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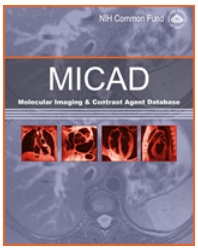

2-(3-Fluoro-[4-^{11}C]tolyl)-4,5-dihydro-1*H*-imidazole

[^{11}C]FTIMD

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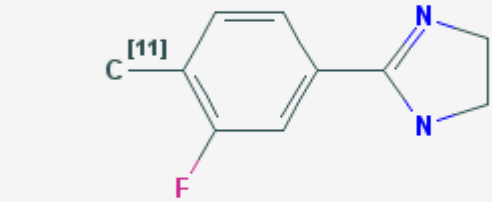
Chemical name:	*2*-(3-Fluoro-[4-^{11}C]tolyl)-4,5-dihydro-1*H*-imidazole
Abbreviated name:	[^{11}C]FTIMD
Synonym:	
Agent category:	Compound
Target:	I_2-imidazoline receptor (I_2R)
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates



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Background

[PubMed]

Two major imidazoline binding sites (I_1R and I_2R) have been identified (1, 2). The I_1R and I_2R exhibit high affinities for clonidine and idazoxan, respectively. Clonidine and its analogs mediate effects independent of α_2-adrenoceptor at the IR receptors. IR receptors are widely distributed in the central and peripheral nervous systems and in various organs such as the pancreas, liver, kidney, lung, and heart (3-6). I_1R is associated with hypertension (7), whereas I_2R is associated with depression (8), Alzheimer's disease (9), Parkinson's disease (10), Huntington's disease (10), and glial cell tumors (11). High densities of I_2R have been observed in the arcuate nucleus, interpeduncular nucleus, pineal gland, and ventricles in human brain (12). The I_2R gene has not been

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identified. Tesson et al. (13) showed that I_2R is localized to the mitochondrial outer membrane of the human and rabbit liver. Anastassiadou et al. (14) showed that *2*-(3-fluoro-4-tolyl)-4,5-dihydro-1*H*-imidazole (FTIMD) has a high and selective affinity for I_2R. Kawamura et al. (15) evaluated [^{11}C]FTIMD as a positron emission tomography (PET) agent for the noninvasive study of I_2R in the brain and peripheral organs.

Related Resource Links:

- Chapters in MICAD (Imidazoline receptors)
- Gene information in NCBI (I_1R, α_2-adrenoceptors)
- Articles in Online Mendelian Inheritance in Man (OMIM) (I_1R, α_2-adrenoceptors)
- Clinical trials (Clonidine)
- Drug information in FDA (Clonidine)

Synthesis

[PubMed]

[^{11}C]FTIMD was synthesized remotely *via* a reaction of [^{11}C]methyl iodine (produced from [^{11}C]CO_2) with the tributylstannyl precursor in the presence of tris(dibenzylideneacetone)dipalladium(0) and tri(*O*-tolyl)phosphine in dimethylformamide for 5 min at 130°C (15). [^{11}C]FTIMD was purified with high-performance liquid chromatography, with a radiochemical yield of 5.4 ± 2.0% (n = 7) from [^{11}C]CO_2 at end of bombardment (EOB). The radiochemical purity was >95%, and the specific activity was 108 ± 33 GBq/μmol (2.9 ± 0.9 Ci/μmol) at end of synthesis (EOS). Total time of synthesis was 30 min from EOB. To prepare [^{11}C]FTIMD with ultra-high specific activity (4,470 ± 1,660 GBq/μmol (120 ± 45 Ci/μmol) at EOS), [^{11}C]methyl iodine (produced from iodination of [^{11}C]methane) was used with (n = 11) (16). The cLogD (pH 7.4) value for FTIMD was 1.42.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

On the basis of *in vitro* competition binding studies, Anastassiadou et al. (14) reported inhibition constant (K_i) values for FTIMD of 3.0 nM for I_2R, >10,000 nM for I_1R, >10,000 nM for α_1-adrenoceptor, and >10,000 nM for α_2-adrenoceptor.

