(S)-*N*-((1-Allyl-2-pyrrolidinyl)methyl)-5-(3-[^{18}F]fluoropropyl)-2-methoxybenzamide

[^{18}F]DMFP

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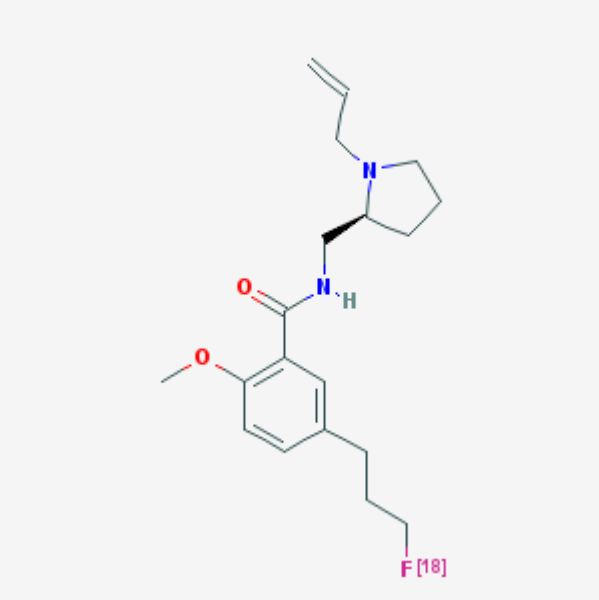
Chemical name:	*(S)*-*N*-((1-Allyl-2-pyrrolidinyl)methyl)-5-(3-[^{18}F]fluoropropyl)-2-methoxybenzamide
Abbreviated name:	[^{18}F]DMFP
Synonym:	[^{18}F]Desmethoxyfallypride
Agent Category:	Compound
Target:	D_2 and D_3 dopamine receptors
Target Category:	Receptor binding
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Non-human primates • Humans



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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.

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 (5-7). 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 (8). 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 (9), and in positron emission tomography (PET) *in vivo* studies (10-12) it identified extrastriatal $D_{2/3}$ receptors. On the other hand, (S)-*N*-((1-Allyl-2-pyrrolidinyl)methyl)-5-(3-fluoropropyl)-2-dimethoxybenzamide (desmethoxyfallypride, or DMFP) has a lower affinity for $D_{2/3}$ receptors than fallypride (IC_{50}15 nM for DMFP *versus* 0.6 nM for fallypride) but is more similar to raclopride (IC_{50} = 30 nM) (13). Therefore, the longer half-life ($t_{1/2}$) of ^{18}F (109.8 min) *versus* ^{11}C (20.4 min) and an affinity comparable to [^{11}C]raclopride provides a fluorine-18 analog of [^{11}C]raclopride as an imaging tracer for studying striatal $D_{2/3}$ receptors with [^{18}F]DMFP PET in humans.

Synthesis

[PubMed]

Mukherjee et al. (13) reported that [^{18}F]DMFP was synthesized by a nucleophilic fluorination of *(S)-N*-[(1-allyl-2-pyrrolidinyl)methyl]-5-(3-toluenesulfonyloxypropyl)-2-methoxybenzamide with K[^{18}F]F/Kryptofix 2.2.2 at 85°C for 30 min, with yields of 20–30% (decay-corrected) and specific activities of 29.6–55.5 GBq/μmol (0.8–1.5 Ci/μmol) after high-performance liquid chromatography purification. Grunder et al. (14) improved the radiochemical yields to 80 ± 10% by using 36 μM potassium carbonate in the nucleophilic fluorination reaction with specific activities of 37–834 GBq/μmol (1.0–22.5 Ci/μmol) at the time of injection.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Fallypride was reported to have high binding affinities for $D_{2/3}$ receptor sites in homogenates of rat striatal membranes (9, 15). The IC_{50}, obtained by use of [^{3}H]spiperone, was 0.6 nM. The dissociation constant (K_d) of [^{18}F]fallypride for $D_{2/3}$ was 0.033 nM in rat striatal homogenates (16). On the other hand, DMFP had a lower affinity (IC_{50} 15 nM using [^{3}H]spiperone) than fallypride. The K_d of [^{18}F]DMFP for $D_{2/3}$ was 0.34 nM in rat striatal homogenates, with a dissociation rate of 0.073 min^{-1} (displacement with 100 μM dopamine) and a $t_{1/2}$ of 9.5 min.

