(*S*,*S*)-2-[α-(2-(2-[^{18}F]Fluoro[$^{2}H_4$]ethoxy)phenoxy)benzyl]morpholine

(*S*,*S*)-[^{18}F]FRB-D_4

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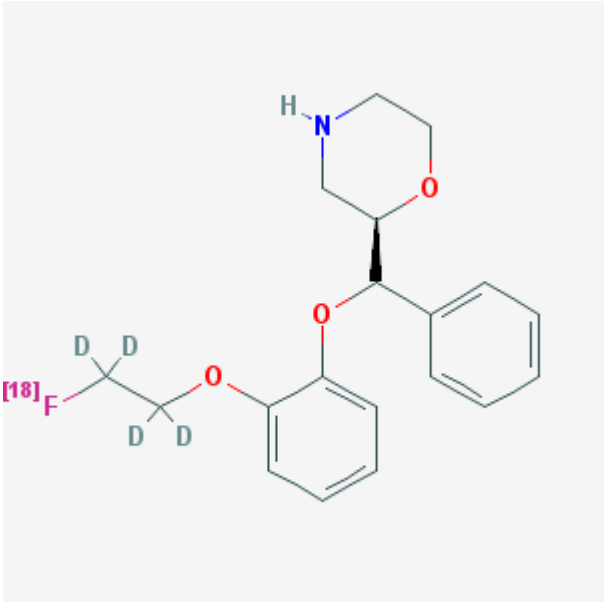
Chemical name:	(*S*,*S*)-2-[α-(2-(2-[^{18}F]Fluoro[$^{2}H_4$]ethoxy)phenoxy)benzyl]morpholine
Abbreviated name:	(*S*,*S*)-[^{18}F]FRB-D_4
Synonym:	(*S*,*S*)-[^{18}F]Fluororeboxetine, [^{18}F]FRB-D_4
Agent Category:	Compound
Target:	Brain norepinephrine transporter (NET)
Target Category:	Transporter binding
Method of detection:	Positron Emission Tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates



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Background

[PubMed]

(*S*,*S*)-2-[α-(2-(2-[^{18}F]Fluoro[$^{2}H_4$]ethoxy)phenoxy)benzyl]morphine ((*S*,*S*)-[^{18}F]FRB-D_4) is a radioligand developed for positron emission tomography (PET) imaging of the brain adrenergic receptors (1, 2). It is a derivative of reboxetine ((*RS*)-2-[(*RS*)-2-ethoxyphenoxy)benzyl]morpholine), which is a norepinephrine (NE) transporter (NET) inhibitor, and is labeled with ^{18}F, which is a positron emitter with a physical half-life ($t_{½}$) of 109.8 min. Four hydrogens on the ethoxy side chain have been replaced with deuterium (^{2}H) in an attempt to slow defluorination, which was observed in earlier studies.

Many diseases affect the sympathetic nervous system (SNS), and imaging of pathologic changes of adrenergic transmission has been an important area of PET research (3, 4). Most postganglionic sympathetic neurons in the autonomic nervous system release the neurotransmitter NE, which stimulates adrenergic receptors in various effector organs (5). There are different types and subtypes of adrenergic receptors, and they are characterized as α_{1a} to α_{1c}, α_{2a} to α_{2c}, and β_1 to β_3 (6). All NE receptors belong to the G-protein–linked receptor superfamily and mediate slow neuromodulatory postsynaptic responses. The NET is a transmembrane protein located in the adrenergic nerve terminals and is responsible for active reuptake (uptake-1) of NE released from neurons (7). NE is stored in the neuronal vesicles and is released upon stimulation. Significant expression of NET is found in major organs of the SNS, such as the heart and brain. Brain NETs are involved in various neurologic and psychiatric diseases, including depression, attention deficit hyperactivity disorder, drug addiction, and eating disorders (8). Brain NETs are also the site of action of many antidepressant drugs in the brain (9).

Molecular probes with structures closely related to NE can be used to assess the integrity of presynaptic sympathetic nerve terminals in patients with various diseases. *In vivo* NE synthesis is similar to dopamine synthesis, and dopamine is converted to NE by the enzyme dopamine-β-hydroxylase (6). [^{123}I]-*meta*-Iodobenzylguanidine, [^{11}C]*meta*-hydroxyephedrine, [^{11}C]norepinephrine, and many other radioligands have been developed and used for peripheral neuronal imaging (10). However, this class of tracers is not suitable for the study of the brain NET system because they are not able to cross the normal blood-brain barrier (2). In the brain, NET levels are relatively lower compared with other receptors, such as dopamine transporters (DATs) and serotonin transporters (9). Several NET reuptake inhibitors, such as [^{11}C]desipramine, have been tested, but they showed high nonspecific binding. Reboxetine is a specific NET inhibitor with a high affinity and selectivity [inhibitory concentration (IC_{50}) DAT/NET = 4,000]. PET imaging has shown specific localization and favorable binding kinetics for ^{11}C-labeled reboxetine derivatives [(*S*,*S*)-[^{11}C]methylreboxetine ((*S*,*S*)-[^{11}C]MRB)] in rats and non-human primates (11). Because of the potential advantages associated with the longer $t_{½}$ of ^{18}F, Lin et al. (1) synthesized a number of ^{18}F–labeled reboxetine analogs as promising radioligands for NET imaging with PET. (*S*,*S*)-[^{18}F]FRB has been shown to have high affinity and selectivity toward NET. (*S*,*S*)-[^{18}F]FRB-D_4, a tetradeuterated analog, was

developed to explore the deuterium isotope effect with the intention of reducing *in vivo* defluorination.

