2-(4-(4-[^{18}F]Fluoro-butyl)-benzylsulfanyl)-3-methyl-chromen-4-one

[^{18}F]RP1005

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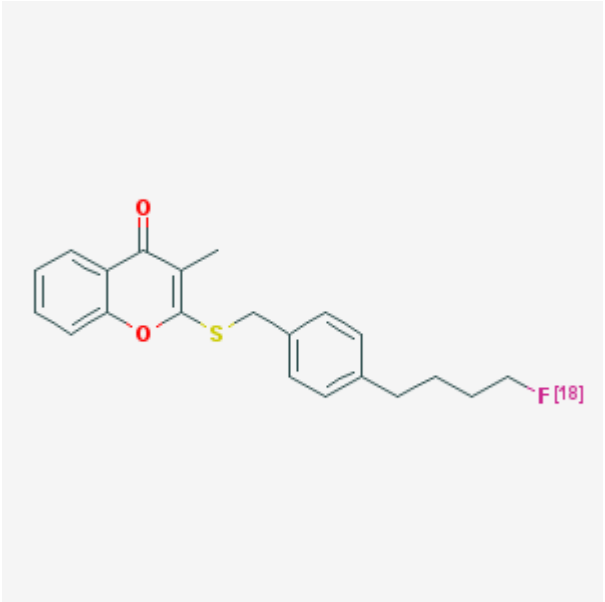
Chemical name:	2-(4-(4-[^{18}F]Fluoro-butyl)-benzylsulfanyl)-3-methyl-chromen-4-one
Abbreviated name:	[^{18}F]RP1005
Synonym:	
Agent category:	Compound
Target:	Mitochondrial complex I (MCI)
Target category:	Enzyme
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals



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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 evaluate myocardial blood flow with the use of positron-emitting radionuclides (e.g., ^{82}RbCl, $^{13}NH_3$, and $H_2{}^{15}O$). However, the majority of these radiotracers exhibit 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 (MCI) of the mammalian electron transfer chain is composed of at least 43 protein subunits, of which seven are encoded by mitochondrial DNA (7). MC-I 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. MC-I 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-(4-(4-[^{18}F]Fluoro-butyl)-benzylsulfanyl)-3-methyl-chromen-4-one ([^{18}F]RP1005) has been found to be a potent MC-I inhibitor with a hydrophobic heterocyclic chromone (8) and its use as a PET agent for imaging myocardium is being studied.

Related Resource Links:

- Chapters in MICAD (MCI)
- Gene information in NCBI (MCI)
- Articles in Online Mendelian Inheritance in Man (OMIM) (MCI)
- Clinical trials (MCI)

Synthesis

[PubMed]

[^{18}F]RP1005 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.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Yu et al. (8) reported that RP1005 inhibited NADH oxidation by bovine heart submitochondrial particles with a 50% inhibition concentration (IC_{50}) value of 14.4 nM. The IC_{50} value of the known MC-I inhibitor rotenone was 18.2 nM.

Animal Studies

Rodents

[PubMed]

Yu et al. (8) performed *ex vivo* biodistribution studies of [^{18}F]RP1005 in rats (n = 12). [^{18}F]RP1005 accumulated mainly in the heart, with 2.28 ± 0.12% injected dose/g (ID/g) and 1.81 ± 0.17% ID/g at 15 min and 60 min after injection, respectively. Retention of [^{18}F]RP1005 in the heart was good, with little washout. The heart/blood, heart/lung, heart/liver, and heart/femur ratios were 20.1, 10.1, 2.2, and 4.5 at 60 min after injection, respectively. The uptake in the femur was 0.40% ID/g at 60 min, indicating little defluorination of [^{18}F]RP1005. 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]RP1005 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 or 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]RP1005 in rabbits (n = 6). [^{18}F]RP1005 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]RP1005 in the heart was good and exhibited little washout, whereas the retention was much lower in the liver. Accumulation of [^{18}F]RP1005 in the heart was clearly visualized at 65 min after injection, with some interference from the lung and liver accumulation of [^{18}F]RP1005.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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