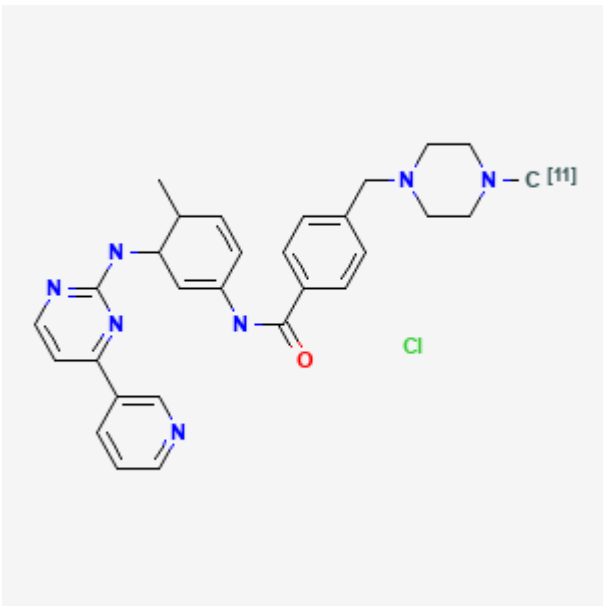


## [ $N$ - $^{11}\text{C}$ -methyl]-[4-[(4-Methyl-1-piperazinyl)methyl]- $N$ -[4-methyl-3-[[4-(3-pyridyl)-2-pyrimidinyl]amino]phenyl]benzamide

[ $N$ - $^{11}\text{C}$ -methyl]Imatinib

Arvind Chopra, PhD<sup>1</sup>

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<b>Chemical name:</b>	[ $N$ - $^{11}\text{C}$ -methyl]-[4-[(4-Methyl-1-piperazinyl)methyl]- $N$ -[4-methyl-3-[[4-(3-pyridyl)-2-pyrimidinyl]amino]phenyl]benzamide	
<b>Abbreviated name:</b>	[ $N$ - $^{11}\text{C}$ -methyl]imatinib	
<b>Synonym:</b>		
<b>Backbone:</b>	Compound	
<b>Target:</b>	Various tyrosine kinases	
<b>Mechanism:</b>	Competitive inhibitor	
<b>Method of detection:</b>	PET	
<b>Source of signal:</b>	$^{11}\text{C}$	
<b>Activation:</b>	Not required	
<b>Studies:</b>	<ul style="list-style-type: none"> <li>Non-human primates</li> </ul>	

## Background

[PubMed]

Imatinib ([4-[(4-methyl-1-piperazinyl)methyl]- $N$ -[4-methyl-3-[[4-(3-pyridyl)-2-pyrimidinyl]amino]phenyl]benzamide) is a synthetic tyrosine kinase (TK) signal transduction inhibitor used for the treatment of a variety of chronic myeloid leukemia (CML) attributed to the Philadelphia chromosome-positive trait (1). This chromosomal abnormality develops after a genetic translocation between chromosome 9

and chromosome 22, which leads to the expression of an abnormal bcr-abl TK that is no longer dependent on normal activation as a result of the interaction between interleukin-3 and its receptor. This drug is also used for the treatment of gastrointestinal stromal tumors (GIST) that are caused by mutations in the closely related c-kit or platelet-derived growth factor (PDGF) TKs (2). In addition, imatinib has been shown to be an effective treatment against a variety of other conditions that are characterized by the expression of abl, c-kit, or PDGF TKs (3). Although imatinib is a useful chemotherapeutic agent for the treatment of CML and GIST, patients undergoing therapy for these conditions often develop resistance to the drug as a result of secondary mutations in the TKs.

The FDA approved imatinib for the treatment of CML in May 2001 and subsequently for the treatment of GIST in January 2002 (4). A detailed description of the indications for which imatinib can be prescribed is available in the product insert from the manufacturer (5).

In an attempt to initiate understanding of the development of drug resistance to imatinib, an *N*-[ $^{11}\text{C}$ ]-methyl derivative of imatinib was synthesized. The radiolabeled compound was then administered to baboons (*Papio anubis*) to determine drug biodistribution and pharmacokinetics in the animals (3).

