IR-786 perchlorate

IR-786

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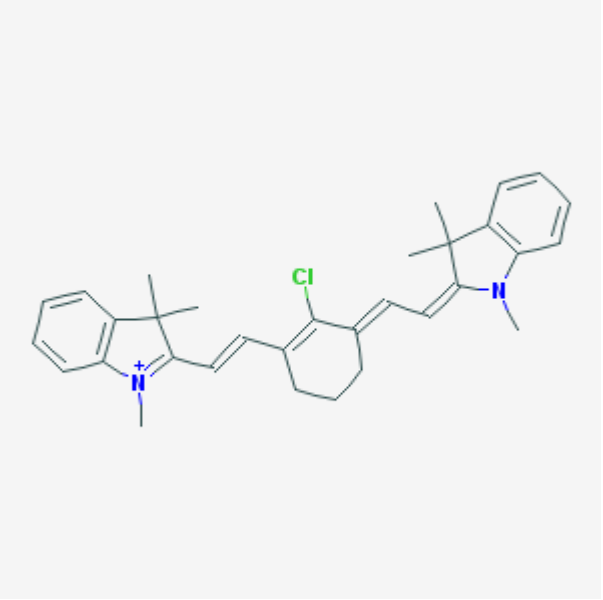
Chemical name:	IR-786 perchlorate
Abbreviated name:	IR-786
Synonym:	2-(2-[2-Chloro-3-([1,3-dihydro-1,3,3-trimethyl-2*H*-indol-2-ylidene]ethylidene)-1-cyclohexen-1-yl]ethenyl)-1,3,3-trimethylindolium perchlorate
Agent category:	Compound
Target:	Mitochondria and endoplasmic reticulum
Target category:	Lipophilic cation
Method of detection:	Optical, near-infrared fluorescence (NIR) imaging
Source of signal \contrast:	IR-786
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

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Background

[PubMed]

Optical fluorescence imaging is increasingly used to obtain biological functions of specific targets (1, 2). However, the intrinsic fluorescence of biomolecules poses a problem when visible light (350-700 nm) absorbing fluorophores are used. Near-infrared (NIR) fluorescence (700-900 nm) detection avoids the background fluorescence interference of natural biomolecules, providing a high contrast between target and background tissues. NIR fluorophores have wider dynamic range and minimal background as a result of reduced scattering compared with visible fluorescence detection. They also have high sensitivity, resulting from low infrared background, and high extinction coefficients, which provide high quantum yields. The NIR region is also compatible with solid-state optical components, such as diode lasers and silicon detectors. NIR fluorescence imaging is becoming a non-invasive alternative to radionuclide imaging.

IR-786 perchlorate (IR-786) is a heptamethine indocyanine-type NIR fluorophore with peak absorption in the 760-780-nm range and peak excitation emission in the 795-815-nm range. It provides a quantum yield of 3.3%. IR-786 is a lipophilic cation, localized to mitochondria at low concentrations and to endoplasmic reticulum (ER) at high concentrations (3). It has a molecular weight of 584. IR-786 proves to be a useful agent in myocardial and brown adipose tissue (BAT) perfusion (4). In mice, two large, lobulated masses of brown fat tissue are found on the dorsal side of the thorax. BAT is located in smaller masses around the aorta and in the hilus of the kidney. BAT is richly vascularised and has numerous unmyelinated nerves, which provide sympathetic stimulation from the hypothalamus to the adipocytes (5). Brown adipocytes express mitochondrial uncoupling proteins, which give the cell's mitochondria an ability to uncouple oxidative phosphorylation and utilize substrates to generate heat rather than ATP (5-8). NIR fluorescence dyes with *N*-hydoxysuccinimide ester can be conjugated to antibodies and low-molecular weight ligands (9).

Related Resource Links:

- Chapters in MICAD (IR-786)

Synthesis

[PubMed]

IR-786 perchlorate is commercially available (LI-COR, Lincoln, NE).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

IR-786 uptake into rat neonatal cardiomyocytes, human T24 bladder carcinoma, and mouse MBT-2 bladder carcinoma was rapid with plateau levels within 30 min (4). These cells incorporated 2.2-6.1 fmol of IR-786 per cell when incubated with 10 μM dye. IR-786 accumulated exclusively in mitochondria of these cells at or below extracellular concentrations of 0.25, 1, and 0.25 μM, respectively, and in both mitochondria and ER at above the threshold concentrations. Pretreatment of cells with 10 μM FCPP, which dissipates the mitochondrial membrane potential abolished mitochondrial uptake of both IR-876 and rhodamine 123. Both the dyes were now localized exclusively in the ER. The cells were visualized directly using NIR fluorescence microscopy. The mitochondria were found to be structurally intact by staining with a mitochondria-specific antibody.

Animal Studies

Rodents

[PubMed]

Rats were injected intravenously with 50 nmol of IR-786 (3). Peak serum concentration of 0.13 μM was reached within 1 min. A peak uptake of 1.7% injected dose (about 0.6 μM) was observed in the explanted heart at 1 min. NIR fluorescence reflectance imaging showed peak emission fluorescence intensity from the exposed heart at 1 min, returning to baseline within 1 h. When left anterior descending coronary artery occlusion was introduced for 5 min, the myocardium distal to the occlusion had a 4-fold decrease in fluorescence signal compared with the perfused myocardium. When the occlusion was removed, IR-786 fluorescence was homogeneous in the heart within 1 min. Prolonged ischemia (30-min occlusion) showed a large area with no IR-786 fluorescence. At 24 h after occlusion, the beating heart was imaged again. IR-786 revealed a 1.6-fold increase in perfusion from dilated arteries, showing a 1.4-mm-wide, crescent-shaped, infarcted band. The infarcted area was confirmed with 2,3,5-triphenyltetrazolium chloride staining and by tissue sectioning as 49.5% of the area at risk and 47.1% as measured by IR-786 fluorescence. IR-786 can be used to finely map myocardial blood flow, perfusion, and infarction.

Nude mice were injected intravenously with 1 nmol of IR-786, and various organs were removed and measured fluorometrically (4). An avid accumulation of IR-786 was found in the lungs within 1 min, decreasing over 24 h. The liver and spleen uptake increased with time, peaking at 1 h. The blood concentration remained low. Negligible uptake was seen in the muscle, kidneys, and brain. The other areas with significant uptake were the heart and thorax BAT. β3-Adrenergic (Cl 316,243) and cold (4°C) stimulation of mice increased uptake in thorax BAT, as imaged by NIR fluorescence reflectance imaging. The β3-adrenergic antagonist, propanolol, blocked the cold stimulation-induced uptake in BAT. BAT perfusion fluorescence intensity of IR-786 was similar in nude mice with or without their skin removed. Using homozygous deletion of uncoupling proteins 1 and 2, these mice had a higher baseline perfusion of BAT but a similar maximal response to Cl

316,243. BAT perfusion can be measured non-invasively, and pharmacological modulators of thermogenesis can be screened in living animals using NIR fluorescence.

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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