In an *in vitro* autoradiography study, the distribution pattern of [^{11}C]FTIMD (200 nM) in the monkey brain was studied (17). The rank order of radioactivity was caudate > hippocampus > globus pallidus > putamen > amygdala > thalamus > cortex > cerebellum, which was similar to that of [^{3}H]idazoxan binging to I_2R sites in the human brain (12). The specific binding of [^{11}C]FTIMD accounted for >97% of total binding in the brain regions expressing I_2R using 10,000 nM FTIMD and BU224 as I_2R inhibitor ligands.

Animal Studies

Rodents

[PubMed]

Ex vivo biodistribution of 11–20 MBq (0.30–0.54 mCi) [^{11}C]FTIMD was studied in normal rats (n = 4/group) at 5, 15, and 30 min after injection (15). The tissue with the highest accumulation (standard uptake value) at 5 min after injection was the kidney (12.20), followed by the lung (4.35), brain (2.51), liver (2.49), small intestine (2.29), spleen (2.12), pancreas (2.08), heart (1.22), muscle (1.17), and blood (0.38). Most tissues showed moderate to rapid washout, except for the liver, which showed a gradual increase. The brain/blood ratio at 15 min after

injection was 7.0. Co-injection of FTIMD (1 mg/kg) reduced the brain accumulation and brain/blood ratio by 22% and 32% ($P < 0.05$), respectively. Co-injection of another I_2R inhibitor BU224 (1 mg/kg) reduced the brain accumulation and brain/blood ratio by 21% and 33% ($P < 0.05$), respectively. On the other hand, co-injection of I_1R/α_2-adrenoceptor ligands moxonidine (1 mg/kg) and efaroxan (1 mg/kg) showed little effect on the brain accumulation and brain/blood ratio. [^{11}C]FTIMD remained >98% intact in the brain at 15 min and 30 min after injection, whereas only 57% and 37% remained intact in the plasma at 15 min and 30 min after injection, respectively. In a separate study in mice, specific accumulation of [^{11}C]FTIMD was observed in the liver and pancreas (18).

Kawamura et al. (15) performed dynamic PET scans in four rats (46–117 MBq, 1.24–3.16 mCi) for 60 min after injection of [^{11}C]FTIMD. High levels of radioactivity were detected in the arcuate nucleus, interpeduncular nucleus, hippocampus, and ependymal cell layer. Pretreatment with BU224 (1 mg/kg, 5 min) reduced radioactivity across the brain regions. Multilinear analysis showed a better fit than one- and two-compartment analysis. Regions of analysis showed the highest distribution volume (V_T) values in the ependymal cell layer (15.09), followed by the hippocampus (14.24), cortex (13.85), arcuate nucleus (13.54), interpeduncular nucleus (12.87), and cerebellum (10.90). Pretreatment with BU224 (1 mg/kg, 5 min) reduced the V_T values by 17%–34%. Using [^{11}C]FTIMD with ultra-high specific activity, the V_T values (13.77–19.02) were higher than those of [^{11}C]FTIMD (10.90-15.09) with normal specific activity (16). Pretreatment with BU224 reduced the V_T values by 29%–45%, which were significantly higher than those of [^{11}C]FTIMD with normal specific activity ($P < 0.05$).

Other Non-Primate Mammals

[PubMed]

No publications are currently available.

Non-Human Primates

[PubMed]

In PET studies, 160 MBq (4.3 mCi) [^{11}C]FTIMD (1.26 nmol) was intravenously injected into a conscious male monkey (17). The radioactivity was accumulated in the thalamus, arcuate nucleus, cingulate cortex, occipital cortex, hippocampus, striatum, cerebellum, and frontal cortex. Pretreatment with BU224 (5 mg/kg, 5 min) reduced the accumulated radioactivity to approximately 66%–75% of the baseline measurement at 15–45 min after injection of [^{11}C]FTIMD.

Human Studies

[PubMed]

No publications are currently available.

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