(*S*)-1-(4–2-[^{11}C]Methoxybenzyl)-5-(2-phenoxymethyl-pyrrolidine-1-sulfonyl)-1*H*-indole-2,3-dione

[^{11}C]**WC-98**

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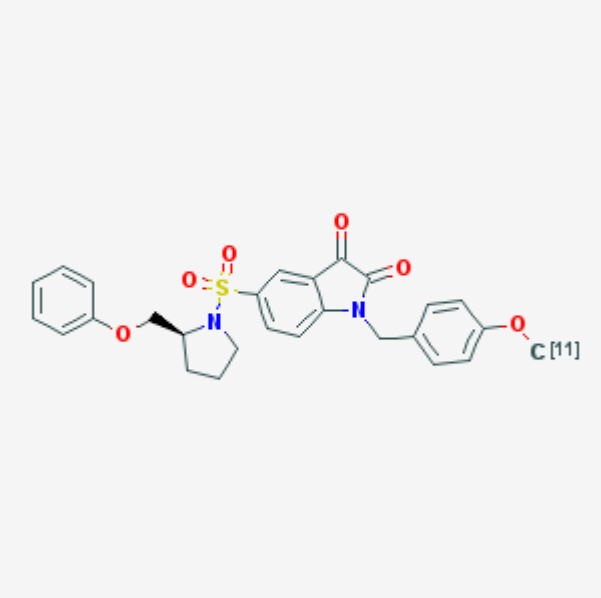
Chemical name:	(*S*)-1-(4–2-[^{11}C]Methoxybenzyl)-5-(2-phenoxymethyl-pyrrolidine-1-sulfonyl)-1*H*-indole-2,3-dione
Abbreviated name:	[^{11}C]WC-98
Synonym:	
Agent category:	Compound
Target:	Caspase-3
Target category:	Enzyme
Method of detection:	PET
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

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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. However, PS is expressed in both cell necrosis and apoptosis and therefore cannot distinguish between the two, whereas caspase 3/7 is only activated in apoptosis. Caspase substrate may be an attractive alternative for imaging cells undergoing apoptosis because caspases are key enzymes that mediate apoptosis (13). Chu et al. (14) reported that isatin sulfonamide analogs exhibited selective inhibition of caspase-3 and caspase-7 (executioner caspases) over caspase-1, -6, and -8 (initiator caspases). 1-[4-(2-[^{18}F]Fluoroethoxy)-benzyl]-5-(2-phenoxymethyl-pyrrolidine-1-sulfonyl)-1*H*-indole-2,3-dione ([^{18}F]WC-II-89) showed higher uptake in the liver and spleen in cycloheximide-treated rats when compared with untreated control rats (15). (*S*)-1-(4–2-[^{11}C]Methoxybenzyl)-5-(2-phenoxymethyl-pyrrolidine-1-sulfonyl)-1*H*-indole-2,3-dione ([^{11}C]WC-98), an analog of [^{18}F]WC-II-89, has been synthesized for imaging caspase-3 activation in apoptosis (16).

Synthesis

[PubMed]

Zhou et al. (16) reported the synthesis of [^{11}C]WC-98 in one-pot reactions. (*S*)-1-(4-Hydroxybenzyl)-5-(2-phenoxymethyl-pyrrolidine-1-sulfonyl)-1*H*-indole-2,3-dione (410 nM) was added to a solution of 1 M Bu_4NOH (830 nM) in CH_3CN. After cooling to 0°C, [^{11}C]CH_3I was bubbled into the mixture and heated at 88°C for 4 min, and then 88°C for

4 min with 1 N HCl. [^{11}C]WC-98 was purified with high-performance liquid chromatography. The radiochemical yield was 62 ± 12% (n = 4) at the end of purification, and the specific activity was 207.2 ± 40.7 GBq/μmol (5.6 ± 1.1 Ci/μmol) at the end of synthesis (EOS). Radiochemical purity was >99% as determined with high-performance liquid chromatography. Total synthesis time was not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro caspase enzyme assays using WC-II-89 showed inhibition concentration (IC_{50}) values of 9.7 ± 1.3 nM for caspase-3, 23.5 ± 3.5 nM for caspase-7, 3,700 ± 390 nM for caspase-6, >50,000 nM for caspase-1, and >50,000 nM for caspase-8 (15).

Animal Studies

Rodents

[PubMed]

Zhou et al. (16) performed *ex vivo* liver accumulation of [^{11}C]WC-98 in normal mice and mice pretreated with anti-Fas (Jo2) antibody to induce apoptosis in the liver (n = 5/group). The initial tracer accumulation (~25%ID/g) was similar in the liver from both mice at 5 min after injection. However, the Fas-treated liver (~13% ID/g) showed a higher retention of radioactivity than the control liver (~2% ID/g) at 30 min after injection. Fluorometric caspase-3 enzymatic assay confirmed a 5-fold increase in the Fas-treated liver over the control livers. The microPET imaging confirmed the approximately 5-fold increase in [^{11}C]WC-98 accumulation in the Fas-treated liver at 30 min after injection as observed in the biodistribution study. The Fas-treated liver (~0.12% ID/ml) was still clearly visualized at 30-60 min, whereas the control liver (~0.02% ID/ml) was barely visualized. No blocking or caspase-3 inhibition experiment was performed.

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

P01 HL13851, K08 EB006702, R21 CA121952

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