(S)-*N*-(1-Ethyl-2-pyrrolidinyl)methyl)-5-bromo-2-[^{11}C]methoxy-3-methoxybenzamide

[^{11}C]FLB 457

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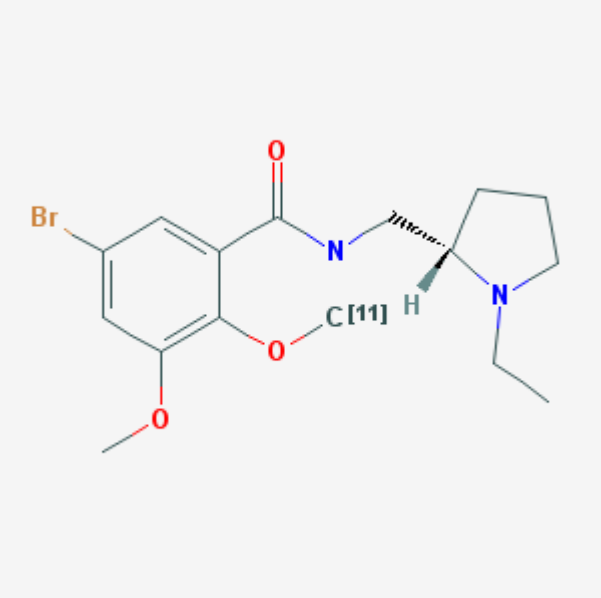
Chemical name:	*(S)*-*N*-(1-Ethyl-2-pyrrolidinyl)methyl)-5-bromo-2-[^{11}C]methoxy-3-methoxybenzamide
Abbreviated name:	[^{11}C]FLB 457
Synonym:	[^{11}C]isoremoxipride
Agent Category:	Compound
Target:	Dopamine receptors (D_2 and D_3)
Target Category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • 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 (PD), 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 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) dopamine receptors. D_1-like and D_2-like receptors exert synergistic as well as opposite effects at both the biochemical and overall system level. A great majority of striatal D_1 and D_2 receptors are localized postsynaptically on caudate-putamen neurons and to a lesser extent presynaptically on nigrostriatal axons. Extrastriatal dopamine receptors have also been suggested to play an important role in the pathophysiology of schizophrenia and other psychiatric disorders (5).

Substituted benzamides, such as sulpiride, raclopride, and iodobenzamide, are specific ligands with only moderate affinity for the D_2 receptors, making studies of extrastriatal D_2 receptors difficult (6-8). In binding studies, ^{123}I-labeled 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 (9). Epidepride has 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 (K_i = 0.03 nM) of $D_{2/3}$ receptors (10), and in positron emission tomography (PET) *in vivo* studies (11-13). (*S*)-*N*-(1-Ethyl-2-pyrrolidinyl)methyl)-5-bromo-2,3-dimethoxybenzamide (FLB 457, or isoremoxipride) had very high affinity for D_2 (K_i = 0.017 nM) and D_3 (K_i = 0.022 nM) receptors but not other neurotransmitter receptors (14). [^{11}C]FLB 457 has been used as a PET agent for the non-invasive study of extrastriatal $D_{2/3}$ receptors in the human brain.

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Related Resource Links:

- Chapters in MICAD (Dopamine receptors)
- Gene information in NCBI (D_2 receptor,D_3 receptor)
- Articles in Online Mendelian Inheritance in Man (OMIM) (D_2 receptor, D_3 receptor)
- Clinical trials (Dopamine receptors)
- Drug information in Food and Drug Administration (Dopamine receptors)

Synthesis

[PubMed]

Halldin et al. (14) reported that they synthesized [^{11}C]FLB 457 by direct O-methylation of 2-hydroxy-FLB 457 with [^{11}C]methyl iodide and NaOH in dimethyl sulfoxide, with a radiochemical yield of 25-35% (end of bombardment) and an average specific activity of 48 GBq/μmol (1,300 Ci/mmol at end of synthesis) after high-performance liquid chromatography (HPLC) purification. Radiochemical purities were >99% with a total synthesis time of 30 min.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro binding assays showed that FLB 457 had high affinities for D_2 (K_i = 0.022 ± 0.001 nM) and D_3 (K_i = 0.017 ± 0.001 nM) receptors but not D_1, α_1, α_2, 5-HT_{1A}, and 5-HT_2 receptors (14). These results indicate that FLB 457 binds equally well to D_2 and D_3 receptors.

Animal Studies

Rodents

[PubMed]

