9-(4-(2-[^{18}F]Fluoroethyl)benzyl)-9-azabicyclo[3.3.1]nonan-3-yl-2-methoxy-5-methyl-phenylcarbamate

[^{18}F]WC-59

Arvind Chopra, PhD[1]

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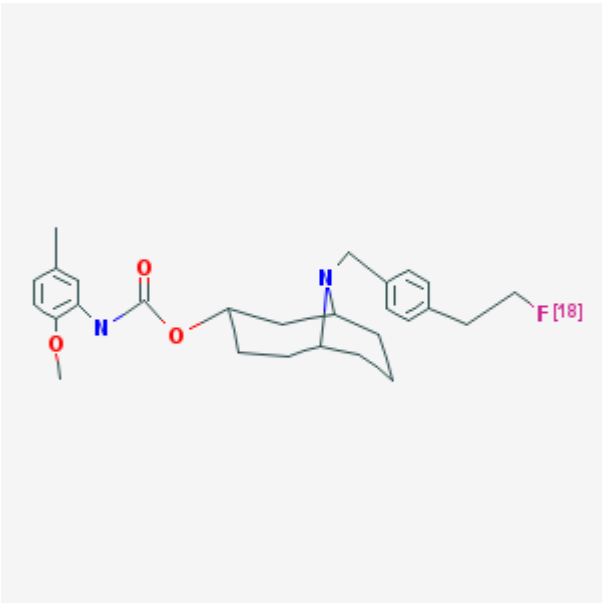
Chemical name:	9-(4-(2-[^{18}F]Fluoroethyl)benzyl)-9-azabicyclo[3.3.1]nonan-3-yl-2-methoxy-5-methyl-phenylcarbamate
Abbreviated name:	[^{18}F]WC-59
Synonym:	
Agent Category:	Compound
Target:	Sigma 2 receptors
Target Category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure of [^{18}F]WC-59 for additional information regarding the compound in PubChem.
Click on gene, nucleotide or protein for information regarding the human sigma receptor.

[1] National Center for Biotechnology Information, NLM, NIH, Bethesda, MD 20894; Email: micad@ncbi.nlm.nih.gov.

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Background

[PubMed]

Sigma receptors (SR) are known to exist as subtypes 1 (Sig-1R) and 2 (Sig-2R) and are found in the central nervous system and the peripheral tissues. Both receptor subtypes have a different distribution in the two types of tissues, and the exact biological function of these receptors is not known (1). Of the two receptor subtypes, only the Sig-1R has been cloned, expressed, and purified (2). The Sig-2R is known to be overexpressed in various malignant tumors and to promote cell proliferation, indicating that these receptors may play a role in the development of some cancers and could be targeted for the development of different anti-cancer drugs or imaging agents for tumors that overexpress Sig-2R (3). Several clinical trials have been approved by the United States Food and Drug Administration for the evaluation of drugs that target the Sig-2R for the imaging and treatment of different clinical conditions. In addition, Sig-2R ligands have been used in preclinical studies to chemosensitize tumors to low doses of anti-cancer drugs that are otherwise toxic when given at high doses to animals bearing mammalian cell line tumors (4, 5).

Investigators have developed and characterized several SR ligands, but most of them are either selective only for the Sig-1R or have similar affinity for both the SR subtypes, therefore limiting their use as anti-cancer or Sig-2R imaging agents (5). In an effort to develop a Sig-2R ligand with high specificity, Chu et al. (5) developed several analogs of 9-benzyl-9-azabicyclo[3.3.1]nonan-3-yl-2-methoxy-5-methylphenylcarbamate, which has been shown previously to have a high binding selectivity for Sig-2R. Among these analogs, 9-(4-(2-fluoroethyl)benzyl)-9-azabicyclo[3.3.1]nonan-3-yl-2-methoxy-5-methyl-phenylcarbamate (designated WC-59) was shown to be a potent Sig-2R ligand under *in vitro* conditions. WC-59 was subsequently labeled with ^{18}F to obtain [^{18}F]WC-59 and characterized under *in vitro* conditions. Biodistribution of the labeled compound was also studied in mice bearing murine EMT-6 cell tumors that express the Sig-2R.

Synthesis

[PubMed]

The synthesis and ^{18}F labeling of WC-59 was described by Chu et al. (5). The total time required for the synthesis and purification of [^{18}F]WC-59 was reported to be 100 min with a decay-corrected radiochemical yield of ~15%. The radiochemical purity of the tracer was >99.9%, and the specific activity at the end of synthesis was 155.4 GBq/μmol (4.2 Ci/μmol). The stability and storage conditions of the labeled compound were not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The binding affinity values of WC-59 for the Sig-1R and Sig-2R were reported to be 1,710.5 ± 84.0 and 0.82 ± 0.13 nM, respectively, with a Sig-1R/Sig-2R ratio of 2,087 (5) as determined with competitive inhibition studies described elsewhere (6).

To evaluate the use of [^{18}F]WC-59 as an imaging agent for solid tumors expressing Sig-2R, receptor binding of the tracer was studied using cell membranes isolated from mouse breast tumors derived from EMT-6 cells (5). The density of Slg-2R on the tumor cells was reported to be ~3,700 fmol/mg protein, and the receptor affinity of the labeled compound was determined to be ~2 nM.

From these studies the investigators concluded that [^{18}F]WC-59 could be evaluated as an imaging agent for solid tumors expressing Sig-2R (5).

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{18}F]WC-59 was studied in BALB/c mice bearing murine EMT-6 cell tumors (5). The radiolabel was administered to the animals through the tail vein, and the mice were euthanized at preselected time points up to 2 h after treatment (the number of animals used per time point was not reported). Blood, tumors, and major organs were harvested from the animals to determine the amount of radioactivity accumulated in the various tissues. Data were presented as percentage uptake of injected dose per gram tissue (% ID/g). Radioactivity was rapidly taken up by the lungs, heart, kidneys, liver, and muscles (111.00 ± 13.52, 18.49 ± 2.50, 22.42 ± 2.91, 21.14 ± 3.59, and 4.60 ± 0.76% ID/g, respectively, at 5 min postinjection), and most of it was lost from the lungs, heart, kidneys, and muscles (4.98 ± 0.27, 1.22 ± 0.18, 5.82 ± 0.33, and 1.62 ± 0.27% ID/g, respectively) by 2 h after treatment, with the exception of the liver (17.11 ± 1.57% ID/g). The tumors had an accumulation of 1.39 ± 0.34% ID/g at 5 min, and it increased to 4.08 ± 0.66% ID/g at 2 h after treatment. The tumor/blood, tumor/muscle, tumor/fat, and tumor/lung ratios were 6.96, 2.53, 0.32, and 0.82, respectively, at 2 h after injection. From these ratios the investigators concluded that, compared with the ^{18}F-labeled ligands available for the Sig-2R (7), [^{18}F]WC-59 was not a superior ligand for the detection and determination of the proliferation potential of tumor cells expressing this receptor. No blocking studies were reported. Subtype specificity under *in vivo* conditions was assumed from the *in vitro* data.

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

Supplemental Information

[Disclaimers]

No information is currently available.

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