(*S*)-1-(4-(2-[^{18}F]Fluoroethoxy)benzyl)-5-[1-(2-methoxymethyl-pyrrolidinyl)sulfonyl]-1*H*-indole-2,3-dione

[^{18}F]CbR**2**

Kam Leung, PhD[1]

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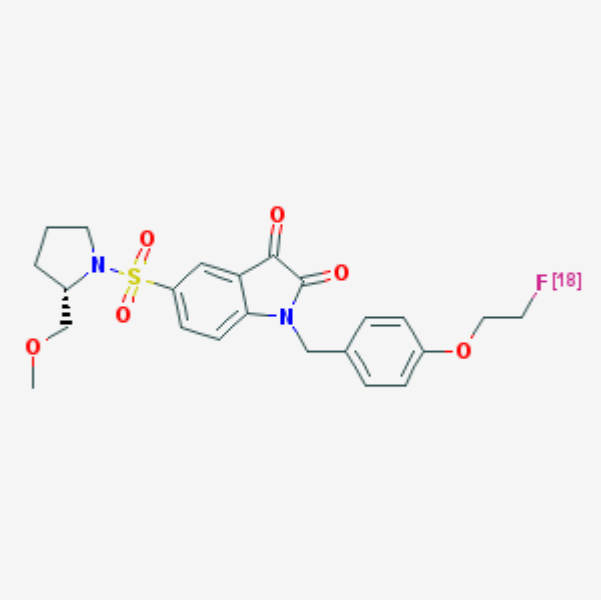
Chemical name:	(*S*)-1-(4-(2-[^{18}F]Fluoroethoxy)benzyl)-5-[1-(2-methoxymethyl-pyrrolidinyl)sulfonyl]-1*H*-indole-2,3-dione
Abbreviated name:	[^{18}F]CbR2
Synonym:	
Agent category:	Compound
Target:	Caspase-3
Target category:	Enzyme
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

[1] National Center for Biotechnology Information, NLM, NIH; Email: MICAD@ncbi.nlm.nih.gov.

Corresponding author.

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Background

[PubMed]

Apoptosis (programmed cell death) plays an important role in the pathophysiology of many diseases, such as cancer, neurodegenerative disorders, vascular disorders, and chronic hepatitis, as well as in the biology of normal cells, such as epithelial cells and immune cells (1). Apoptosis is gene-regulated (2) and is the result of proteolysis of intracellular components by activation of a series of proteolytic enzymes called caspases and changes of plasma membrane structure by translocase, floppase, and scramblase (3-5). As a result, there is rapid redistribution of phosphatidylserine (PS) from the inner membrane leaflet to the outer membrane leaflet, exposing the anionic head group of PS. On the other hand, PS is also accessible for annexin V binding in necrosis because of disruption of the plasma membrane.

Annexin V is a 36-kDa endogenous human protein produced in particular by epithelial cells from many tissues, such as the placenta, umbilical vessels, liver, spleen, kidney, heart, uterus, and skeletal muscle, as well as by erythrocytes, leukocytes, endothelial cells, and platelets (6). Annexin V binds to PS with high affinity (K_d = 7 nM) (3, 7, 8). Apoptosis can be induced by chemicals, radiation, cytokines, hormones, and various pathological conditions (5); therefore, the ability to monitor apoptosis in association with disease progression or regression should provide important information for clinical applications. Annexin V has been radiolabeled with ^{18}F, ^{123}I, ^{125}I, and ^{99m}Tc for imaging (9-12). However, annexin V is not able to distinguish between apoptosis and necrosis. Caspase ligand may be an attractive alternative for imaging cells undergoing apoptosis because caspases are key enzymes that mediate apoptosis (13). Kopka et al. (14) reported that 5-pyrrolidinylsulfonyl isatins exhibited selective inhibition of caspase-3 and caspase-7 (executioner caspases) over caspase-1, -6, and -8 (initiator caspases). (*S*)-1-(4-(2-[^{18}F]Fluoroethoxy)benzyl)-5-[1-(2-methoxymethyl-pyrrolidinyl)sulfonyl]-1*H*-indole-2,3-dione ([^{18}F]CbR2), one of the *N*-1–substituted 5-pyrrolidinylsulfonyl isatin analogs, has been synthesized for imaging caspase-3 activation in apoptosis (15).

Synthesis

[PubMed]

Faust et al. (15) report the synthesis of [^{18}F]CbR2 by nucleophilic displacement of the tosylate group of the tosylate precursor with [^{18}F]KF (Kryptofix 2.2.2./K_2CO_3) at 85°C for 5 min. Subsequent high-performance liquid chromatography separation gave radiochemical yields of ~32% (decay-corrected) and radiochemical purities >90% with a total synthesis time of 82 min. The specific activity was 48 GBq/μmol (1.3 Ci/μmol) at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro caspase enzyme assays using CbR2 showed inhibition concentration (IC_{50}) values of 36.4 ± 5.5 nM for caspase-3, 93.3 ± 1.0 nM for caspase-7, and >25,000 nM for caspase-6, -1, and -8 (14).

Animal Studies

Rodents

[PubMed]

Faust et al. (15) performed a preliminary biodistribution study in nude mice (n = 2/group) at 10 and 32 min after injection of 7 MBq (0.19 mCi) [^{18}F]CbR2. The highest accumulation of radioactivity was observed at 10 min after injection in the gall bladder, followed by the duodenum, liver, and kidney. Radioactivity in the blood and most peripheral organs was cleared by 32 min, with the main fraction of radioactivity remaining in the urinary bladder. The microPET imaging at 165–180 min confirmed that the radioactivity remained in the liver, bowels, and urinary bladder as observed in the biodistribution study. The authors suggested that further preclinical *in vivo* studies are needed to confirm the usefulness of [^{18}F]CbR2 as a caspase-3 probe in imaging apoptosis in humans.

Other Non-Primate Mammals

[PubMed]

No publications are currently available.

Non-Human Primates

[PubMed]

No publications are currently available.

Human Studies

[PubMed]

No publications are currently available.

NIH Support

HL13851, EB 001729, CA121952

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([18F]CbR) as potential positron emission tomography-compatible apoptosis imaging agent. Q J Nucl Med Mol Imaging. 2007;51(1):67–73. PubMed PMID: 17372575.