6,7-Dimethoxy-2-[3-(5-[^{11}C]methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-propyl]-1,2,3,4-tetrahydro-isoquinoline

[^{11}C]MC-266

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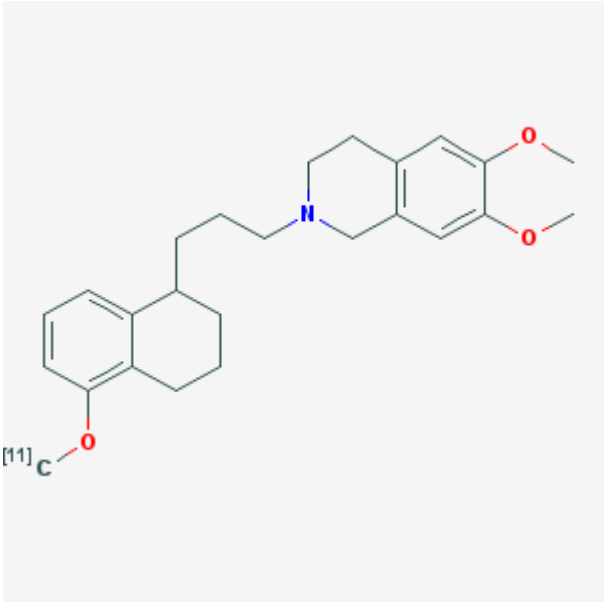
Chemical name:	6,7-Dimethoxy-2-[3-(5-[^{11}C]methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-propyl]-1,2,3,4-tetrahydro-isoquinoline
Abbreviated name:	[^{11}C]MC-266, [11C]7
Synonym:	
Agent category:	Compound
Target:	P-glycoprotein multidrug transporter, MDR-1
Target category:	Transporter
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

One of the mechanisms of tumor cells to escape the cytotoxic effects of chemotherapeutic agents, such as adriamycin, vinca alkaloids, epipodophyllotoxins, actinomycin D, and paclitaxel, is to limit their presence inside the cells by way of a multidrug resistance (MDR-1) gene protein (1, 2). The MDR-1 gene encodes a transmembrane P-glycoprotein (P-gp) as an ATP-dependent multidrug transporter that is capable of actively pumping a variety of agents out of the cells. Injection of unlabeled efflux pump substrates increases the retention of the radioactivity in the tumor by blocking the efflux rather than reducing radioactivity as seen with receptor-binding radiotracer blocking studies. Overexpression of P-gp in tumor cells (such as renal carcinoma, hepatoma, pheochromocytoma, and colon carcinoma) leads to resistance to anticancer drugs (3). P-gp is also present in a variety of normal cells, such as intestinal mucosal cells, hepatocytes, renal proximal tubule epithelial cells, and endothelial cells of the blood–brain barrier (BBB) (4, 5). Calcium channel blockers (such as verapamil), cyclosporine (CsA, P-gp inhibitor) and CsA's non-immunosuppressive analog PSC 833 (other mechanism) are MDR modulators that inhibit the transport of P-gp substrates out of the cells (6, 7).

^{99m}Tc-Sestamibi (MIBI) has been approved by the United States Food and Drug Administration as a myocardial perfusion imaging agent for use with single-photon emission computed tomography to assess the risk of future cardiac events (8). It is also used as a tumor-imaging agent in breast, lung, thyroid, and brain cancers (8-10). MIBI is a substrate for P-gp (4, 11). 6,7-Dimethoxy-2-[3-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-propyl]-1,2,3,4-tetrahydro-isoquinoline (MC-266) is another substrate for P-gp (12). [^{11}C]MC-266 has been developed as a positron emission tomography (PET) agent for the non-invasive study of the P-gp function and MDR in tumors and normal tissues (13).

Related Resource Links:

- Chapters in MICAD (P-glycoprotein)
- Gene information in NCBI (P-glycoprotein)
- Articles in OMIM (P-glycoprotein)
- Clinical trials (P-glycoprotein)
- Drug information in FDA (^{99m}Tc-MIBI)

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Synthesis

[PubMed]

[^{11}C]MC-266 was synthesized by reaction of the desmethyl precursor with [^{11}C]methyl iodide for 4 min at 80°C (13). The radiochemical purity of purified [^{11}C]MC-266 was >98% with a specific activity of >100 GBq/μmol (2.7 Ci/μmol) at the end of synthesis. The total synthesis time was 45 min with a radiochemical yield of ~30%.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Colabufo et al. (12) showed that MC-266 (5 μM) increased the intracellular uptake of doxorubicin in MCF7/adr cells by 4.8-fold and potentiated the anti-proliferation effect of doxorubicin (5 μM) from 5% to 85%. MC-266 activated ATPase of Caco-2 the monolayer. Therefore, MC-266 was classified as a P-gp substrate.

Animal Studies

Rodents

[PubMed]

van Waarde et al. (13) performed ex vivo biodistribution studies with 30–40 MBq (0.8–1.1 mCi) [^{11}C]MC-266 in control rats (n = 5) and CsA-treated (50 mg/kg) rats (n = 4) at 60 min after injection. CsA is a P-gp inhibitor. The accumulation of radioactivity expressed as standard uptake value (SUV) in various brain regions was 0.30–0.50. Pretreatment with CsA increased the accumulation into the various brain regions by 1.0- to 2.5-fold ($P < 0.05$). The peripheral organ with the highest SUV was the liver (3.27), followed by the pancreas (3.16), spleen (1.64), and kidney (1.45). CsA did not affect the accumulation of radioactivity in any peripheral organ.

PET imaging showed an initial high accumulation in the brains of both control and CsA-treated rats at 0.5 min after injection, followed by an exponential washout. CsA exhibited a 1.5-fold increase in brain radioactivity at 25 min after [^{11}C]MC-266 injection. The brain SUV was 0.88 for the control rats and 2.17 for the CsA-treated rats. Logan plot analysis with arterial input showed that CsA treatment increased the cerebral distribution volume from 1.86 to 5.26 ($P < 0.002$) and the influx rate constant from 0.18 to 0.64 ($P < 0.0001$). As a comparison at 25 min after injection, [^{11}C]verapamil exhibited a lower SUV (0.15), which increased to 1.34 with CsA treatment. Logan plot analysis with arterial input showed that CsA treatment increased the cerebral distribution volume from 0.64 to 5.85 ($P < 0.0001$) and the influx rate constant from 0.22 to 0.81 ($P < 0.002$).

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.

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