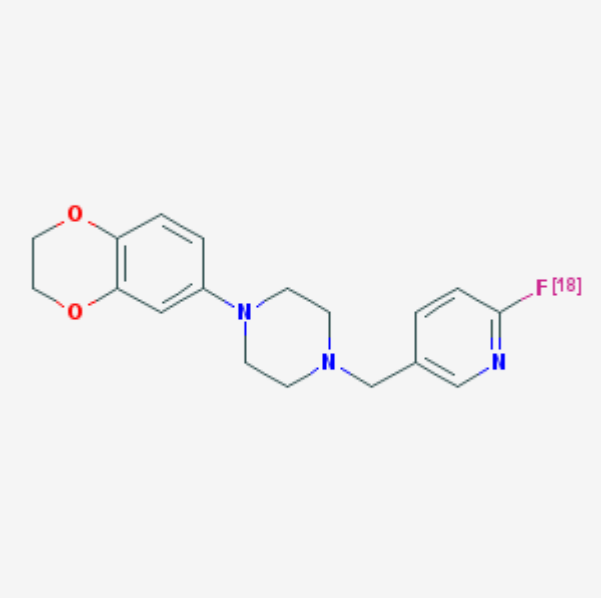
Chemical name:	1-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-4-((6-[^{18}F]fluoropyridin-3-yl)methyl)piperazine
Abbreviated name:	[^{18}F]3d
Synonym:	
Agent category:	Compound
Target:	Dopamine D_4 receptor
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

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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, $D_{1\text{-}5}$, 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 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 to 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 and other pharmacological issues. Kugler et al. (11) reported that 1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-4-((6-fluoropyridin-3-yl)methyl)piperazine (3d) is a potent antagonist of D_4 receptors, with >1,100-fold selectivity over D_2 and D_3 receptors. This led to the development of 1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-4-((6-[^{18}F]fluoropyridin-3-yl)methyl)piperazine ([^{18}F]3d) 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]

6-[^{18}F]Fluoronicotinaldehyde was produced *via* nucleophilic aromatic substitution of the chloro derivative with K[^{18}F]F/Kryptofix2.2.2 in dimethyl sulfoxide (11). [^{18}F]3d radiosynthesis was accomplished by the reductive amination of 6-[^{18}F]fluoronicotinaldehyde with 1-(1,4-benzodioxine-6-yl)piperazine in one-pot synthesis, followed by high-performance liquid chromatography purification. The overall radiochemical yield of [^{18}F]3d was 15 ± 5%, with a specific radioactivity of 60 GBq/μmol (1.6 Ci/μmol) at the end of synthesis. The radiochemical purity was >98%, with a total synthesis time of ~80 min. Compound 3d exhibited a log$D_{7.4}$ value of 1.81 ± 0.05.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Compound 3d was reported to have high binding affinities to D_4 receptor sites but not to $D_{1/2/3}$ receptors in recombinant cell lines (11). The K_i values for D_1, D_{2long}, D_{2short}, D_3, and D_4 receptors were 35,000, 29,000, 45,000, 17,000, and 1.5 ± 0.7 nM, respectively. The D_2/D_4K_i ratio was calculated to be >2,000. Compound 3d exhibited little affinity for 5-HT_{1A}, 5-HT_2, and sigma-1 receptors (K_i values > 5,800 nM). *In vitro* autoradiography studies of rat brain sections showed that [^{18}F]3d (5 nM) displayed radioactivity throughout the brain with a distinct high accumulation of radioactivity in the colliculus and cerebellum. Compound 3d (10 μM) blocked the radioactivity to homogeneity. Non-specific binding of [^{18}F]3d on horizontal rat brain slices was ~7%.

Animal Studies

Rodents

[PubMed]

Kugler et al. (11) performed *ex vivo* biodistribution studies in normal mice (n = 3/group) at 5, 10, 15, and 30 min after intravenous injection of 1.1–2.6 MBq (0.03–0.07 mCi) [^{18}F]3d. Radioactivity accumulation in the brain was 4.93%, 2.85%, 2.27%, and 1.47% injected dose per gram (ID/g) at 5, 10, 15, and 30 min, respectively. The organ with the highest radioactivity accumulation at 30 min was the liver (7.79% ID/g), followed by the pancreas (7.43% ID/g), kidney (6.03% ID/g), intestine (4.47% ID/g), spleen (3.13% ID/g), lung (2.68% ID/g), heart (1.13% ID/g), bone (0.93% ID/g), and blood (0.53% ID/g). [^{18}F]3d remained >98% and ~50% intact in the brain and plasma, respectively, at 10 min after injection. *Ex vivo* autoradiography studies of the brain at 15 min showed high radioactivity in the colliculus, cerebral cortex, and cerebellum, with moderate radioactivity in the hippocampus and striatum. No blocking studies were performed. Further studies are needed to define the selectivity of [^{18}F]3d as a D_4 PET radioligand *in vivo*.

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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