Animal Studies

Rodents

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Mukherjee et al. (9) observed selective uptake in the striatum [0.06–0.08% injected dose per ml (ID/ml)] of rhesus monkey brain with a striatum/cerebellum ratio of 3 at 40 min after injection. Specifically bound [^{18}F]DMFP had a dissociation rate of 0.0083 min^{-1} ($t_{1/2}$ = 83 min). The striatal accumulation of [^{18}F]DMFP was reversed by treatment with haloperidol (a $D_{2/3}$ antagonist, 1 mg/kg) and D-amphetamine (1 mg/kg) at approximately 17 min after tracer injection, with a dissociation rate of 0.058 min^{-1} ($t_{1/2}$ = 12 min) and 0.01 min^{-1} ($t_{1/2}$ = 69.3 min), respectively. Pretreatment with D-amphetamine (1 mg/kg) 28 min before tracer injection provided a dissociation rate of 0.018 min^{-1} ($t_{1/2}$ = 38.5 min). D-Amphetamine is known to induce a marked release of dopamine to the synaptic cleft (17). [^{18}F]DMFP was able to detect the change in dopamine levels induced by D-amphetamine in these studies as indicated by increases in the dissociation rate of [^{18}F]DMFP.

Human Studies

[PubMed]

[^{18}F]DMFP PET studies of $D_{2/3}$ receptor distribution in the human brain have shown significant localization of radioactivity in the striatum and a significant minor accumulation in the thalamus (10, 14). Quantitative analysis of [^{18}F]DMFP binding was usually performed by use of distribution volume (DV), from which binding potentials (BPs) were derived to measure receptor concentrations with cerebellum as reference. Grunder et al. (14) reported on [^{18}F]DMFP PET studies in 10 normal subjects. PET brain scans showed a high accumulation of radioactivity in the putamen (BP = 2.19–2.36) and caudate (BP = 1.70–1.92), and a small but detectable accumulation in the thalamus (BP = 0.13–0.23) after injection of 214 ± 54 MBq (5.8 ± 1.5 mCi) [^{18}F]DMFP using compartmental, graphical, and equilibrium methods of analyses. The ratio of striatum/cerebellum binding was approximately 3 at 120 min after injection. Treatment of a schizophrenic patient with a high dose of amisulpride (1,000 mg/d) resulted in a 90% reduction of [^{18}F]DMFP accumulation in the striatum. At 120 min post-injection, >50% of [^{18}F]DMFP radioactivity remained intact in the blood.

Siessmeier et al. (10) compared striatal binding of [^{11}C]raclopride, [^{18}F]fallypride, and [^{18}F]DMFP for $D_{2/3}$ receptor sites in 6 healthy control subjects (19–51 years of age). A conventional model of graphical analysis using metabolite-corrected arterial inputs and models with reference tissue inputs were used to calculate voxel-wise parametric maps of the equilibrium DVs and the BPs of the three radioligands in the brain. The DV and BP estimates obtained by volume-of-interest analysis did not differ from the mean of voxel-wise estimates in the same striatal volumes. In the striatum, the mean [^{18}F]DMFP BP ranged from 1.9 to 2.5, whereas the mean [^{11}C]raclopride BP ranged from 3 to 4. In contrast, the mean BP of [^{18}F]fallypride ranged from 16 to 27 in the striatum and could also be readily measured in the thalamus. In the cerebellum, the DVs for [^{11}C]raclopride, [^{18}F]fallypride, and [^{18}F]DMFP were 0.38 ± 0.11, 0.98 ± 0.47, and 3.43 ± 1.36, respectively. Therefore, [^{18}F]DMFP has the highest nonspecific binding in the cerebellum.

Vernaleken et al. (18) reported that occupancy of $D_{2/3}$ receptors was 43–85% in the putamen and 67–90% in the caudate in a [^{18}F]DMFP PET study of 9 schizophrenic patients treated with amisulpride and 12 healthy controls. Calculated plasma levels of amisulpride to attain 60–80% receptor occupancy were 119–474 ng/ml in the caudate and 241–732 ng/ml in the putamen.

Schreckenberger et al. (19) reported the [^{18}F]DMFP striatum/cerebellum ratio to be significantly reduced ($P < 0.01$) in 19 patients with atypical Parkinsonian syndromes (2.44 ± 0.42) compared with 16 healthy control subjects (3.61 ± 0.43) and 16 patients with idiopathic Parkinsonian syndrome (3.21 ± 0.78). For the differential diagnosis of atypical *versus* idiopathic Parkinsonian syndromes, the [^{18}F]DMFP binding in the caudate showed a specificity, sensitivity, and accuracy of 100%, 74%, and 86%, respectively, as well as positive and negative predictive values of 100% and 76%, respectively.

[^{18}F]DMFP PET is suitable for objective monitoring of striatal $D_{2/3}$ receptor binding during dopamine release and drug occupancy in patients with dopaminergic disorders.

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