2-[^{18}F]Fluoro-3-[2-((*S*)-3-pyrrolinyl)methoxy]pyridine

[^{18}F]Nifene

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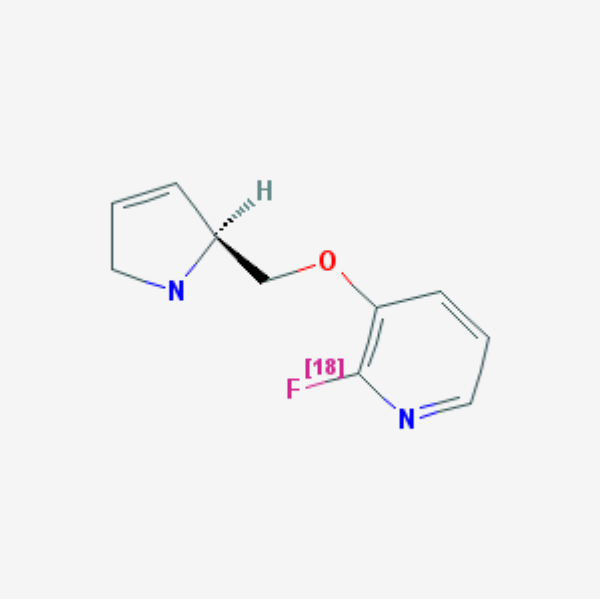
Chemical name:	2-[^{18}F]Fluoro-3-[2-((*S*)-3-pyrrolinyl)methoxy]pyridine
Abbreviated name:	
Synonym:	[^{18}F]Nifene
Agent Category:	Compound
Target:	α4β2 nicotinic acetylcholine receptor (nAChR)
Target Category:	Receptor binding
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Non-human primates



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Background

[PubMed]

Neuronal nicotinic cholinergic receptors (nAChRs) are a heterogeneous family of ligand-gated ion channels expressed in the central nervous system, where their activation by

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acetylcholine and nicotine always causes a rapid increase in cellular permeability to ions such as Na^+ and Ca^{2+} (1-3). Nicotinic receptors exist as pentamers (homomeric or heteromeric) in various brain regions and ganglia. There are nine subtypes of ligand-binding α (α2–α10) and four subtypes of structural β (β2–β5). nAChRs have been demonstrated to be involved in cognitive processes such as learning, memory, and control of movement in normal subjects. Dysfunction of nAChRs has been implicated in a number of human diseases such as schizophrenia, Huntington's disease, Alzheimer's disease, and Parkinson's disease. nAChRs also play a significant role in nicotine addiction.

2-[^{18}F]Fluoro-A-85380 (2-[^{18}F]FA) and 6-[^{18}F]FA have been evaluated as positron emission tomography (PET) agents for the non-invasive study of nAChRs in humans (4, 5). However, prolonged imaging times (2–4 h) are required for reliable quantification because of their slow kinetics. 2-Fluoro-3-[2-((*S*)-3-pyrrolinyl)methoxy]pyridine (nifene) is a highly potent and selective nAChR agonist with subnanomolar affinity (6). [^{18}F]Nifene is being developed as a PET agent with faster kinetics than 2-[^{18}F]FA and 6-[^{18}F]FA for the non-invasive study of nAChRs in the brain.

Synthesis

[PubMed]

Pichika et al. (6) reported synthesis of [^{18}F]nifene by a two-step reaction consisting of standard ^{18}F-nucleophilic fluorination of 2-nitro-3-[2-((*S*)-*N*-*tert*-butoxycarbonyl-3-pyrroline)methoxy]pyridine and acidic deprotection of the product. An average radiochemical yield was 40–50%, with a total synthesis time of 150 min. Specific activities were 37–186 GBq/μmol (1–5 Ci/μmol) at end of synthesis with a radiochemical purity of >99%.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Pichika et al. (6) reported that nifene, nifrolidine, and nicotine had respective K_i values of 0.50 ± 0.14, 0.80 ± 0.11, and 1.68 ± 0.28 nM in [^{3}H]cytosine (α4β2 nicotinic acetylcholine receptor) binding assays using rat brain membranes. *In vitro* autoradiography studies of rat brain slices indicated selective binding of [^{18}F]nifene to anteroventral thalamic (AVT) nucleus > thalamus > subiculum > striatum > cortex > cerebellum, consistent with α4β2 receptor distribution. The ratios of brain regions to cerebellum for AVT, thalamus, subiculum, striatum, and cortex were in the range of 13-19, 10-12, 7-8, 5, and 4, respectively. Nicotine blocked 60% (10 nM) and >95% (300 μM) of [^{18}F]nifene-specific binding across the brain regions.

Easwaramoorthy et al. (7) estimated α4β2 receptor occupancy by acetylcholine using *in vitro* [^{18}F]nifene autoradiography studies of rat brain slices in the presence of acetylcholinesterase inhibitors, physostigmine (PHY) and galanthamine (GAL). PHY (0.2-20 μM), GAL (0.4-4 μM) or acetylcholine (100 nM) alone had little effect on the

[18F]nifene binding to AVT, thalamus, subiculum, striatum, and cortex. The combination of PHY (20 μM) and acetylcholine (100 nM) or GAL (4 μM) and acetylcholine (100 nM) exhibited 63-70% and 10-20% acetylcholine receptor occupancy, respectively.

Animal Studies

Rodents

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

A biodistribution PET study performed by Pichika et al. (6) in one anesthetized male rhesus monkey injected with 130 MBq (3.5 mCi) [18F]nifene showed rapid accumulation of radioactivity in the brain. PET study showed selective maximal uptake in the regions of the thalamus, lateral geniculate, cingulate gyrus, and temporal cortex including the subiculum. The cerebellum showed lower binding than the other brain regions. The thalamus/cerebellum ratio peaked at a value of 2.2 30–35 min after injection and subsequently decreased, whereas the cortex/cerebellum ratio was 1.3. The peak level (0.02% injected dose/ml) was reached in the thalamus at 7 min. [18F]Nifene radioactivity was cleared out rapidly in all brain regions. Ding et al. (8) reported that the thalamus/cerebellum distribution volume ratio in a baboon study was higher for 6-[18F]FA (2.5–3.5) than for 2-[18F]FA (1.9–2.1) at 180 min. Therefore, [18F]nifene exhibited faster binding kinetics than 2-[18F]FA and 6-[18F]FA.

Human Studies

[PubMed]

No publication is currently available.

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