[^{11}C]2-(Dimethylamino)-N-(5,6-dihydro-6-oxophenanthridin-2-yl)acetamide

[^{11}C]PJ34

The MICAD Research Team

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Chemical name:	[^{11}C]2-(Dimethylamino)-*N*-(5,6-dihydro-6-oxophenanthridin-2-yl)acetamide	
Abbreviated name:	[^{11}C]PJ34	
Synonym:		
Agent Category:	Amino acid	
Target:	Poly(ADP-ribose)polymerase-1 (PARP-1)	
Target Category:	Binding to PARP-1	
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.

Background

[PubMed]

Cellular death can occur through two different chemical pathways: apoptosis and necrosis. Apoptosis is a highly regulated mechanism involving an externalization process of amino-phospholipids, primarily phosphatidylserine (PS), that normally face the cytoplasm (1). Through this process, PS residues are exposed at the outer plasma membrane and face the extracellular fluid (2). Necrosis, on the other hand, is a chaotic, unregulated mode of cell death followed by invasion of inflammatory cells (3).

Imaging of apoptosis through PS exposure using annexin V has been a growing trend over recent years (4, 5). However, because PS inversion occurs in both necrosis and apoptosis,

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the imaging strategy of quantifying the exposed PS does not differentiate between necrosis from apoptosis. For that reason, other imaging approaches using targeted pathways that are specific to each mechanism are currently under investigation.

The hyperactivation of poly(ADP-ribose) polymerase 1 (PARP-1) followed by depletion of NAD^+ pools is thought to be the mechanism taking place specifically during necrosis, and probing PARP-1 activity is currently being investigated as a possible route for imaging and evaluating cellular death through necrosis. The phenanthridinone derivative 2-(dimethylamino)-*N*-(5,6-dihydro-6-oxophenanthridin-2-yl)acetamide (PJ34) is known to inhibit PARP-1 by competing for the NAD^+ binding site in the activated form of the enzyme (6, 7). Preliminary studies using PJ34 labeled with ^{11}C gave favorable data about the possible use of [^{11}C]PJ34 in positron emission tomography studies for imaging tissues undergoing cellular death through necrosis (8).

Synthesis

[PubMed]

[^{11}C]PJ34 can be synthesized by reaction of the desmethyl precursor *N*-(5,6-dihydro-6-oxophenanthridin-2-yl)-2(methylamino)acetamide with the labeling agent [^{11}C]methyl iodide ([^{11}C]MeI), using sodium hydroxide as a base catalyst. Details of such a procedure were reported by Tu et al. (8) in 2005.

Briefly, synthesis of the precursor was accomplished by treatment of phenanthridin-6(5*H*)-one with 90% nitric acid in acetic acid to produce the corresponding 2-nitro derivative, which was then reduced with iron in aqueous dimethyl formamide to produce the 2-amino analog. This analog was then condensed with *N*-BOC-protected sarcosine followed by deprotection with ethanolic HCl to finally give the precursor in an overall yield of 74%. ([^{11}C]MeI was obtained from [^{11}C]carbon dioxide converted to [^{11}C]methane and reacted with iodine in the gas phase at 690 °C).

Tu et al. (8) obtained a radiochemical yield >60% for [^{11}C]PJ34 (decay-corrected at end of bombardment (EOB)), and a radiochemical purity >99%. The total synthesis time was 50-55 min. The specific activity of the radiotracer produced was ~74,000 MBq/μmol (2,000 mCi/μmol; decay-corrected at EOB; n = 10).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Tu et al. (8) performed immunochemistry studies to obtain further data supporting previous observations (9, 10) of increased uptake of [^{11}C]PJ34 in the pancreas of streptozocin (STZ)-treated rats via hyperactivation of PARP-1. The authors used pancreatic tissue slices in conjunction with a rabbit antibody specific for poly(ADP-ribose) residues formed by the enzymatic activity of PARP-1. Observations showed

staining inside the nuclei of cells within pancreatic islets for STZ-treated tissues but no poly(ADP-ribose) staining for control rats.

STZ is used as a model of type 1 diabetes. It is taken up by islet beta cells in the pancreas and causes damage to the DNA, which then leads to hyperactivation of PARP-1. Eventually, the cells are depleted of NAD^+ and cellular death – via necrosis – eventually follows (9).

Animal Studies

Rodents

[PubMed]

Biodistribution studies of [^{11}C]PJ34 were performed by Tu et al. (8) in Wistar Furth rats (160-180 g) given an intravenous injection of STZ (80 mg/kg of tissue; ~6.6 MBq (180 μCi) per rat). The animals were sacrificed at 5 and 30 min after injection of the radiotracer, organs of interest were removed, and radioactivity was counted.

Results of the studies showed that in STZ-treated animals, the highest uptakes of [^{11}C]PJ34 were in the liver (1.138 ± 0.066% injected dose (ID)/g of tissue at 30 min post injection) and pancreas (1.027 ± 0.109% ID/g of tissue at 30 min post injection), compared with control animals (0.767 ± 0.093% ID/g of tissue for the pancreas and 0.885 ± 0.104% ID/g of tissue for the liver at 30 min post injection). These data reflect previous studies showing that hepatocytes and pancreatic islet cells express the GLUT-2 transporter and can be affected by the DNA damage induced by STZ (9, 10).

The following uptake values at 30 min post injection were also reported by Tu et al. (8): in the heart, 0.498 ± 0.055% ID/g of tissue for STZ-treated rats and 0.445 ± 0.044% ID/g of tissue for control animals; in the muscle, 0.233 ± 0.009% ID/g of tissue for STZ-treated rats and 0.0228 ± 0.016% ID/g of tissue for control animals, and in the lung, 0.814 ± 0.043% ID/g of tissue for STZ-treated rats and 0.755 ± 0.136% ID/g of tissue for control animals.

At 5 min post injection, the uptake values obtained for the liver and pancreas were 2.766 ± 0.439 and 1.812 ± 0.234% ID/g of tissue, respectively, for STZ-treated rats and 1.837 ± 0.367 and 1.150 ± 0.118% ID/g of tissue, respectively, for control animals.

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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