(S)-5-Methoxymethyl-3-[6-(4,4,4-trifluorobutoxy)benzo[*d*]isoxazol-3-yl]-oxazolidin-2-[^{11}C]one

[^{11}C]SL25.1188

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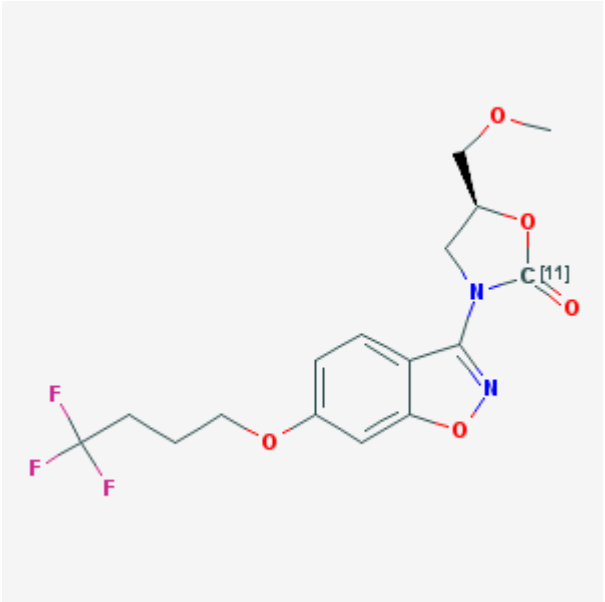
Chemical name:	(S)-5-Methoxymethyl-3-[6-(4,4,4-trifluorobutoxy)benzo[*d*]isoxazol-3-yl]-oxazolidin-2-[^{11}C]one
Abbreviated name:	[^{11}C]SL25.1188
Synonym:	
Agent category:	Compound
Target:	Monoamine oxidase B (MAO-B)
Target category:	Enzyme
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Non-human primates



Click on the above structure for additional information in PubChem.

Background

[PubMed]

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Monoamine oxidase (MAO) is a mitochondrial enzyme that inactivates dopamine, noradrenaline, and serotonin in the brain (1, 2). Two isoforms, A and B, of the enzyme have been identified. MAO-A preferentially oxidizes serotonin and noradrenaline, whereas MAO-B preferentially oxidizes phenethylamine. Dopamine is a substrate for both enzymes. MAO-A is predominately associated with depression and anxiety disorders, whereas MAO-B is predominately associated with neurodegenerative diseases, such as Parkinson's disease (PD), as indicated by studies with specific MAO isoform inhibitors (3-5). MAO-A is selectively inhibited by clorgyline, whereas MAO-B is selectively and irreversibly inhibited by L-depreny. In the human brain, MAO-B predominates and is present in both glial cells and neurons (6), most abundantly in serotonin and histamine neurons (7).

(*S*)-5-Methoxymethyl-3-[6-(4,4,4-trifluorobutoxy)-benzo[*d*]isoxazol-3-yl]-oxazolidin-2-one (SL25.1188) is a selective and reversible MAO-B inhibitor (8). For measurements of MAO-B activity, (*S*)-5-methoxymethyl-3-[6-(4,4,4-trifluorobutoxy)benzo[*d*]isoxazol-3-yl]-oxazolidin-2-[^{11}C]one ([^{11}C]SL25.1188) has been prepared for use in positron emission tomography (PET) studies.

Related Resource Links:

- Chapters in MICAD
- Gene information in NCBI (MAO-B).
- Articles in OMIM
- Clinical trials (MAO-B)
- Drug information in FDA

Synthesis

[PubMed]

Saba et al. (8) reported the synthesis of [^{11}C]SL25.1188 by cyclization reaction of [^{11}C]phosgene with the corresponding ring-open precursor in CH_2Cl_2 (100°C for 2 min), with a radiochemical yield of ~7% (based on [^{11}C]methane, decay-corrected) after purification with high-performance liquid chromatography (HPLC). The total synthesis time was 30–32 min, with a radiochemical purity of >95% and a specific activity of 50–70 GBq/μmol (1.35–1.89 Ci/μmol) at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

SL25.1188 inhibited rat brain MAO-B with an 50% inhibitory concentration (IC_{50}) value of 11.8 nM and an 84-fold selectivity over MAO-A (8).

Animal Studies

Rodents

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Saba et al. (8) performed PET imaging studies in four male baboons after injection of 88 MBq (2.4 mCi) [^{11}C]SL25.1188. [^{11}C]SL25.1188 exhibited a rapid phase of distribution in blood at 5 min after injection, followed by an elimination half-life of 85 ± 14 min. Plasma metabolism analysis with HPLC showed that no radioactive metabolite of [^{11}C]SL25.1188 could be detected at 30 min. Brain accumulation was rapid with ~5% injected dose/100 ml. The highest regional brain accumulation (distribution volume (VT)) was observed in the thalamus (10.9), followed by the striatum (10.3), hippocampus (8.9), temporal cortex (7.7), parietal cortex (7.4), frontal cortex (7.4), white matter (7.4), occipital cortex (7.2), and pons (6.1). Pretreatment (30 min before the tracer injection) with deprenyl (2 mg/kg) or lazabemide (0.5 mg/kg) reduced VT values in all brain areas up to 50%. In displacement experiments (30 min after the tracer injection), injection of SL25.1188 (1 mg/kg) or deprenyl (2 mg/kg) strongly reduced the accumulation of [^{11}C]SL25.1188 in all brain areas (85–100%) at 50 min after the inhibitor injection, while a lesser displacement was observed with lazabemide (0.5 mg/kg) (55–70%). Therefore, [^{11}C]SL25.1188 binding to MAO-B in the brain is reversible.

Human Studies

[PubMed]

No publication is currently available.

References

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