O-[^{11}C]methyl derivative of 6,7-dimethoxy-2-(4-methoxy-biphenyl-4-yl-methyl)-1,2,3,4-tetrahydro-isoquinoline

[^{11}C]MC113

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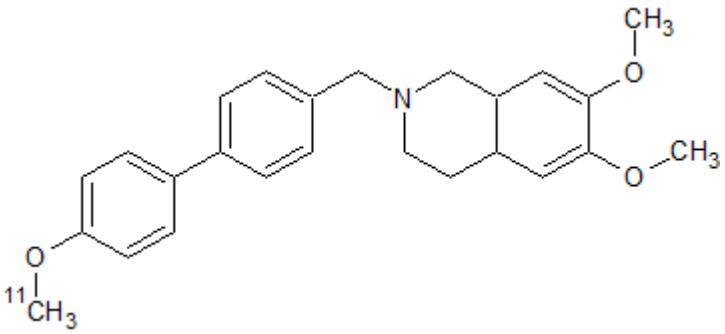
Chemical name:	O-[^{11}C]methyl derivative of 6,7-dimethoxy-2-(4-methoxy-biphenyl-4-yl-methyl)-1,2,3,4-tetrahydro-isoquinoline
Abbreviated name:	[^{11}C]MC113
Synonym:	
Agent Category:	Compound
Target:	P-glycoprotein transporter
Target Category:	Transporter
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents



Structure of [^{11}C]MC113

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Background

[PubMed]

The P-glycoprotein (P-gp) is one of the members of the ATP-binding cassette transporter family of proteins that is responsible for the rapid transportation of drugs across the cell membrane (uptake and efflux) (1). The multi-drug resistance protein and the breast cancer resistance protein (BCRP) are the other two members of this group of proteins. The structure, functions, and activities of P-gp have been discussed in detail by Giacomini et al. (2) and Sharom (3). Overexpression of these transporters, particularly P-gp, affects the distribution of drugs in various parts of the body, including the central nervous system (CNS), and this overexpression is responsible for the development of drug resistance in cancer cells (4). In addition, a reduced function and expression of P-gp has been suggested to result in a slow or reduced clearance of neurotoxic peptides such as the amyloid-β peptide from the neuronal cells, and this has been hypothesized to contribute to the development of Alzheimer's and Parkinson's diseases and other neurological conditions (5).

P-gp is expressed on the luminal side of the capillary endothelial cells of the blood–brain barrier (BBB) and is believed to protect the CNS from the effects of toxic compounds that may be circulating in the blood by actively pumping them from the CNS back into circulation (6). A variety of ^{11}C-labeled substrates of the P-gp, such as [^{11}C]verapamil, [^{11}C]loperamide, and [^{11}C]desmethyl loperamide, have been used with positron emission tomography (PET) to investigate the *in vivo* functioning of the transporter in humans (6). However, slight changes in the function or expression of P-gp that may occur in different regions of the brain may not be detected accurately with these labeled compounds because they have a low uptake in the brain (6). As an alternative to the use of labeled substrates for the detection and quantification of P-gp in the brain, it was proposed that radiolabeled inhibitors of P-gp, such as [^{11}C]laniquidar, [^{11}C]elacridar, and [^{11}C]traiquidar, would probably yield superior results because these compounds bind to the protein with a high affinity (rather than being transported), and overexpression of the transporter would result in the generation of an increased PET signal that can be used to detect and quantify P-gp (7). Surprisingly, a very low uptake of the P-gp inhibitor probes was observed in the rodent brain; this phenomenon was attributed to the substrate-like behavior of the tracers toward the BCRP present in the organ, and this transporter was suggested to rapidly transport the radiochemicals out of the CNS across the BBB (8). Therefore, the radiolabeled inhibitors of P-gp are considered to be unsuitable to detect and determine the density of this transporter in the CNS.

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In a continuing effort to develop radiolabeled inhibitors of P-gp that can be used to detect and quantify expression of the transporter in the brain, it was shown that [^{11}C]MC18, a tracer containing the same basic isoquinoline structure as traiquidar and elacridar, had a four-fold higher uptake in the organ compared with [^{11}C]traiquidar (9). This indicated that, compared with the other inhibitors, [^{11}C]MC18 was not transported very efficiently by P-gp and/or BCRP through the BBB. In another study, it was shown that MC70 (6,7-dimethoxy-2-(4-methoxy-biphenyl-4-yl-methyl)-1,2,3,4-tetrahydro-isoquinoline), a derivative of MC18, was ~30-fold more potent than MC18 for inhibiting the P-gp–mediated transport of [^{3}H]vinblastine (this drug interferes with the amino acid metabolic pathways of the cell) in Caco-2 cells (10). On the basis of this information, Mairinger et al. synthesized and evaluated a ^{11}C-labeled *O*-methyl derivative of MC70 ([^{11}C]MC113) for the detection and measurement of P-gp expression in wild-type (WT) mice and P-gp knockout (*Mdr1a/b*$^{(-/-)}$) mice (7).

