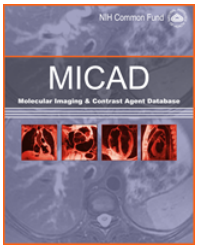
U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Shan L. ^{99m}Tc-Labeled acetylated, 2,3,5-triiodobenzoic acid- and diethylenetriamine pentaacetic acid-conjugated, and PEGylated ethylenediamine-core generation 4 polyamidoamine dendrimers. 2012 Mar 5 [Updated 2012 Apr 25]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/



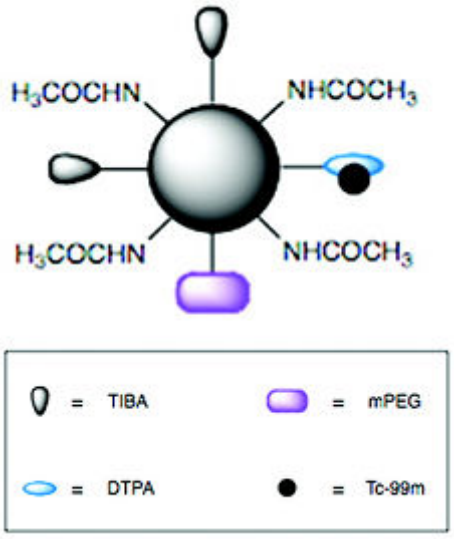
^{99m}Tc-Labeled acetylated, 2,3,5-triiodobenzoic acid- and diethylenetriamine pentaacetic acid-conjugated, and PEGylated ethylenediamine-core generation 4 polyamidoamine dendrimers

^{99m}Tc-G4-[[[[Ac]-TIBA]-DTPA]-mPEG$_{12}$]

Liang Shan, PhD[1]

Created: March 5, 2012; Updated: April 25, 2012.

Chemical name:	^{99m}Tc-Labeled acetylated, 2,3,5-triiodobenzoic acid- and diethylenetriamine pentaacetic acid-conjugated, and PEGylated ethylenediamine-core generation 4 polyamidoamine dendrimers
Abbreviated name:	^{99m}Tc-G4-[[[[Ac]-TIBA]-DTPA]-mPEG$_{12}$]
Synonym:	
Agent Category:	Compounds
Target:	Non-targeted
Target Category:	Non-targeted
Method of detection:	Multimodality imaging (SPECT and CT)
Source of signal / contrast:	^{99m}Tc and iodine (2,3,5-triiodobenzoic acid (TIBA))
Activation:	No
Studies:	• *In vitro* • Rodents



Schematic structure of ^{99m}Tc-G4-[[[[Ac]-TIBA]-DTPA]-mPEG$_{12}$] by Criscione et al. (1).

Author Affiliation: 1 National Center for Biotechnology Information, NLM, NIH; Email: micad@ncbi.nlm.nih.gov.

Corresponding author.

Background

[PubMed]

^{99m}Tc-Labeled acetylated, 2,3,5-triiodobenzoic acid (TIBA)- and diethylenetriamine pentaacetic acid (DTPA)-conjugated, and PEGylated ethylenediamine-core generation 4 polyamidoamine dendrimers (G4 PAMAM), abbreviated as ^{99m}Tc-G4-[[[[Ac]-TIBA]-DTPA]-mPEG$_{12}$], is a blood pool multimodal agent synthesized by Criscione et al. for single-photon emission computed tomography (SPECT)/computed tomography (2) (1).

In the recent years, the fact that imaging modalities with high sensitivity have relatively poor resolution, while those with high resolution have relatively poor sensitivity, has triggered the integration of multiple modalities and the use of hybrid instrument technology in imaging (3, 4). This has also boosted the development of multimodal imaging agents, which further enhances the benefits of hybrid technology, allowing better characterization of diseases and disease processes (5-7). However, it is still challenging to incorporate enough labels for detection by the relatively low-sensitive modalities and to select an appropriate radionuclide in a radiotracer-based imaging approach in the development of multimodal agents (1).

