2-*tert*-Butyl-4-chloro-5-[4-(2-[^{18}F]fluoro-ethoxymethyl)-benzyloxy]-3-(2*H*)-pyridazinone

[^{18}F]MC1-27

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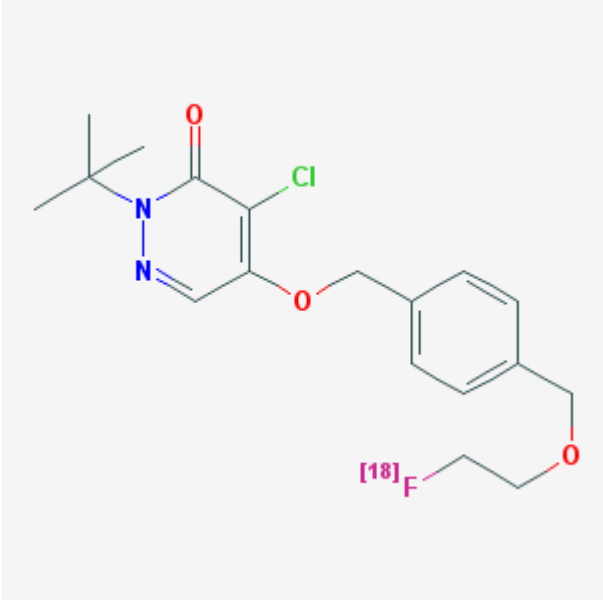
Chemical name:	2-*tert*-Butyl-4-chloro-5-[4-(2-[^{18}F]fluoro-ethoxymethyl)-benzyloxy]-3-(2*H*)-pyridazinone
Abbreviated name:	[^{18}F]MC1-27
Synonym:	
Agent category:	Compound
Target:	Mitochondrial complex 1 (MC1)
Target category:	Enzyme
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-Human Primates



Click on the above structure for additional information in PubChem.

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Background

[PubMed]

Lipophilic cations are capable of passing through biological membranes by passive diffusion into the cytoplasm and mitochondria of cells in response to large negative plasma and mitochondrial membrane potentials. ^{99m}Tc-2-Methoxyisobutylisonitrile (^{99m}TcMIBI) and ^{99m}Tc-tetrofosmin are delocalized lipophilic cations, which are rapidly taken up into cells driven by mitochondrial metabolism and membrane potential (1-4). They are used as myocardial-perfusion single-photon emission computed tomography (SPECT) as well as tumor imaging agents. However, the high accumulation of technetium tracers in the lung and liver may interfere with the detection of flow abnormalities in the myocardium. More recently, positron emission tomography (PET) imaging has emerged as an alternative approach to evaluating myocardial blood flow by use of positron-emitting radionuclides (e.g. ^{82}RbCl, $^{13}NH_3$, and $H_2{}^{15}O$). However, the majority of these radiotracers exhibited short physical half-lives (<10 min). Lipophilic cations, such as [^{11}C]triphenylmethylphosphonium ([^{11}C]TPMP) (5) and 4-[^{18}F]fluorobenzyl-triphenylphosphonium ([^{18}F]FBnTP) have been investigated as PET agents for myocardial and tumor imaging (6).

Mitochondrial complex I (MC1) of the mammalian electron transfer chain is composed of at least 43 protein subunits, of which 7 are encoded by mitochondrial DNA (7). MC1 catalyzes the transfer of electrons from NADH to ubiquinone and translocates protons from the mitochondrial matrix to the intermembrane space to generate ATP and thereby the energy supply of the cell. MC1 may also play direct roles in the mitochondrial permeability transition and in cell death pathways. Myocardium has a high mitochondrial content because of high energy usage. 2-*tert*-Butyl-4-chloro-5-[4-(2-fluoro-ethoxymethyl)-benzyloxy]-3-(2*H*)-pyridazinone (MC1-27) is found to be a potent MC1 inhibitor with a hydrophobic heterocyclic chromone core (8). 2-*tert*-Butyl-4-chloro-5-[4-(2-[^{18}F]fluoro-ethoxymethyl)-benzyloxy]-3-(2*H*)-pyridazinone ([^{18}F]MC1-27) has been synthesized to study as a myocardium imaging PET agent.

Related Resource Links:

- Chapters in MICAD
- Gene information in NCBI (MC1)
- Articles in OMIM
- Clinical trials (MC1)

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Synthesis

[PubMed]

[^{18}F]MC1-27 was prepared as described by Purohit et al. (8). [^{18}F]Fluoride/Kryptofix 2.2.2/K_2CO_3 and the tosylate precursor were heated in acetonitrile at 90°C for 30 min followed by high-performance liquid chromatography purification. Average radiochemical yield was 35% with a total synthesis time of 90 min. Radiochemical purity was >99% with specific activities of 27.8-74.0 GBq/μmol (0.75-2.0 Ci/μmol) at the end of bombardment.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Purohit et al. (8) reported that MC1-27 inhibited NADH oxidation (MC1) by bovine heart submitochondrial particles with an IC_{50} value of 11 nM.

Animal Studies

Rodents

[PubMed]

Purohit et al. (8) performed *ex vivo* biodistribution studies of [^{18}F]MC1-27 in rats. [^{18}F]MC1-27 accumulated mainly in the heart with 3.41 ± 0.27% injected dose/g (ID/g) and 3.47 ± 0.37% ID/g at 30 and 120 min after injection, respectively. Retention of [^{18}F]MC1-27 in the heart was good with no washout. The heart/blood, heart/lung, heart/liver and heart/femur ratios were 30.0, 16.1, 2.7, and 7.5 at 30 min after injection, respectively. The uptake in the femur was ~0.5% ID/g at 30 min indicating some defluorination of [^{18}F]MC1-27. PET imaging showed that [^{18}F]MC1-27 accumulated mainly in the heart and liver with low accumulation in the lung. Good myocardial images were observed at 25-35 min after injection and complete by 55-60 min with little interference from the lung and liver. Some bone uptake was observed in images after 30 min. No blocking experiment was performed.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Purohit et al. (8) performed PET imaging studies of [^{18}F]MC1-27 in male and female Rhesus monkeys. [^{18}F]MC1-27 accumulated mainly in the heart within minutes after

injection. Retention of [^{18}F]MC1-27 in the heart was good with little washout, whereas the retention was much less in the liver. Accumulation of [^{18}F]MC1-27 in the heart was clearly visualized over 120 min of imaging with no interference from the lung accumulation of [^{18}F]MC1-27. No accumulation of [^{18}F]MC1-27 in the bone was detected up to 120 min after injection.

Human Studies

[PubMed]

No publication is currently available.

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