Gadolinium-diethylenetriamine tetraacetic acid-icosahedral *closo*-borane$_{12}$ scaffold

CA-9

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Created: April 11, 2013; Updated: May 30, 2013.

Chemical name:	Gadolinium-diethylenetriamine tetraacetic acid-icosahedral *closo*-borane$_{12}$ scaffold	
Abbreviated name:	CA-9	
Synonym:	Gd-DTTA-*closo*-B_{12} scaffold	
Agent category:	Peptide	
Target:	Nontargeted	
Target category:	Nontargeted	
Method of detection:	Magnetic resonance imaging (MRI)	
Source of signal/contrast:	Gadolinium, Gd	
Activation:	No	
Studies:	• *In vitro* • Rodents	No structure is available in PubChem.

Background

[PubMed]

Magnetic resonance imaging (MRI) maps information about tissues spatially and functionally (1). Protons (hydrogen nuclei) are widely used in imaging because of their abundance in water molecules. Water comprises ~80% of most soft tissue. The contrast of proton MRI depends primarily on the density of the nucleus (proton spins), the relaxation times of the nuclear magnetization (T1, longitudinal, and T2, transverse), the magnetic

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NLM Citation: Leung K. Gadolinium-diethylenetriamine tetraacetic acid-icosahedral *closo*-borane$_{12}$ scaffold. 2013 Apr 11 [Updated 2013 May 30]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

environment of the tissues, and the blood flow to the tissues. However, insufficient contrast between normal and diseased tissues requires the development of contrast agents. Most contrast agents affect the T1 and T2 relaxation times of the surrounding nuclei, mainly the protons of water. T2* is the spin–spin relaxation time composed of variations from molecular interactions and intrinsic magnetic heterogeneities of tissues in the magnetic field. Cross-linked iron oxide nanoparticles and other iron oxide formulations affect T2 primarily and lead to decreased signals. On the other hand, paramagnetic T1 agents, such as gadolinium (Gd^{3+}) and manganese (Mn^{2+}), accelerate T1 relaxation and lead to brighter contrast images (2).

Gadolinium (Gd), a lanthanide metal ion with seven unpaired electrons, has been shown to be very effective in enhancing proton relaxation because of its high magnetic moment and water coordination (3, 4). Gd-Labeled diethylenetriamine pentaacetic acid (Gd-DTPA) was the first intravenous MRI contrast agent used clinically, and a number of similar Gd chelates have been developed in an effort to further improve clinical use. However, these low molecular weight Gd chelates have short blood and tissue retention times, which limit their use as imaging agents in the vasculature and cancer. Furthermore, these low molecular weight MRI contrast agents exhibit low r_1 relaxivity value (~4 $mM^{-1}s^{-1}$ per Gd), high toxicity (nephrogenic systemic fibrosis in patients with renal dysfunction), and a lack of tissue specificity (5). Li et al. (6) have developed polyhedral boranes as a scaffold for the targeted high payload delivery of drugs and imaging agents. A functionalizable monodisperse molecular borane scaffold, $[closoB_{12}(OH)_{12}]^{2-}$, conjugated with twelve radial ethylene glycol $(PEG)_3$ arms with attachments of Gd-labeled diethylenetriamine tetraacetic acid (Gd-DTTA) (CA-9). Goswami et al. (7) evaluated CA-9 for use as a high-performance MRI contrast agent in nude mice bearing human PC-3 prostate tumors.

Related Resource Links:

- Chapters in MICAD (Gd)
- Clinical trials (Gd-DTPA, Gd-DOTA)
- Drug information in FDA (Gd-DTPA, Gd-DOTA)

Synthesis

[PubMed]

The 12-fold azidoacetate closomer 7 reacted with the alkyne terminated DTTA-$(PEG)_3$ ligand 4 to form DTTA-conjugated closomer 8 with 76% yield (7). Closomer 8 was isolated with column chromatography and then treated with trifluoroacetic acid to remove the *tert*-butyl ester protecting groups. The deprotected closomer 8 was incubated with $GdCl_3$ in a citrate buffer (pH 7) to produce closomer CA-9 with 82% yield. CA-9 was purified with dialysis in ultrapure water. There were 11.3 Gd^{3+} ions per CA-9 as measured with inductively coupled plasma optical emission spectroscopy.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The average particle size of CA-9 was 12 nm as measured with dynamic laser scattering (7). CA-9 exhibited an r_1 value (7 T) of 13.8 ± 0.5 $mM^{-1}s^{-1}$ per Gd to provide a molar relaxivity value of 155.9 $mM^{-1}s^{-1}$. Gd-DTPA-BMA had a molar relaxivity value of 4.2 $mM^{-1}s^{-1}$. CA-9 remained >98% intact in bovine serum for 4 h at 37°C.

Animal Studies

Rodents

[PubMed]

Goswami et al. (7) performed dynamic T1-weighted MRI (7 T) studies with intravenous injection of 0.04 mmol Gd/kg CA-9 or Gd-DTPA-BMA in nude mice (n = 3) bearing PC-3 xenografts. Contrast-enhanced MRI signal intensity (SI) levels were obtained before injection and at 30 min and 60 min after injection. Enhanced contrast in the tumor tissues was visualized for CA-9 at 30 min and 60 min after injection. Contrast enhancement ratios (CERs) [$CER = (SI_{post} - SI_{pre})/SI_{pre}$ X 100%] for CA-9 were 36% and 23% at 30 min and 60 min after injection, respectively. The CERs of tumors for Gd-DTPA-BMA were 19% and 5% at 30 min and 60 min, respectively. Both agents showed high CERs in the kidneys at 30 min, with 70% for CA-9 and 40% for Gd-DTPA-BMA; at 60 min the CERs decreased to 40% and 5%, respectively. Little contrast enhancement was observed for either agent in the liver and muscle at the two time points.

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.

NIH Support

R21 CA114090

References

1. Wang Y.X., Hussain S.M., Krestin G.P. *Superparamagnetic iron oxide contrast agents: physicochemical characteristics and applications in MR imaging.* Eur Radiol. 2001;11(11):2319–31. PubMed PMID: 11702180.
2. Burtea, C., S. Laurent, L. Vander Elst, and R.N. Muller, *Contrast agents: magnetic resonance.* Handb Exp Pharmacol, 2008(185 Pt 1): p. 135-65.
3. Brasch R.C. *New directions in the development of MR imaging contrast media.* Radiology. 1992;183(1):1–11. PubMed PMID: 1549653.
4. Runge V.M., Gelblum D.Y. *Future directions in magnetic resonance contrast media.* Top Magn Reson Imaging. 1991;3(2):85–97. PubMed PMID: 2025435.
5. Laurent S., Elst L.V., Muller R.N. *Comparative study of the physicochemical properties of six clinical low molecular weight gadolinium contrast agents.* Contrast Media Mol Imaging. 2006;1(3):128–37. PubMed PMID: 17193689.
6. Li T., Jalisatgi S.S., Bayer M.J., Maderna A., Khan S.I., Hawthorne M.F. *Organic syntheses on an icosahedral borane surface: closomer structures with twelvefold functionality.* J Am Chem Soc. 2005;127(50):17832–41. PubMed PMID: 16351114.
7. Goswami L.N., Ma L., Chakravarty S., Cai Q., Jalisatgi S.S., Hawthorne M.F. *Discrete nanomolecular polyhedral borane scaffold supporting multiple gadolinium(III) complexes as a high performance MRI contrast agent.* Inorg Chem. 2013;52(4):1694–700. PubMed PMID: 23126285.