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

[^{18}F]RP1004

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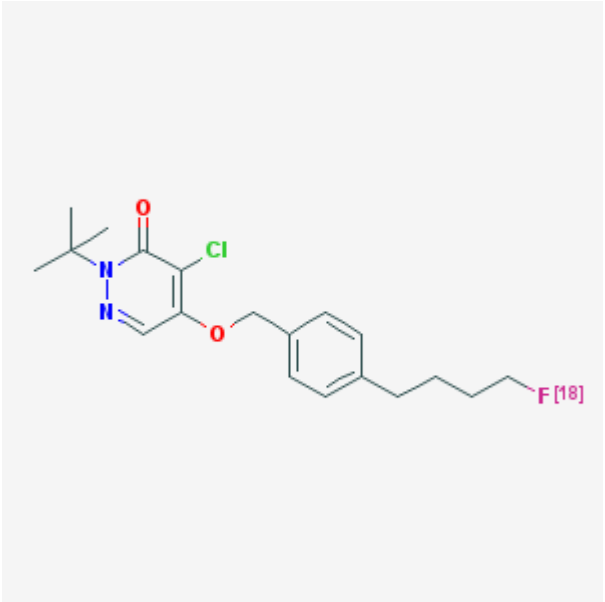
Chemical name:	2-*tert*-Butyl-4-chloro-5-[4-(4-[^{18}F]fluoro-butyl)-benzyloxy]-2*H*-pyridazin-3-one
Abbreviated name:	[^{18}F]RP1004
Synonym:	
Agent category:	Compound
Target:	Mitochondrial complex 1 (MC1)
Target category:	Enzyme
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Non-human primates



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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}Tc-MIBI) and ^{99m}Tc-tetrofosmin are delocalized lipophilic cations, which are rapidly taken up into cells driven by metabolic demand and membrane potential (1-4). They are used as myocardial-perfusion single-photon emission computed tomography agents and as tumor-imaging agents. However, the high accumulation of Tc 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 thus 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-(4-fluoro-butyl)-benzyloxy]-2*H*-pyridazin-3-one (RP1004) is found to be a potent MC1 inhibitor with a hydrophobic heterocyclic pyridazinone (8). 2-*tert*-Butyl-4-chloro-5-[4-(4-[^{18}F]fluoro-butyl)-benzyloxy]-2*H*-pyridazin-3-one ([^{18}F]RP1004) has been synthesized to study its use as a PET agent for imaging myocardium.

Related Resource Links:

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

NLM Citation: Leung K. 2-*tert*-Butyl-4-chloro-5-[4-(4-[^{18}F]fluoro-butyl)-benzyloxy]-2*H*-pyridazin-3-one. 2010 Jun 15 [Updated 2010 Aug 26]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

Synthesis

[PubMed]

[^{18}F]RP1004 was prepared as described by Yu et al. (8). [^{18}F]Fluoride/Kryptofix 2.2.2/K_2CO_3 and the tosylate precursor were heated in acetonitrile for 30 min at 90°C, followed by high-performance liquid chromatography purification. Total synthesis time was 90 min. Radiochemical purity was >90% with specific activities of 27.8–55.5 GBq/μmol (0.75–1.5 Ci/μmol) at the end of synthesis. [^{18}F]RP1004 exhibited a calculated log *P* value of 4.84.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Yu et al. (8) reported that RP1004 inhibited NADH oxidation by bovine heart submitochondrial particles with a 50% inhibition concentration (IC_{50}) value of 16.7 nM. The IC_{50} value of known MC1 inhibitor rotenone was 18.2 nM.

Animal Studies

Rodents

[PubMed]

Yu et al. (8) performed *ex vivo* biodistribution studies of [^{18}F]RP1004 in rats (n = 9). [^{18}F]RP1004 accumulated mainly in the heart with 2.40 ± 0.21% injected dose/g (ID/g) and 2.67± 0.27% ID/g at 15 min and 60 min after injection, respectively. Retention of [^{18}F]RP1004 in the heart was good with no washout. The heart/blood, heart/lung, heart/liver, and heart/femur ratios were 33.3, 12.1, 1.5, and 3.4 at 60 min after injection, respectively. The uptake in the femur was 0.78% ID/g at 60 min, indicating some defluorination of [^{18}F]RP1004. For comparison, heart accumulation of ^{99m}Tc-sestamibi was 2.0% ID/g at 60 min with a heart/lung ratio of 5.9 at 60 min after injection. PET imaging showed that [^{18}F]RP1004 accumulated mainly in the heart and liver with low accumulation in the lung. Good myocardial images were observed at 25–35 min after injection with little interference from the lung and liver at 55–60 min. No blocking experiment was performed. The first pass extraction efficiency was not addressed.

Other Non-Primate Mammals

[PubMed]

Yu et al. (8) performed PET imaging studies of [^{18}F]RP1004 in rabbits (n = 6). [^{18}F]RP1004 accumulated mainly in the myocardium within minutes after injection, with some interference from the lung and liver at 5–15 min after injection. Retention of [^{18}F]RP1004 in the heart was good with little washout, whereas the retention was much lower in the liver. Accumulation of [^{18}F]RP1004 in the heart was clearly visualized at 65

min after injection with no interference from the lung and liver accumulation of [^{18}F]RP1004.

Non-Human Primates

[PubMed]

Yu et al. (8) performed PET imaging studies of [^{18}F]RP1004 in two rhesus monkeys. [^{18}F]RP1004 accumulated mainly in the myocardium within 5–15 min of injection. Retention of [^{18}F]RP1004 in the heart was good with no washout, whereas the retention was much lower in the liver with >58% loss of radioactivity. Accumulation of [^{18}F]RP1004 in the heart was clearly visualized at 60 min after injection with no interference from the liver accumulation of [^{18}F]RP1004.

Human Studies

[PubMed]

No publication is currently available.

References

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