Synthesis

[PubMed]

Lin et al. (11) described the radiosynthesis of (*S*,*S*)-[^{18}F]FRB from (*S*,*S*)-*N*-*tert*-butyloxycarbonyl-2-[α-(2-hydroxyphenoxy)benzyl]morpholine (*N*-Boc-desethylIRB). *N*-Boc-desethylIRB was prepared by the *N*-protection of (S,S)/(R,R)-*N*-desethylIRB with a *tert*-butyloxycarbonyl (Boc) group followed by enantiomeric resolution by chiral high-performance liquid chromatobraphy (HPLC) with >99% enantiomeric purity. In the radiosynthesis, 1-bromo-2-[^{18}F]fluoro[^{2}H$_4$]ethane ([^{18}F]BFE-D$_4$) was first prepared as a secondary radiolabeling synthon by the nucleophilic displacement of 2-bromoethyl triflate-D$_4$ with [^{18}F]F−. Briefly, 2-bromoethyl triflate-D$_4$ was added to [^{18}F]KF/Kryptofix 222 and vortexed for 20 s, followed by incubation at ambient temperature for 5 min. The solution was heated at 80°C, and the volatiles were distilled into a solution of *N*-Boc-desethylIRB and 5 N sodium hydroxide in *N*,*N*-dimethylformamide and cooled in an acetonitrile/dry ice bath. This step produced the coupling of *N*-Boc-desethylIRB with [^{18}F]BFE-D$_4$.The mixture was then heated in an oil bath at 130°C for 30 min. After cooling, trifluoroacetic acid was added to remove the Boc group and the mixture was heated at 75°C for 17 min. Water was added and (*S*,*S*)-[^{18}F]FRB-D$_4$ was purified by high performance liquid chromatography (HPLC). After HPLC purification, (*S*,*S*)-[^{18}F]FRB-D$_4$ was obtained in 11–27% decay-corrected radiochemical yields from [^{18}F]F−. The total synthesis time was 120 min with a radiochemical purity of >98%. The specific activity of the final product was 21–48 GBq/μmo (0.57–1.3 Ci/μmol) at the end of bombardment.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Lin et al. (1) determined the log P_{oct} (pH 7.4) value of FRB to be 0.91 ± 0.01 (n = 8) by traditional extraction with octanol and pH 7.4 phosphate buffer. In comparison, (*S*,*S*)-[^{11}C]MRB had log P_{oct} of 1.17.

Animal Studies

Rodents

[PubMed]

Whole-body biodistribution studies of (*S*,*S*)-[^{18}F]FRB-D$_4$ were conducted in mice (1). At 10 min after i.v. injection of 0.185 MBq (5 μCi) (*S*,*S*)-[^{18}F]FRB-D$_4$, the percent injected dose per gram (%ID/g; n = 4) radioactivity levels for major organs were 15.6 ± 1.01 (liver), 10.9 ± 1.96 (intestine), 5.81 ± 0.62 (kidney), 4.71 ± 0.13 (lung), 1.58 ± 0.07 (bone), 1.08 ± 0.03 (blood), and 0.46 ± 0.01 (brain), At 2 h, these radioactivity levels changed to 5.00

± 0.85 (liver), 32.7 ± 4.43 (intestine), 0.69 ± 0.07 (kidney), 0.38 ± 0.07 (lung), 0.25 ± 0.03 (bone), 0.22 ± 0.03 (blood), and 0.13 ± 0.01 (brain). The results showed that the radioligand was excreted through both the hepatobiliary and the renal systems. There was moderate brain radioactivity uptake and the washout was slow. In comparison, (*S*,*S*)-[^{11}C]methylreboxetine had 0.53% ID brain uptake at 5 min after injection (9). (*S*,*S*)-[^{18}F]FRB-D_4 showed faster blood clearance than (*S*,*S*)-[^{18}F]FRB. The bone and blood radioactivity levels of (*S*,*S*)-[^{18}F]FRB-D_4 were similar at 2 h. The radioactivity accumulation in the bone appeared to decrease continuously. In comparison, (*S*,*S*)-[^{18}F]FRB showed a slight increase in bone radioactivity from 0.65 ± 0.08% ID/g at 1 h to 0.83% ID/g at 2 h. The authors suggested that this was evidence of *in vivo* defluorination inhibition *via* a deuterium isotope effect with (*S*,*S*)-[^{18}F]FRB-D_4.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Ding et al. (12) used PET imaging to evaluate (*S*,*S*)-[^{18}F]FRB-D_4 in baboons. The radioactivity uptake of (*S*,*S*)-[^{18}F]FRB-D_4 in the baboon brain was consistent with the known NET distribution, and the uptake could be blocked by a selective NET inhibitor (1 mg/kg i.y. nisoxetine pretreatment). The signal-to-noise ratios in the brain were similar to those of (*S*,*S*)-[^{18}F]FRB. The bone radioactivity of (*S*,*S*)-[^{18}F]FRB_4 was low and did not increase with time. The blood clearance of (*S*,*S*)-[^{18}F]FRB-D_4 was faster than (*S*,*S*)-[^{18}F]FRB.

Human Studies

[PubMed]

No publication is currently available.

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