## Synthesis

[PubMed]

The synthesis of imatinib has been described by Kil et al. (3). Briefly, [4-[(4-benzyloxycarbonyl-1-piperazinyl)methyl]-*N*-[4-methyl-3-[[4-(3-pyridyl)-2-pyrimidinyl]amino]phenyl]benzamide was prepared by *via* amide bond formation between *N*-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidinamine and benzyl 4-(4'-hydroxycarbonylbenzyl)-1-piperazinecarboxylate. The yield of this reaction was 54%. The compound was then used to prepare norimatinib by use of a procedure modified from that of Baker et al. (6).

To radiolabel the agent, norimatinib in dimethyl sulfoxide was mixed with  $^{11}\text{C}$ -labeled methyl iodide. When the radioactivity as determined with a sodium iodide detector peaked in the reaction vessel, the vessel was sealed and heated at 80°C for 10 min in an oil bath. The reaction mixture was then diluted in 0.06 N hydrochloric acid (HCl) and the product was isolated by high-performance liquid chromatography (HPLC) on a Luna semi-preparative C18 column. The product was transferred to a rotary evaporator containing 1 N HCl and the solvent was allowed to co-evaporate. The resulting residue was dissolved in saline and filtered through a 0.22- $\mu\text{m}$  filter in a sterile vial for positron emission tomography (PET) studies.

The radiochemical purity of the labeled product as determined by thin-layer chromatography and HPLC was >98%. The synthesis time was 1 h from the end of bombardment. Specific activity of the radiochemical ranged from 40.7–51.8 GBq/ $\mu\text{mol}$  (1.1–1.4 Ci/ $\mu\text{mol}$ ) at the end of bombardment.

## In Vitro Studies: Testing in Cells and Tissues

[PubMed]

No publications are currently available.

## Animal Studies

### Rodents

[PubMed]

No publications are currently available.

## Other Non-Primate Mammals

[PubMed]

No publications are currently available.

## Non-Human Primates

[PubMed]

PET studies with [N-<sup>11</sup>C-methyl]imatinib were performed in baboons (3). Two i.v. injections of the radiochemical were administered to each animal and the animals were scanned twice. The second scan was performed 2 h after the first scan. From the PET images it was evident that the radiochemical was not taken up by the brain or concentrated in the sinuses and tissue surrounding the brain. A P-glycoprotein-mediated efflux was suggested to contribute to elimination of the [N-<sup>11</sup>C-methyl]imatinib from the blood-brain barrier and also for development of resistance to the drug (7). The radiolabel was concentrated primarily in the liver, kidney, and gallbladder after the injections. The radioactivity from [N-<sup>11</sup>C-methyl]imatinib and/or its metabolites peaked early in the heart, lungs, and spleen and cleared rapidly from these organs. In the liver and kidneys, the label peaked and cleared more slowly, and it accumulated over time in the gallbladder. The accumulation of <sup>11</sup>C in the gallbladder indicated the excretion of imatinib and its metabolites through the gastrointestinal tract.

A rapid clearance of imatinib and its metabolites was observed in the plasma. Treatment of the animals with [N-<sup>11</sup>C-methyl]imatinib after administration of unlabeled imatinib reduced the uptake in the heart, lungs, kidneys, and spleen at the early time points, but paralleled one another after 40 min. During the same period the uptake was higher in the liver and gallbladder after the pretreatment. When the uptake in the liver, kidneys, and spleen were normalized for plasma, no difference in the uptake was noticed, indicating that the reduction in uptake was driven by the reduction in plasma. The normalized time-activity curves for liver and gallbladder showed an increase in uptake of the label, indicating an increased accumulation of the drug metabolites in these organs.

It was concluded that [N-<sup>11</sup>C-methyl]imatinib can be used to assess the distribution and kinetics of imatinib in humans and to determine whether it can target tumors. It may also be used to help plan a chemotherapy regimen for a patient, to monitor treatment response, and to investigate the development of drug resistance.

## Human Studies

[PubMed]

No publications are currently available.

## References

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