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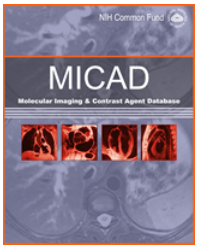

[*N-methyl*-^{11}C]4-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl)-2,2-diphenyl-N-methyl-butanamide

[^{11}C]dLop

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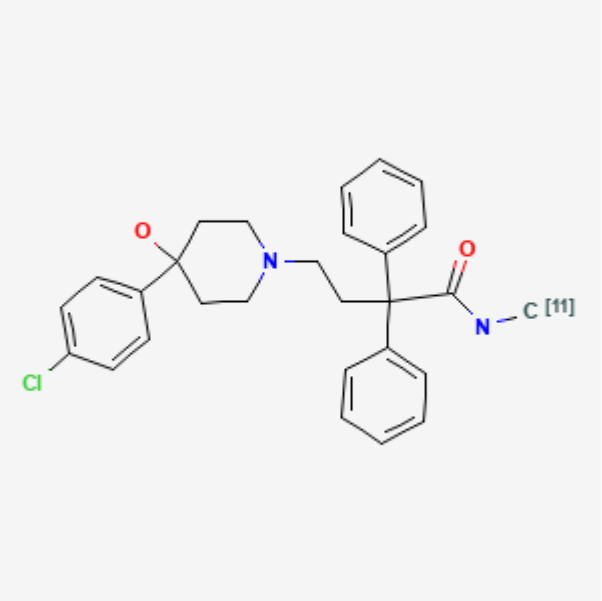
Chemical name:	[*N-methyl*-^{11}C]4-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl)-2,2-diphenyl-N-methyl-butanamide
Abbreviated name:	[^{11}C]dLop
Synonym:	[*N-methyl*-^{11}C]*N*-desmethyl-loperamide
Agent category:	Compound
Target:	P-glycoprotein (Pgp), multidrug transporter
Target category:	Transporter
Method of detection:	PET
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates



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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 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

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agents out of the cells. Injection of unlabeled efflux pump substrates increases the retention of the radioactivity in the tumor rather than less radioactivity as seen with receptor binding radiotracers. Over-expression 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, cyclosporin and its non-immunosuppressive analogue PSC 833 are MDR modulators inhibiting transport of P-gp substrates out of the cells (6, 7).

Sestamibi (MIBI) is a substrate for P-gp. ^{99m}Tc-MIBI has been approved by the FDA as a myocardial perfusion imaging agent with single photon emission computed tomography (SPECT) 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 (9-13). Loperamide is an opiate agonist (14) and an avid substrate for P-gp at the BBB (15). [^{11}C]Loperamide ([^{11}C]Lop) has been studied as a positron emission tomography (PET) agent for studying P-gp function and multidrug resistance in tumors and normal tissues non-invasively (16). However, demethylation of [^{11}C]Lop to [*N-methyl*-^{11}C]*N*-desmethyl-loperamide ([^{11}C]dLop) precludes quantification of P-gp function with PET if [^{11}C]dLop is also an avid substrate for P-gp. Therefore, [^{11}C]dLop has been studied as a positron emission tomography (PET) agent for studying P-gp function and multidrug resistance in tumors and normal tissues non-invasively (17).

Synthesis

[PubMed]

[^{11}C]dLop was synthesized by a reaction of 4-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)-2,2-diphenylbutanamide with [^{11}C]methyl iodide at 80°C for 6 min (17). The radiochemical purity of purified [^{11}C]dLop was >99% with specific activities of 152 ± 48 GBq/μmol (4.11 ± 1.30 Ci/μmol) at the end of synthesis. The total synthesis time was 40 min with a radiochemical yield of 18% (decay-corrected) based on [^{11}C]CO_2.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro binding studies using cloned receptors with dLop showed inhibition constant (K_i) values were 0.56, 73 and 328 nM for μ, δ and κ opiate receptor, respectively (16). The measured Log $D_{7.4}$ of [^{11}C]dLop was 2.60.

Animal Studies

Rodents

[PubMed]

PET imaging studies with [^{11}C]dLop PET imaging in three normal and three P-gp knockout mice showed a higher accumulation of radioactivity in the forebrain in the knockout mice than the wide type mice by 3.6 fold (17). The maximal brain accumulation in the knockout mice occurred at 8-20 min after injection. Three hydrophilic radiometabolites were detected in the plasma and brains with high-performance liquid chromatography (HPLC). In the knockout mice, the fraction of unchanged [^{11}C]dLop in the plasma and brain determined with HPLC was 7.7% and 92% at 60 min after injection, respectively. In the wide type mice, the fraction of unchanged [^{11}C]dLop in the plasma and brain was 11.1% and 42.6% at 60 min after injection, respectively. The *ex vivo* brain concentrations of [^{11}C]dLop were ~16-fold greater in the knockout mice than in wild-type mice, whereas little differences were observed in the plasma of these mice. There was a 7-fold increase in total ([^{11}C]dLop plus its radiometabolites) radioactivity in the forebrain in the knockout mice as compared with the wide type mice.

Other Non-Primate Mammals

[PubMed]

No publications are currently available.

Non-Human Primates

[PubMed]

Lazarova et al. (17) showed that DCPQ (P-gp blocker, 8 mg/kg) pretreatment of six rhesus monkeys enhanced brain [^{11}C]dLop PET radioactivity by 7-fold in the frontal cortex and 13-fold in the cerebellum at 30 min after injection. The increase of brain radioactivity was not blocked by administration of naloxone (opiate antagonist) or dLop at 30 min after [^{11}C]dLop injection in the DCPQ-pretreated monkeys. Three hydrophilic radiometabolites were detected in monkey arterial plasma at as early as 10 min after injection. The fraction of unchanged [^{11}C]dLop in the plasma was ~30% at 60 min after injection. DCPQ had little effect on the rate at which each radiometabolite appeared in the plasma. Liow et al. (18) performed similar PET studies showing that the brain (2% ID), liver (39% ID), lung (31% ID) and kidney (11% ID) were the main organs with visually accumulation of radioactivity at 2-30 min after injection. P-gp blockade increased the brain radioactivity to 3% ID, whereas no effects on the other organs. Furthermore, the accumulation of radioactivity among brain regions with P-gp blockade correlated linearly with blood flow, suggesting a high single-pass extraction.

Human Studies

[PubMed]

Seneca et al. (19) performed whole-body scans for 120 min after injection of 744 MBq (20 mCi) [^{11}C]dLop in 8 healthy subjects. The highest absorbed doses were in the kidneys (50.1 ± 6.0 μSv/MBq), spleen (30.5 ± 6.8 μSv/MBq), lungs (27.0 ± 3.4 μSv/MBq), thyroid (14.7 ± 6.2 μSv/MBq), liver (12.9 ± 2.7 μSv/MBq), and urinary bladder wall (10.8 ± 3.3 μSv/MBq). The effective dose (ED) was 7.6 ± 0.6 μSv/MBq. There were minimal brain uptake of [^{11}C]dLop with the rate of brain entry of <0.01 $mL.cm^{-3}.min^{-1}$. The plasma concentration of [^{11}C]dLop declined rapidly with a biexponential function. The half-lives were 0.4 and 15 min. The fraction of intact [^{11}C]dLop in plasma was 85% at 5 and 120 min after injection. There were 5 hydrophilic radiometabolites.

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Intramural research program

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