3-(4-[^{18}F]Fluorobenzyl)-8-methoxy-1,2,3,4 tetrahydrochromeno[3,4-c]pyridin-5-one

[^{18}F]FMTP

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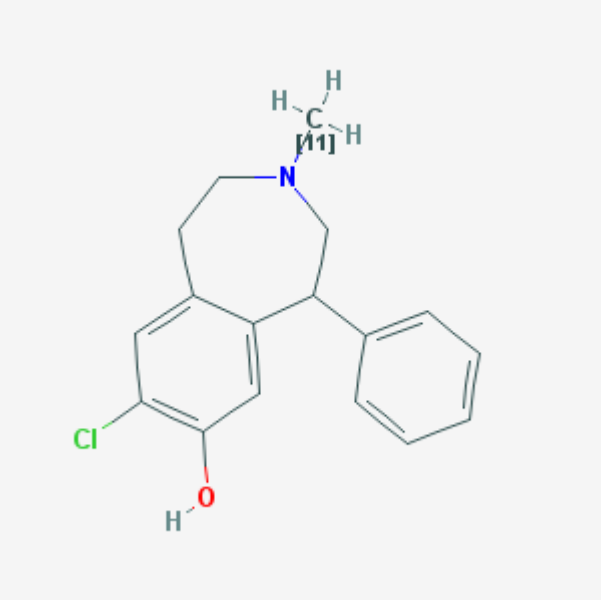
Chemical name:	3-(4-[^{18}F]Fluorobenzyl)-8-methoxy-1,2,3,4-tetrahydrochromeno[3,4-c]pyridin-5-one
Abbreviated name:	[^{18}F]FMTP
Synonym:	
Agent category:	Compound
Target:	Dopamine D_4 receptor
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

Background

[PubMed]

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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, $D_{1\text{-}5}$, were well-characterized pharmacologically and biochemically (4). These five subtypes were 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 nigrostiatal 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.

Beside D_2 receptors, D_4 receptors may play an important role in the pathophysiology of schizophrenia from clinical studies of the atypical neuroleptic clozapine in patients (5, 6). Clozapine is not only effective against positive symptoms of schizophrenia but also is efficacious against the negative symptoms. Clozapine has a 10-fold greater affinity for D_4 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 neurophysiologic 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 antagonists for PET radioligands for D_4 receptors (8-10). However, none has proved suitable because of lack of selectivity and other pharmacological issues. Unangst et al. (11) reported that 3-(4-fluorobenzyl)-8-methoxy-1,2,3,4-tetrahydrochromeno[3,4-c]pyridin-5-one is a potent inhibitor of D_4 receptors with >100-fold selectivity over D_2 and D_3 receptors. This led to the development of 3-(4-[^{18}F]fluorobenzyl)-8-methoxy-1,2,3,4-tetrahydrochromeno[3,4-c]pyridin-5-one ([^{18}F]FMTP) as a potential D_4 receptor radioligand (12). [^{18}F]FMTP was shown to identify extrastriatal D_4 receptors in the regions of cortex and medulla in rat 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]

4-[^{18}F]Fluorobenzaldehyde was obtained by nucleophilic aromatic substitution of 4-trimethylammonium-benzaldehyde triflate with K[^{18}F]F/Kryptofix2.2.2 in DMSO. [^{18}F]FMTP radiosynthesis was accomplished by the reductive amination of 4-

[^{18}F]fluorobenzaldehyde with 8-methoxy-1,2,3,4-tetrahydrochromeno[3,4-c]pyridin-5-one, followed by high-performance liquid chromatography (HPLC) purification (12). The overall radiochemical yield of the radiosynthesis was 19.5% (decay corrected), the specific radioactivity was about 110 GBq/μmol (2.5 Ci/μmol) and the radiochemical purity was greater than 99%, the time of synthesis and purification was approximately 110 min.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

FMTP was reported to have high-affinity binding affinities to D_4 receptor sites and not to $D_{2/3}$ receptors in recombinant cell lines (11). The K_i values for D_2, D_3, and D_4 receptors using [^{3}H]spiperone were 5800, 548 and 4.3 nM, respectively. The D_2/D_4 K_i ratio was calculated to be 1,350.

Animal Studies

Rodents

[PubMed]

Biodistribution studies in rat showed a moderate accumulation of radioactivity in the whole brain, showing 0.6%, 0.5%, 0.4%, and 0.2% ID/g. at 2, 15, 30, and 120 min after injection of [^{18}F]FMTP, respectively (12). There was a marked accumulation of the tracer in the frontal cortex within the first 10 min (0.69% ID/g), followed by a slow decrease of radioactivity to 0.35% ID/g at 60 min. The medulla exhibited a slightly higher radioactivity compared to other brain regions at 15, 30, 60 and 120 min. The maximum medulla-to-striatum and cortex-to-striatum ratios were 2.03 and 1.15, respectively. The accumulation of [^{18}F]FMTP in frontal cortex and medulla were blocked by 1 mg/kg of unlabeled FMTP injected 15 min before the tracer with 84-86% decrease in radioactivity. The fraction of unchanged [^{18}F]FMTP in blood samples determined by HPLC was 40% after 60 min after injection. The radioactivity remained intact in the brain. Further studies are needed to define the selectivity of [^{18}F]FMTP 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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