Related Resource Links

Related chapters in MICAD

Protein sequence of human P-gp

Information on human P-gp in Gene database (Gene ID: 5243)

P-gp in Online Mendelian Inheritance in Man database (OMIM)

Clinical trials related to P-gp

Synthesis

[PubMed]

The synthesis of MC113 and its labeling with ^{11}C have been described by Mairinger et al. (7). Based on the ^{11}C-methane used in the reaction, the radiochemical yield of [^{11}C]MC113 was 6 ± 4%. The total time required for the synthesis was ~34 min, and the radiochemical purity of the final product was >98% as determined with high-performance liquid chromatography (HPLC). The specific activity of [^{11}C]MC113 at the end of synthesis was >700 GBq/μmol (>2.59 Ci/μmol). The identity of the final labeled product was confirmed with HPLC by coinjecting the tracer with a nonradioactive MC113 standard.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The expression of P-gp was determined in tumors generated with WT EMT6 cells and EMT6Ar1.0 cells in nude mice (7). The EMT6Ar1.0 cells were derived by repeated growth of EMT6 WT cells in medium supplemented with increased concentrations of doxorubicin as described elsewhere (11). The lesions were harvested from the animals at

the end of the PET imaging session, and the expression of the transporter in the tumor lysates was assessed with Western blot analysis using C219, a commercially available primary anti-P-gp monoclonal antibody (7). From the Western blot analysis it was evident that the WT cell tumors had a low expression of P-gp and the transporter was overexpressed by the EMT6Ar1.0 cell lesions.

The IC_{50} values for elacridar, tariquidar, MC18, MC113, and MC70 (in increasing order) were determined with a rhodamine 123 efflux assay with CCRFvcr1000 cells (derived from CCRF-CEM cells, a human T lymphoblast cell line that expresses P-gp) to be 3.2 ± 0.5 nM, 8.5 ± 2.5 nM, 351 ± 40 nM, 375 ± 60 nM, and 2,229 ± 207 nM, respectively, for these inhibitors (7). This assay indicated that MC113 did not have a very high affinity for the P-gp transporter in these cells.

A radio thin-layer chromatographic analysis of plasma obtained from WT mice at 30 min after injection of [^{11}C]MC113 showed that 91 ± 2% of the radiochemical was intact at this time point (7).

Animal Studies

Rodents

[PubMed]

For PET imaging, WT mice and *Mdr1a/b*$^{(-/-)}$ mice (n = 3 anesthetized animals/group) were co-injected through the tail vein with 28 ± 10 MBq (1.03 ± 0.37 mCi) [^{11}C]MC113 and <0.1 nmol nonradioactive MC113 (7). Dynamic PET scans of the animals were acquired for up to 60 min postinjection (p.i.) after initiation of the tracer injection. Data were generated from the images as described elsewhere (7). For the duration of the study, the time-activity curves (TAC) of the *Mdr1a/b*$^{(-/-)}$ mice were higher than those of the WT animals. A similar trend was evident for the area under the curve (AUC) values of the brain for the *Mdr1a/b*$^{(-/-)}$ and the WT rodents, but the differences in the values were not statistically significant (P = 0.1).

In another study, two consecutive PET scans were acquired from nude mice bearing EMT6 cell and EMT6Ar1.0 cell tumors (n = 5 animals/group) (7). Scan 1 was started immediately after the administration of [^{11}C]MC113 and lasted for 150 min p.i. At 60 min p.i. (while scan 1 was still in progress), the animals were intravenously injected with 15 mg/kg body weight nonradioactive tariquidar. Scan 2 was initiated at 120 min after the administration of nonradioactive tariquidar and lasted for 60 min. At the end of scan 2, [^{18}F]fluoro-deoxyglucose was administered to the animals to define the regions of interest around the tumors, and a 20-min static scan was performed on the rodents. Although the EMT6 cell tumors and the EMT6Ar1.0 cell tumors were clearly visible in the PET images, the TACs with [^{11}C]MC113 were higher in the EMT6 lesions than in the EMT6Ar1.0 tumors in both scans. No significant difference was noticed in the AUC values for both the tumor types (AUC_{0-60}, scan 1: EMT6: 76 ± 19 min, EMT6Ar1.0: 65 ± 6 min, P = 0.313; AUC_{0-60}, scan 2: EMT6: 90 ± 23 min, EMT6Ar1.0: 69 ± 8 min, P = 0.063,

Wilcoxon matched-pairs signed rank test). The peak uptake of radioactivity in the brain of the animals (~1.7 standardized uptake value (SUV) at 9 min p.i.) was comparable with that of the tumors (~1.5 SUV at 9 min p.i.). However, during the course of the study, the label cleared rapidly from the brain, while the tracer continued to accumulate in the tumor during the period. No significant difference in the brain AUC values was observed between the two scans ($P = 0.063$).

From these studies, it is apparent that the accumulation of radioactivity from [^{11}C]MC113 in the brain was due to a reduced transport of the tracer by the P-gp and/or the BCRP in the BBB (7). The signal obtained from the BBB and the tumors was probably due to nonspecific binding of radioactivity because MC113 was observed to have a low affinity for P-gp as determined with the rhodamine 123 efflux assays. Therefore, the investigators concluded that [^{11}C]MC113 was not suitable for the visualization of P-gp expression in the CNS and the cancerous lesions of rodents (7).

Other Non-Primate Mammals

[PubMed]

No reference is currently available.

Non-Human Primates

[PubMed]

No reference is currently available.

Human Studies

[PubMed]

No reference is currently available.

Supplemental Information

[Disclaimers]

No information is currently available.

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