2-[4-(4-[^{18}F]Fluorobutyl)benzylsulfanyl]-3-methylchromene-4-one

[^{18}F]10

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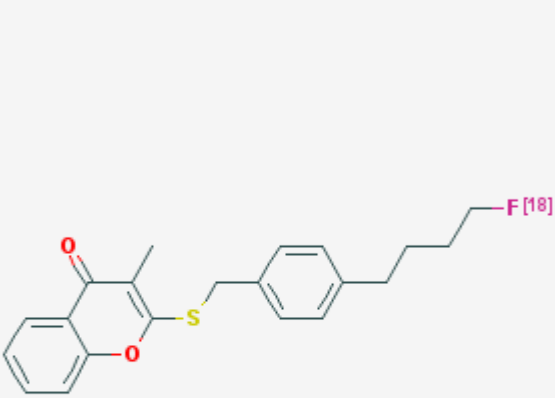
Chemical name:	2-[4-(4-[^{18}F]Fluorobutyl)benzylsulfanyl]-3-methylchromene-4-one
Abbreviated name:	[^{18}F]10
Synonym:	
Backbone:	Compound
Target:	Mitochondrial complex I (MCI)
Mechanism:	Enzyme inhibitor
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



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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

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plasma and mitochondrial membrane potentials. ^{99m}Tc-2-Methoxyisobutylisonitrile (^{99m}Tc-MIBI) and ^{99m}Tc-tetrofosmin are delocalized lipophilic cations that are rapidly taken up into cells in response to metabolic demand and membrane potential (1-4). They are used as myocardial-perfusion single-photon emission computed tomography (SPECT) 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 (<20 min). Lipophilic cations like [^{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 7 are encoded by mitochondrial DNA (7). MCI 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. It may also play direct roles in the mitochondrial permeability transition and cell death pathways. Myocardium has a high mitochondrial content because of high energy usage. 2-[4-(4-Fluorobutyl)benzylsulfanyl]-3-methylchromene-4-one (compound 10) is a potent MCI inhibitor with a hydrophobic heterocyclic chromone core (8). 2-[4-(4-[^{18}F]Fluorobutyl)benzylsulfanyl]-3-methylchromene-4-one ([^{18}F]10) has been synthesized for use in studies as a myocardium imaging PET agent.

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]10 was prepared as described by Radeke et al. (8). [^{18}F]KF/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 6% with a total synthesis time of 90 min. Radiochemical purity was >99% with specific activities of 27.8–74.0 TBq/μmol (750–2,000 Ci/mmol) at end of synthesis. [^{18}F]10 has a clog $D_{7.4}$ value of 5.6.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Radeke et al. (8) reported that compound 10 inhibited NADH oxidation by bovine heart submitochondrial particles with a 50% inhibitory concentration value of 9 nM.

Animal Studies

Rodents

[PubMed]

Radeke et al. (8) performed biodistribution and PET imaging studies of [^{18}F]10 in rats. [^{18}F]10 accumulated mainly in the heart (2.24 ± 0.27% injected dose (ID/g)), kidney (2.00 ± 0.31% ID/g), and liver (1.93 ± 0.14% ID/g), with low blood (0.11 ± 0.02% ID/g) and brain radioactivity (~0.26% ID/g) at 30 min after injection. Retention of [^{18}F]10 in the heart was good in that 66% of the radioactivity at 30 min was present at 120 min, whereas retention was much less in the other organs with the exception of the femur. The uptake in the femur was 0.36 ± 0.04% ID/g at 30 min and 0.74 ± 0.06% ID/g at 120 min, indicating some defluorination of [^{18}F]10. PET imaging showed that [^{18}F]10 accumulated mainly in the heart, followed by the kidney and liver, with low accumulation in the lung. Good myocardial images were observed at 25–35 min after injection, and complete images were observed at 55–60 min with little interference from the lung. Bone uptake was observed in images after 30 min. No blocking experiments were performed.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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