6,7-Dimethoxy-2-{3-[4-[^{11}C]methoxy-3,4-dihydro-2*H*-naphthalen-(1*E*)-ylidene]-propyl}-1,2,3,4-tetrahydro-isoquinoline

[^{11}C]6

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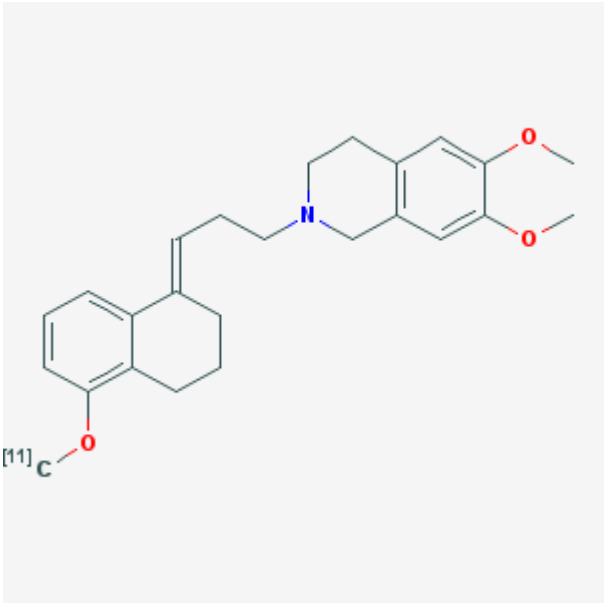
Chemical name:	6,7-Dimethoxy-2-{3-[4-[^{11}C]methoxy-3,4-dihydro-2*H*-naphthalen-(1*E*)-ylidene]-propyl}1,2,3,4-tetrahydro-isoquinoline
Abbreviated name:	[^{11}C]6
Synonym:	
Agent category:	Compound
Target:	P-glycoprotein multidrug transporter, MDR-1
Target category:	Transporter
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{11}C
Activation:	No



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Studies:	• *In vitro* • Rodents	Click on the above structure for additional information in PubChem.

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) 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 uptake 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-[4-methoxy-3,4-dihydro-2*H*-naphthalen-(1*E*)-ylidene]-propyl}-1,2,3,4-tetrahydro-isoquinoline (compound 6) is a P-gp inhibitor (12). 6,7-Dimethoxy-2-{3-[4-[^{11}C]methoxy-3,4-dihydro-2*H*-naphthalen-(1*E*)-ylidene]-propyl}-1,2,3,4-tetrahydro-isoquinoline ([^{11}C]6) is being 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).

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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)

Synthesis

[PubMed]

[^{11}C]6 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]6 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 compound 6 (5 μM) increased the intracellular uptake of doxorubicin in MCF7/adr cells by 4.7-fold and potentiated the anti-proliferation effect of doxorubicin (5 μM) from 5% to 95%. Compound 6 did not activate ATPase of the Caco-2 monolayer. Therefore, compound 6 was classified as a P-gp inhibitor.

Animal Studies

Rodents

[PubMed]

van Waarde et al. (13) performed *ex vivo* biodistribution studies with ~12 MBq (0.32 mCi) [^{11}C]6 in normal rats (n = 4) at 60 min after injection. The accumulation of radioactivity expressed as standard uptake value (SUV) in various brain regions was 0.45–0.69. Pretreatment with compound 6 reduced the accumulation into the various brain regions by 30–40% ($P < 0.05$). Significant reduction ($P < 0.05$) was also observed in the colon (60%), duodenum (67%), ileum (53%), and spleen (35%). Significant enhancement ($P < 0.05$) was observed in the heart (42%) and lung (60%). The peripheral organ with the highest SUV was the pancreas (4.02), followed by the duodenum (3.06), spleen (2.66), ileum (1.94), and colon (1.85).

PET imaging showed an initial high accumulation of [^{11}C]6 in the brains of rats at 0.5 min after injection, followed by a gradual washout. The brain was clearly visualized. Pretreatment with compound 6 (15 mg/kg) resulted in a 23% decrease in brain radioactivity at 56 min after [^{11}C]6 injection. The brain SUV was 0.88 ± 0.04 for the control rats and 0.68 ± 0.03 for the rats treated with compound 6 ($P < 0.01$). Logan plot

analysis with arterial input showed that compound 6 treatment decreased the cerebral distribution volume from 2.35 ± 0.11 to 1.65 ± 0.03 ($P < 0.005$) and the influx rate constant from 0.90 ± 0.08 to 0.45 ± 0.45.

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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