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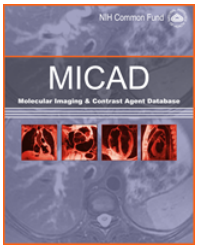

(*S*,*S*)-2-[α-(2-(2-[^{18}F]Fluoroethoxy)phenoxy)benzyl]morpholine

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

Kenneth T. Cheng, PhD[1]

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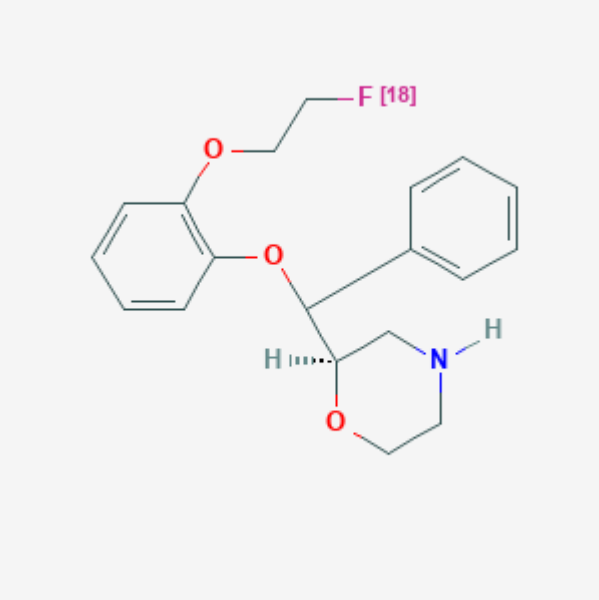
Chemical name:	(*S*,*S*)-2-[α-(2-(2-[^{18}F]Fluoroethoxy)phenoxy)benzyl]morpholine
Abbreviated name:	(*S*,*S*)-[^{18}F]FRB
Synonym:	(*S*,*S*)-[^{18}F]Fluororeboxetine, [^{18}F]FRB
Agent Category:	Compound
Target:	Brain norepinephrine transporter (NET)
Target Category:	Transporter binding
Method of detection:	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]Fluoroethoxy)phenoxy)benzyl]morphine ((*S*,*S*)-[^{18}F]FRB) is a radioligand developed for positron emission tomography (PET) imaging of the brain adrenergic receptors (1, 2). It is a derivative of

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reboxetine ((*RS*)-2-[(*RS*)-2-ethoxyphenoxy)benzyl]morpholine), a norepinephrine (NE) transporter (NET) inhibitor, labeled with ^{18}F, a positron emitter with a physical half-life ($t_{½}$) of 109.8 min.

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 on 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 brain NET system because they are not able to cross the blood-brain barrier (2). In the brain, NET levels are relatively lower than 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]. ^{11}C-labeled reboxetine derivatives ((*S,S*)-[^{11}C]methylreboxetine((*S,S*)-[^{11}C]MRB)) have shown specific localization and favorable binding kinetics in rats and non-human primates with PET imaging (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.

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 HPLC with >99% enantiomeric purity. In the radiosynthesis, 1-bromo-2-[^{18}F]fluoroethane ([^{18}F]BFE) was first prepared as a secondary radiolabeling synthon by the nucleophilic displacement of 2-bromoethyl triflate with [^{18}F]F–. Briefly, 2-bromoethyl triflate 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 cooled in an acetonitrile/dry ice bath. This step produced the coupling of *N*-Boc-desethylIRB with [^{18}F]BFE.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 heated at 75°C for 17 min. Water was added and (*S,S*)-[^{18}F]FRB was purified by high performance liquid chromatography (HPLC). After HPLC purification, (*S,S*)-[^{18}F]FRB 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 (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 of 1.17.

Animal Studies

Rodents

[PubMed]

Whole-body biodistribution studies of (*S*,*S*)-[^{18}F]FRB were conducted in mice (1). At 10 min after i.v. injection of 0.185 MBq (5 μCi) (*S*,*S*)-[^{18}F]FRB, the percent injected dose per gram (%ID/g; n = 4) radioactivity levels for major organs were 17.5 ± 1.43 (liver), 9.99 ± 0.55 (intestine), 5.54 ± 1.07 (kidney), 4.52 ± 1.14 (lung), 1.74 ± 0.08 (bone), 1.31 ± 0.07 (blood), and 0.42 ± 0.03 (brain), At 2 h, these radioactivity levels changed to 5.82 ± 1.16 (liver), 30.7 ± 1.78 (intestine), 0.77 ± 0.11 (kidney), 0.31 ± 0.03 (lung), 0.83 ± 0.04 (bone), 0.44 ± 0.03 (blood), and 0.16 ± 0.01 (brain), The results showed that the radioligand was excreted through both hepatobiliary and renal systems. There was a moderate brain radioactivity uptake and the washout was slow. In comparison, (*S*,*S*)-[^{11}C]MRB had 0.53% ID brain uptake at 5 min after injection (9). The bone radioactivity level decreased initially but there appeared to be a slight increase from 1 h (0.65% ID) to 2 h (0.83% ID). This might indicate evidence of *in vivo* defluorination.

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 in baboons. The radioactivity uptake of (*S*,*S*)-[^{18}F]FRB in the baboon brain was consistent with the known NET distribution, and the uptake could be blocked by a selective NET inhibitor (i.y. nisoxetine pretreatment, 1 mg/kg). In comparison, no regional specificity or blocking effect was observed for the (*R*,*R*)-[^{18}F]FRB. The peak brain uptake and signal to noise ratio [distribution volume ratio DVR $_{(TH/Ref)}$] of (*S*,*S*)-[^{18}F]FRB were 1.8% ID and 1.3-1.6, respectively. The results of the HPLC analysis and solid-phase extraction of the baboon plasma samples showed that (*R*,*R*)-[^{18}F]FRB was metabolized faster than (*S*,*S*)-[^{18}F]FRB. The plasma protein binding (% unbound) of (*S*,*S*)-[^{18}F]FRB was 13. The %unchanged parent compound was 96% at 1 min and 20% at 120 min. (*S*,*S*)-[^{18}F]FRB displayed relatively fast kinetics in NET-rich brain regions, which might facilitate its central nervous system kinetic analysis.

Human Studies

[PubMed]

No publication is currently available.

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