N-[^{11}C]Methyl-3-[[(dimethylamino)carbonyl]oxy]-2-(2′,2′-diphenylpropionoxymethyl)pyridinium

[^{11}C]MDDP

The MICAD Research Team

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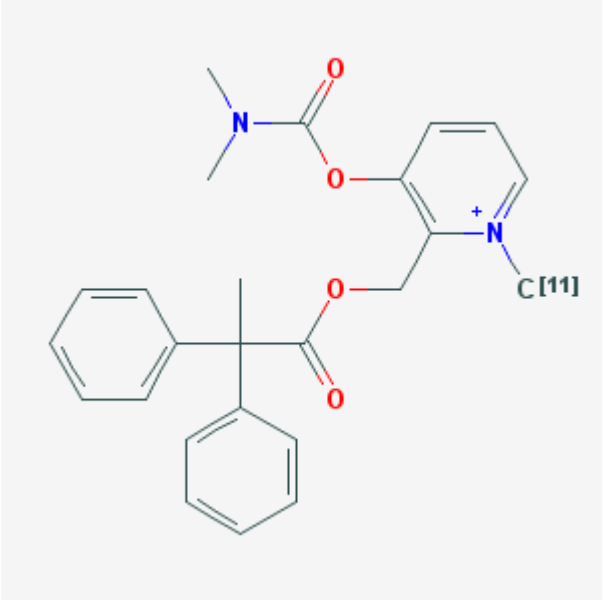
Chemical name:	*N*-[^{11}C]methyl-3-[[(dimethylamino)carbonyl]oxy]-2-(2',2'-diphenylpropionoxymethyl)pyridinium
Abbreviated name:	[^{11}C]MDDP
Synonym:	
Agent Category:	Compound
Target:	Acetylcholinerase (AChE)
Target Category:	Binding
Method of detection:	PET
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents



Background

[PubMed]

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Acetylcholinerase (AChE) is an enzyme involved in terminating nerve impulses by hydrolyzing the neurotransmitter acetylcholine (ACh). It plays an important role in heart rate and cardiac contractions, for example, by decreasing the ACh levels associated with cardiac parasympathetic responses (1).

AChE, and more exactly the inhibition of its enzymatic function, also seems to play an important role in poisoning from organophosphorus (OP) agents (2). Current treatments consisting of a reversible covalent AChE inhibitor (pyridostigmine (3)), a receptor antagonist atropine (ATR), and a AChE reactivator (pralidoxime chloride) have shown good protection against OP intoxication in animals. Research efforts are being made to find drugs with multiple protective functions. For example, Leader et al. (4) synthesized and evaluated a group of pyridophen analogues, binary pyridogstigmine-aprophen prodrugs with differential inhibition of AChE, butyrylcholinesterase (BChE), and muscarinic receptors (5).

Most of the AChE heart tracers developed for cardiac neurotransmission using positron emission tomography (PET) have shown low selectivity of AChE over BChE, and non-specific binding in AChE enzyme overexpressed regions (6). [^{11}C]Nedrophonium and [^{11}C]Neostigmine, originally developed as potential PET heart imaging agents, have shown either high nonspecific binding or poor myocardial uptake and were therefore unsuitable for PET imaging of the heart vagal system.

[^{11}C]pyridostigmine and its para- and ortho-analogs, as well as *N*-[^{11}C]methyl-3-[[(dimethylamino)carbonyl]oxy]-2-(2',2'-diphenylpropionoxymethyl)pyridinium ([^{11}C]MDDP), were synthesized by Wang et al. (7) as potential PET agents for imaging heart AChE *in vivo*. Leader et al. (4) showed that MDDP iodide selectively inhibited AChE more than BChE. However, the first rodent studies performed by Wang et al. (7) using PET- [^{11}C]MDDP did show the presence of nonspecific binding (see the Rodents section for details).

Synthesis

[PubMed]

A multi-step synthesis procedure for [^{11}C]MDDP was reported by Wang et al. (7) in 2005. The authors used a modified version of a method by Leader et al. (4) to obtain the precursor and reference standard. Briefly, the preparation of [^{11}C]MDDP involved an acylation of the key intermediate 2-hydroxymethyl-3-dimethylaminocarbonyl-oxypyridine with 2,2-diphenylpropionyl chloride to produce the carbamyl-ester precursor 3-[[(dimethylamino)carbonyl]oxy]-2-(2',2'-diphenylpropionoxymethyl)pyridine in 51% yield.

The key intermediate used in this synthetic method was obtained in 31% yield from carbamylation of 3-hydroxy-2-hydroxymethylpyridine HCl with dimethylcarbamyl chloride; the acylation agent was produced in 96% yield from 2,2-diphenylpropionic acid with thionyl chloride in 96% yield.

The tertiary pyridine precursor was labeled with [^{11}C]methyl triflate to provide the quaternary pyridinium tracer [^{11}C]MDDP in 40–65% radiochemical yield (decay corrected at end of bombardment). The final product [^{11}C]MDDP was eluted with an aqueous solution of 2% acetic acid (containing up to 8% ethanol to enhance recovery of some [^{11}C-methyl]quaternary cations. The total synthesis time reported by Wang et al. (7) was 10–15 min. The chemical and radiochemical purities (determined by analytical HPLC) were >95% and >99% respectively. The specific radioactivity of the tracer [^{11}C]MDDP was ~0.05 MBq/mol (1.0–1.5 Ci/μmol) at end of the synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro studies performed by Leader et al. (4) showed that MDDP iodide preferentially inhibited AChE over BChE, and that the inhibition of both enzymes was at least as strong as that obtained with pyridogstigmine (8). The mean values of the affinity constant for the initial reaction obtained for AChE and BChE were 5.62 x 10^{-6} M and 3.14 x 10^{-6} M respectively. In comparison, for pyridostigmine, those values were 1.97 x 10^{-5} M (AChE) and 1.14 x 10^{-4} M (BChE).

Animal Studies

Rodents

[PubMed]

Wang et al. (7) performed *in vivo* dynamic PET imaging studies using [^{11}C]MDDP in 3 young adult female Sprague–Dawley rats for a 60min time period after intravenous injection of 7.4 MBq (0.2 mCi) of the tracer for each animal. Those studies showed a rapid heart uptake of the tracer, and a fast blood clearance in 10 to 20 min. The mean standard uptake value (SUV) for [^{11}C]MDDP reported by the authors was 0.125 ± 0.034 (n = 3).

Competitive inhibition studies were then performed to assess the specificity of the tracer to heart tissue AChE. Animals were pretreated with an injection of the drug neostigmine, used as unlabeled AChE inhibitor. A partial blocking effect was observed. However, a t test comparing the mean SUVs with no blocking agent (0.125 ± 0.034) and with blocker neostigmine (0.128 ± 0.0066) led to a p value of 0.87, indicating no statistically significant difference between the two and therefore the presence of nonspecific binding. Wang et al. (7) also suggested the possibility of an insufficient blockade of cholinesterase binding sites, because 2 of 3 rats exhibited actual increases in [^{11}C]MDDP retention after administration of neostigmine.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available

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