Criscione et al. synthesized a radiolabeled, multimodal contrast agent, ^{99m}Tc-G4-[[[[Ac]-TIBA]-DTPA]-mPEG$_{12}$], for preclinical microSPECT/CT imaging (1). The design of this agent is based on the G4 PAMAM dendrimers, which were used as the core structure of the multimodal agent. Dendrimers have been selected for two main reasons. First, their well-defined, multifunctional surface (64 primary amines) offers the ability to conjugate several different moieties with negligible steric hindrance. Second, dendrimer-based contrast agents have already been successfully designed and examined with different imaging modalities (1, 8, 9). However, PAMAM dendrimers have a highly cationic surface, which limits their water solubility and can cause hemolysis in humans (1). Dendrimers also have a relatively short circulation time when they are used for developing blood pool imaging agents. To overcome these problems, Criscione et al. partially acetylated the dendrimer surface to reduce the positive surface charge and PEGylated the remaining surface amines to enhance the circulation time and limit the clearance by the reticuloendothelial system (1). These modifications provided dendrimers the desired water solubility, long intravascular residence time, and predominant renal clearance (1). To induce the dendrimer construct's multimodal capability, Criscione et al. selected TIBA and ^{99m}Tc-DTPA for X-ray attenuation and radioactive signal, respectively (1). TIBA possesses X-ray attenuation properties similar to those of the clinically used, small-molecule triiodobenzoic acid derivative Omnipaque 350. The studies by Criscione et al. have also shown that sufficient iodine weight percent for effective X-ray attenuation without sacrificing aqueous solubility can be achieved by conjugating TIBA to dendrimers (1). The acyclic chelator DTPA was used to chelate tin(II)-reduced ^{99m}Tc because of its established chemistry and stability. *In vitro* and animal studies have confirmed the potential usefulness of this multimodal agent in the quantification of intramyocardial blood volume and blood flow (1).

Related Resource Links:

Multimodal imaging agents in MICAD

Drug information for Omnipaque 350 at Drugs@FDA

Synthesis

[PubMed]

Criscione et al. described the synthesis of ^{99m}Tc-G4-[[[[Ac]-TIBA]-DTPA]-mPEG$_{12}$] in detail (1). The synthesis could be roughly divided into five steps. The G4 dendrimers were partially acetylated with sulfosuccinimidyl acetate to generate acetylated dendrimers (G4-[Ac]). Then TIBA was covalently conjugated to G4-[Ac] through the surface amines to generate G4-[[Ac]-TIBA]. To chelate the nuclear probe ^{99m}Tc, 1-(4-

isothiocyanatobenzyl)diethylenetriamine pentaacetic acid (*p*-SCN-Bn-DTPA) was coupled to the primary surface amines of the dendrimer *via* isothiocyanate linkage. This step resulted in the product G4-[[[Ac]-TIBA]-DTPA]. G4-[[[Ac]-TIBA]-DTPA] was subsequently PEGylated with succinimidyl-(*N*-methyl-dodecaethylene glycol)ester (mPEG$_{12}$) to generate the G4-[[[[Ac]-TIBA]-DTPA]-mPEG$_{12}$]. The chemical yields of the intermediate products were 97% for G4-[Ac], 82% for G4-[[Ac]-TIBA], 89% for G4-[[[Ac]-TIBA]-DTPA], and 83% for G4-[[[[Ac]-TIBA]-DTPA]-mPEG$_{12}$]. Finally, ^{99m}Tc-labeling was completed with the reaction of G4-[[[[Ac]-TIBA]-DTPA]-mPEG$_{12}$] (50 mg for imaging purposes and 20 mg for biodistribution studies) and $^{99m}TcO_4^-$ (18.5 MBq (500 μCi)) for 2 min (for imaging purposes) or for 10 min (for biodistribution studies) at 25°C. The reaction mixture was directly used for studies without further purification. The radiochemical purity was >80%.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Criscione et al. characterized the intermediate products with ^{1}H nuclear magnetic resonance (NMR) spectroscopy and dynamic light scattering (1). The results showed that G4-[[[[Ac]-TIBA]-DTPA]-mPEG$_{12}$] had 3 remaining primary amines, 35 coupled acetyl groups, ~15 TIBA moieties, 4 DTPA, and 7 mPEG$_{12}$. The hydrodynamic diameter and molecular weight of G4-[[[[Ac]-TIBA]-DTPA]-mPEG$_{12}$] were 12.37 ± 6.09 nm and 19,762, respectively.

