^{99m}Tc-Labeled O-[3-(1,4,8,11-tetraazabicyclohexadecane)-propyl]-α-methyl tyrosine

[^{99m}Tc]-N4-AMT

Arvind Chopra, PhD[1]

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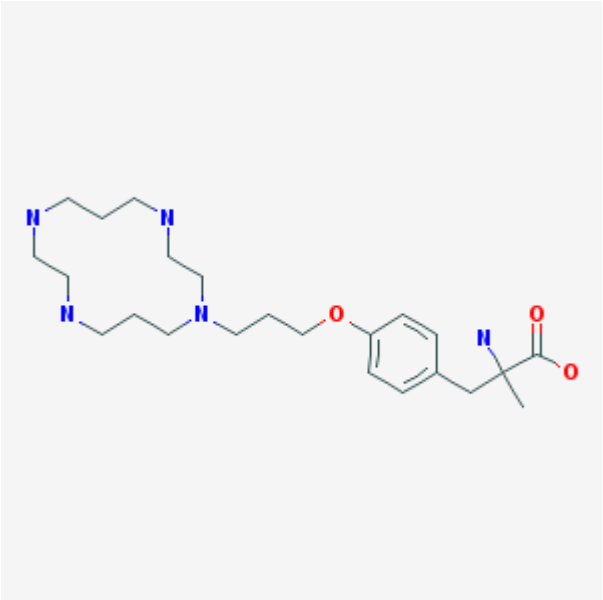
Chemical name:	^{99m}Tc-Labeled O-[3-(1,4,8,11-tetraazabicyclohexadecane)-propyl]-α-methyl tyrosine
Abbreviated name:	[^{99m}Tc]-N4-AMT
Synonym:	
Agent Category:	Compound
Target:	L-type amino acid transporter
Target Category:	Transporter
Method of detection:	Single-photon emission computed tomography (SPECT); gamma planar imaging
Source of signal / contrast:	^{99m}Tc
Activation:	No
Studies:	• *In vitro* • Rodents



Click on above structure of N4-AMT for information in PubChem.

[1] National Center for Biotechnology Information, NLM, Bethesda, MD 20894; Email: micad@ncbi.nlm.nih.gov.

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Background

[PubMed]

High energy consumption and rapid proliferation are the distinct characteristics of all cells with a malignant phenotype. To maintain a high pace of protein and DNA synthesis, such cells have an increased demand for various nutrients, glucose, and amino acids (aa). Therefore, radiotracers such as ^{18}F-labeled fluorodeoxyglucose, which is taken up by the cell through the glucose transporter, are often used with positron emission tomography to detect cancerous tumors. This agent, however, is not suitable to distinguish between malignant tissue, inflammation, and tissues that normally have high glucose consumption, such as the brain (1). As an alternative, radiolabeled aa and their derivatives, such as those of phenylalanine and tyrosine, have been used by investigators to detect neoplastic tumors because these lesions show increased utilization of aa for the synthesis of proteins and other cellular components (2, 3). To accommodate the increased demand for aa, the malignant cells overexpress the aa transporters (phenylalanine and tyrosine use the L-type transporter), and this phenomenon promotes the rapid uptake and accumulation of the radiolabeled aa in the tumors. Therefore, noninvasive imaging with a radiolabeled aa can be used to detect cancerous lesions within a short time after administration of the tracer aa. Among the various radiolabeled aa tracers, [^{18}F]- α-methyl-tyrosine ([^{18}F]-AMT) is often used in the clinic, but the low yield of the final labeled product and the requirement of an on-site cyclotron to produce ^{18}F (half-life, ~110 min) prohibit the use of this labeled compound in most oncology centers (1).

In an effort to develop an alternative to [^{18}F]-AMT, Kong et al. conjugated O-[3-(1,4,8,11-tetraazabicyclohexadecane)-propyl] (N4; a metal chelator) to α-methyl tyrosine (AMT) and labeled it with ^{99m}Tc ([^{99m}Tc]-N4-AMT) (1). The main advantage of using ^{99m}Tc instead of ^{18}F is that the former nuclide has a longer half-life (~ 6 h) and can be produced in-house with a generator instead of a cyclotron. In addition, the N4 chelator in N4-AMT can also bind ^{188}Re, a therapeutic nuclide that can be used to treat cancers. The biodistribution of [^{99m}Tc]-N4-AMT has been investigated in normal rats, and in a separate study the labeled compound was evaluated with gamma planar imaging for the visualization of rat 13762 cell tumors in the animals (1).