Biodistribution studies by Ahmad et al. (15) in rats showed rapid accumulation of radioactivity in all brain regions within minutes after injection of [^{11}C]FLB 457. Thereafter, radioactivity accumulated further only in the striata. On the other hand, all other regions showed various washout rates. Kinetic analysis with a two-tissue model using plasma input function (5 samples/rat) was used to derive the binding potential (BP) of each region. The striatum had the highest BP (83), followed by the inferior colliculi (11.0), olfactory tubercles (5.9), superior colliculi (5.1), hypothalamus (3.3), pons with medulla (2.7), thalamus (2.5), frontal cortex (2.3), prefrontal cortex (2.1), hippocampus (1.8), occipital cortex (1.1), and cerebellum (0.8). Thus, the hypothalamus, prefrontal cortex, and cerebellum represent extrastriatal tissues with moderate, low, and minimal $D_{2/3}$ receptor density. Apparent K_d values were in the range of 2-3 nmol/kg in the extrastriatal regions. The extrastriatal basal occupancy by dopamine was minimal (<10%). [^{11}C]FLB 457 thus displays uptake and washout kinetics characteristic of reversible radiotracers.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Halldin et al. (14) performed PET studies with [^{11}C]FLB 457 in three cynomolgus monkeys and found rapid accumulation in the brain (3.5% of injected radioactivity) at 4 min after injection. The highest uptake was in the striatum, with striatum/cerebellum ratios of 15 at 60 min and 25 at 93 min after injection of 37 MBq (1 mCi) of [^{11}C]FLB 457. The thalamus/cerebellum and neocortex/cerebellum ratios were 4.0 and 2.5. The accumulation of [^{11}C]FLB 457 in the striatum, thalamus, and neocortex was almost completely displaced after injection of raclopride (1 mg/kg) or haloperidol (2 mg/kg) at 15-20 min after the tracer injection. The fraction of unchanged [^{11}C]FLB 457 in plasma, as determined by HPLC, was 80 and 34% at 5 and 86 min after injection, respectively. All radiolabeled metabolites were more hydrophilic than the parent compound and not expected to cross the blood-brain barrier.

Human Studies

[PubMed]

[^{11}C]FLB 457 PET studies of $D_{2/3}$ receptor distribution in human brain have been reported, showing major localization of radioactivity in the striata and significant minor accumulation in the extrastriatal regions. Quantitative analysis of [^{11}C]FLB 457 binding was usually performed to derive BPs (with cerebellum as reference) to measure receptor concentrations. Olsson et al. (16) reported on [^{11}C]FLB 457 PET studies in eight normal subjects (23-38 years of age), using the standard three-compartment model with arterial input function. PET brain scans showed high accumulation of radioactivity in the putamen (BP = 19.04 ± 10.8), followed by the thalamus (BP = 2.82 ± 0.46), temporal cortex (BP = 1.29 ± 0.23), anterior cinguli (BP = 0.76 ± 0.17), and frontal cortex (BP = 0.65 ± 0.13), with good reproducibility. However, the short time of a PET measurement using [^{11}C]FLB 457 (63 min) seemed insufficient for reliable determination of the high BP in the striatum.

Farde et al. (17) found that pretreatment with haloperidol and fluphenazine blocked [^{11}C]raclopride binding in the striatum and [^{11}C]FLB 457 binding in the thalamus and neocortex in two healthy subjects and two patients with schizophrenia. Subsequent studies by Vilkman et al. (18) and Sudo et al. (19) showed good test-retest reproducibility for [^{11}C]FLB 457 binding in extrastriatal regions in normal subjects. Two other groups (20, 21) found that there was an age-dependent decrease (>10% per decade) of [^{11}C]FLB 457 binding in most extrastriatal regions (decreases of 5-5% per decade in the thalamus and 7% in the amygdale) in healthy volunteers.

Kaasinen et al. (22) reported on a [^{11}C]FLB 457 PET study of 14 drug-naive patients with idiopathic early PD with predominantly left-sided symptoms, 14 levodopa-medicated patients with advanced PD, and 20 normal age-matched controls. In advanced PD, the BP of [^{11}C]FLB 457 was decreased by 40% ($P < 0.01$) in the dorsolateral prefrontal cortex, by 20% ($P < 0.01$) in the anterior cingulate cortex, and by 17% ($P < 0.05$) in the medial thalamus compared with healthy controls. In early PD, the extrastriatal [^{11}C]FLB 457 BPs were not significantly different compared with the control group. However, the BP in the

anterior cingulate cortex (29%; $P < 0.05$) was higher in early PD compared with advanced PD. This indicates that the $D_{2/3}$ receptor subtypes outside the striatum are affected in advanced PD but not in the early stages of the disease and that this receptor decline is present in the anterior cingulate cortex, the dorsolateral prefrontal cortex, and the thalamus.

Talvik et al. (23) studied extrastriatal binding of [^{11}C]FLB 457 binding for $D_{2/3}$ receptor sites in nine drug-naive patients (36 ± 12 years of age) with schizophrenia and in eight healthy control subjects (31 ± 12 years of age). The patients exhibited significantly lower BP values (3.13 ± 0.33) than the healthy controls (4.06 ± 1.05) in the right medial thalamus. There was also a significant decrease in BPs with age in the frontal and temporal cortex for both groups.

Aalto et al. (24) compared regional brain BPs of [^{11}C]FLB 457 in eight normal volunteers with ketamine infusion and eight normal volunteers. There was a significant decrease in [^{11}C]FLB 457 BP in the posterior cingulated/retrosplenial cortices of ketamine-infused subjects compared with controls, suggesting an increase in dopamine release. No significant differences were observed in other cortical regions. Ketamine-induced psychotic symptoms were associated with changes in the [^{11}C]FLB 457 BP in the dorsolateral prefrontal and anterior cingulated cortices. This is similar to what was found by Breier et al. (25) using ketamine and [^{11}C]raclopride.

[^{11}C]FLB 457 PET is useful for objective monitoring of $D_{2/3}$ receptor binding and drug occupancy in patients with dopaminergic disorders. Internal dosimetry data for [^{11}C]FLB 457 in humans are not available in the literature.

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