The X-ray attenuation property of G4-[[[[Ac]-TIBA]-DTPA]-mPEG$_{12}$] was analyzed with serially diluted G4-[[[[Ac]-TIBA]-DTPA]-mPEG$_{12}$] in deionized water using microCT imaging (1). A linear attenuation *versus* the iodine concentration curve, an essential criterion for X-ray contrast agents, was obtained for G4-[[[[Ac]-TIBA]-DTPA]-mPEG$_{12}$]. The extrapolated iodine concentrations in G4-[[[[Ac]-TIBA]-DTPA]-mPEG$_{12}$] were consistent with the estimated iodine weight percent (~19% wt) determined with ^{1}H NMR.

Animal Studies

Rodents

[PubMed]

The biodistribution and pharmacokinetics of ^{99m}Tc-G4-[[[[Ac]-TIBA]-DTPA]-mPEG$_{12}$] were evaluated in C57BL/6 mice after injection of 4.255 MBq (115 μCi) of the agent. Mice were euthanized at 0.5, 1, 2, 4, and 6 h after injection (n = 4 mice/time point) (1). Blood samples and organs were harvested, and radioactivity was counted. The analysis showed that the agent's half-life was 0.72 h (43 min), and the agent was cleared from the blood pool predominantly by the kidneys.

The efficacy of G4-[[[[Ac]-TIBA]-DTPA]-mPEG$_{12}$] as a blood pool CT contrast agent was assessed in C57BL/6 mice with serial cardiac microCT after intravenous injection of either 1.27 μmol (n = 2 mice) or 2.53 μmol (n = 2 mice) of the agent (1). Intravascular and intraventricular enhancement with an excellent contrast/noise ratio in the right and left ventricles of the heart was observed with both doses. The enhancement persisted for >90 min after injection.

The multimodal capability of G4-[[[[Ac]-TIBA]-DTPA]-mPEG$_{12}$] was assessed in mice euthanized 5 min after injection of 16.28 ± 0.96 MBq (440 ± 26 μCi) ^{99m}Tc-G4-[[[[Ac]-TIBA]-DTPA]-mPEG$_{12}$] (n = 5 mice) (1). Post-mortem microSPECT/CT imaging revealed intravascular retention, minimal liver accumulation, and substantial colocalization of the radioactivity and the dendritic iodinated contrast within the intravascular and intraventricular cavities in the absence of motion artifacts. These results demonstrate the potential usefulness of the agent as a blood pool multimodal agent and also provide evidence for the formation of a sufficiently pure

and stable chelate, as either colloidal or free hydrolyzed/reduced ^{99m}Tc would be cleared predominantly by the liver.

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

References

1. Criscione J.M.et al. *Development and application of a multimodal contrast agent for SPECT/CT hybrid imaging.* . Bioconjug Chem. 2011;22(9):1784–92. PubMed PMID: 21851119.
2. Hoekzema E.et al. *[(11)C]-DASB microPET imaging in the aged rat: frontal and meso-thalamic increases in serotonin transporter binding.* . Exp Gerontol. 2011;46(12):1020–5. PubMed PMID: 21983171.
3. Cherry S.R. *Multimodality in vivo imaging systems: twice the power or double the trouble?* . Annu Rev Biomed Eng. 2006;8:35–62. PubMed PMID: 16834551.
4. Cherry S.R. *Multimodality imaging: beyond PET/CT and SPECT/CT.* . Semin Nucl Med. 2009;39(5):348–53. PubMed PMID: 19646559.
5. Lee S., Chen X. *Dual-modality probes for in vivo molecular imaging.* . Mol Imaging. 2009;8(2):87–100. PubMed PMID: 19397854.
6. Louie A. *Multimodality imaging probes: design and challenges.* . Chem Rev. 2010;110(5):3146–95. PubMed PMID: 20225900.
7. Jennings L.E., Long N.J. *'Two is better than one'--probes for dual-modality molecular imaging.* . Chem Commun (Camb). 2009;(24):3511–24. PubMed PMID: 19521594.
8. Mintzer M.A., Grinstaff M.W. *Biomedical applications of dendrimers: a tutorial.* . Chem Soc Rev. 2011;40(1):173–90. PubMed PMID: 20877875.
9. Cheng Y.et al. *Design of biocompatible dendrimers for cancer diagnosis and therapy: current status and future perspectives.* . Chem Soc Rev. 2011;40(5):2673–703. PubMed PMID: 21286593.