Related Resource Links

Related chapters in MICAD

Information on L-type amino acid transporters in PubMed

Inhibition of amino acid transport PubMed

Nucleotide and protein sequences of mammalian amino acid transporters

L-type amino acid transporter in Online Mandelian Inheritance in Man Database (OMIM)

Synthesis

[PubMed]

The synthesis of N4-AMT and its labeling with ^{99m}Tc have been described by Kong et al. (1). The radiochemical purity (RCP) of the labeled compound was reported to be >96% as assessed using a C18 column with reversed-phase high-performance liquid chromatography (retention time, 6.899 min). The radiochemical yield (RCY), specific activity, and stability of [^{99m}Tc]-N4-AMT were not reported.

In some studies, [^{99m}Tc]-N4 was used as a control, but its RCY, RCP, and specific activity were not reported (1).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The uptake of [^{99m}Tc]-N4-AMT and [^{99m}Tc]-N4 was investigated in rat 13762 cells (1). The cells were observed to gradually accumulate radioactivity for up to 240 min only with [^{99m}Tc]-N4-AMT. No such uptake by the cells was observed with [^{99m}Tc]-N4. This indicated that the labeled amino acid derivative was probably taken up by the cells through the aa transport system; however, this was not confirmed with the use of appropriate aa transport inhibitors.

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{99m}Tc]-N4-AMT was investigated in normal Fischer 344 rats (n = 3 animals/time point) as described by Kong et al. (1). Each rat was injected intravenously with either 0.92 ± 0.01 MBq (25 ± 0.5 μCi) [^{99m}Tc]-N4-AMT or [^{99m}Tc]-N4, and the animals were euthanized at 0.5, 2, and 4 h postinjection (p.i.) to determine the amount of radioactivity accumulated in the various organs. Data obtained from this study were presented as percent of injected dose per gram tissue (% ID/g). With [^{99m}Tc]-N4-AMT, maximum uptake of radioactivity was observed in the kidneys (5.77 ± 0.35% ID/g), followed by the liver (1.40 ± 0.07% ID/g) and thyroid (0.57 ± 0.04% ID/g) at 0.5 h p.i., and the label in these organs decreased to 4.74 ± 0.33% ID/g, 0.60 ± 0.02% ID/g, and 0.24 ± 0.1% ID/g, respectively, at 4 h p.i. All other organs showed an uptake between 0.03 ± 0.00% ID/g (brain) and 0.50 ± 0.02% ID/g (stomach) at 0.5 h p.i., which decreased to between 0.01 ± 0.00% ID/g (brain) and 0.43 ± 0.02% ID/g (stomach) at 4 h p.i. Data for [^{99m}Tc]-N4 and blocking studies with [^{99m}Tc]-N4-AMT were not reported.

In another study, Fisher 344 rats (n = 3 animals/tracer) bearing rat 13762 cell tumors on the right posterior leg were injected with either 11.11 MBq/rat (300 μCi/rat) [^{99m}Tc]-N4-

AMT (0.3 mg/rat) or [^{99m}Tc]-N4 (0.15 mg/rat) as described above (1). Planar scintigraphic images of the animals were then acquired at 0.5, 1, and 2 h p.i. Radioactivity counts per pixel were calculated from computer-outlined regions of interest from the images of the tumors, and the normal surrounding muscle and the tumor/muscle (T/M) ratios were calculated at the different time points. The tumors were clearly visible at the various time points only in rats injected with [^{99m}Tc]-N4-AMT. The T/M ratios for [^{99m}Tc]-N4-AMT and [^{99m}Tc]-N4 were reported to be 2.3 and 1.28, respectively, at 0.5 h p.i., and these ratios for the two tracers increased to 4 and 2.3, respectively, at 2 h p.i.

From these studies, the investigators concluded that [^{99m}Tc]-N4-AMT can be used for the imaging of tumors in rodents (1).

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.

Supplemental Information

[Disclaimers]

No information is currently available.

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References

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