Tri-gadolinium nitride PEGylated-hydroxylated endohedral metallofullerene

$Gd_3N@C_{80}[DiPEG_{5000}(OH)_x]$

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Chemical name:	Tri-gadolinium nitride PEGylated-hydroxylated endohedral metallofullerene	
Abbreviated name:	$Gd_3N@C_{80}[DiPEG_{5000}(OH)_x]$	
Synonym:		
Agent category:	Cage molecule	
Target:	Other	
Target category:	Other - Retention	
Method of detection:	Magnetic resonance imaging (MRI)	
Source of signal/contrast:	Gadolinium	
Activation:	No	
Studies:	• *In vitro* • Rodents	No structure is currently available in PubChem.

Background

[PubMed]

Fullerenes, also known as buckyballs, are spheroidal carbon cages with a molecular formula of C_{2n} (n = 30–41) and a diameter of ~1 nm (1). The high chemical stability of fullerenes can resist any potential metabolic cage-opening process and hence prevents them from degradation in various biological conditions (2). Fullerenes contain hollow interiors that can hold atoms or ions as payloads for various biomedical applications (1). For example, Gd atoms or the trimetallic nitride Gd_3N can be trapped inside the cage to

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form endohedral metallofullerenes denoted as $Gd@C_{2n}$ or $Gd_3N@C_{2n}$, where the "@" symbol refers to the encapsulated nature of the Gd or Gd_3N. For the $Gd@C_{2n}$, the encapsulation of electropositive Gd atom leads to the transfer of electrons from the Gd atom to the electronegative fullerene cage, resulting in a zwitterion $[Gd^{3+}@C_{82}^{3-}]$. For $Gd_3N@C_{2n}$, each Gd atom shares one electron with the N atom and donates the other two electrons to the C80 cage that is in I_h-symmetry to produce a zwitterion $[Gd_3N^{6+}@C_{80}^{6-}]$ (3, 4). These endohedral metallofullerenes thus lead to the generation of a novel type of contrast agent for magnetic resonance imaging (MRI), which possesses a high biological safety in that the carbon cage completely prevents the release of toxic Gd^{3+} ions into surrounding tissues (5, 6). The surface of fullerenes can be functionalized with a variety of groups or specific ligands; i.e., the addition of hydroxyls or polyethylene glycols (PEG) substantially increases their aqueous solubility (7).

The tri-gadolinium nitride PEGylated-hydroxylated endohedral metallofullerene ($Gd_3N@C_{80}[DiPEG_{5000}(OH)_x]$) is a PEG_{5000}-functionalized trimetallic nitride endohedral metallofullerene for *in vivo* MRI (2). The encapsulation of three Gd ions inside the carbon cage prevents direct coordination and exchange of water to Gd^{3+}. The relaxation enhancement of $Gd_3N@C_{80}[DiPEG_{5000}(OH)_x]$ is therefore quite different from the classic inner-sphere mechanism in conventional Gd chelates such as Gd-DOTA (1). Depending on the symmetry of Gd_3N (pyramidal) and the C_{80} cage (icosahedral), $Gd_3N@C_{80}[DiPEG_{5000}(OH)_x]$ can possess a permanent dipolar moment to induce an increase of T_1 relaxivity as much as 30 times more than that of Gd-DOTA (2).

Synthesis

[PubMed]

Fatouros et al. described the preparation of $Gd_3N@C_{80}[DiPEG_{5000}(OH)_x]$ in two steps (2). Initially, $Gd_3N@C_{80}$ was obtained by arc-vaporization of graphite rods packed with Gd_2O_3, Fe_xN, and graphite powder in a Krätschmer-Huffman (K-H) electric-arc generator in a N_2/He atmosphere (3). The obtained soot was mixed with CBr_4 in toluene under sonication, and the resulting mixture was reacted with PEG malonate (Mw ~10,000) and 1,8-diazabicyclo[5.4.0]-undec-7-ene for 20 h under nitrogen atmosphere at room temperature (2). The produced $Gd_3N@C_{80}[DiPEG_{5000}(OH)_x]$ was purified with silica gel column chromatography and the gadolinium content was measured with the inductively coupled plasma optical emission spectroscopy (ICP-OES).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The T_1/T_2 relaxivity of $Gd_3N@C_{80}[DiPEG_{5000}(OH)_x]$ appeared to be dependent on concentration (2). In the low concentration range of 0.0016–0.0126 mM, the T_1 relaxivity was 102 $mM^{-1}s^{-1}$ at 0.35 T, 143 $mM^{-1}s^{-1}$ at 2.4 T, and 32 $mM^{-1}s^{-1}$ at 9.4 T, and the corresponding T_2 relaxivity values were 144 $mM^{-1}s^{-1}$, 222 $mM^{-1}s^{-1}$, and 137 $mM^{-1}s^{-1}$, respectively. A nonlinear relaxivity pattern was found over the concentration range of

0.0016–0.202 mM at 2.4 T. Compared to conventional MRI contrast agents such as Gd-DOTA, which has a T_1 relaxivity value of 3.84 $mM^{-1}s^{-1}$ at 0.47 T, the T^1 relaxivity of $Gd_3N@C_{80}[DiPEG_{5000}(OH)_x]$ increased ~30-fold per fullerene molecule or ~10-fold per Gd ion.

Animal Studies

Rodents

[PubMed]

Fatouros et al. examined the relaxation enhancement of $Gd_3N@C_{80}[DiPEG_{5000}(OH)_x]$ with *in vivo* MRI (2). Rats were implanted intracerebrally with glioma RT2 tumors. Fourteen days after implantation, the rats were infused with 18 µl 0.0131 mM $Gd_3N@C_{80}[DiPEG_{5000}(OH)_x]$ through the convention-enhanced delivery (CED) procedure at a rate of 0.2 µl/min for 90 min. T_2-Weighted images were collected with a 2.4-T imager at the end of the infusion and at 17, 18, and 19 days after tumor implantation. At 19 days after implantation, the same rat was injected intravenously with 0.2 mM gadodiamide, a conventional MRI contrast agent, to assess the tumor. The T_2-weighted images exhibited a prolonged residence of $Gd_3N@C_{80}[DiPEG_{5000}(OH)_x]$ within the tumor region and an improved sensitivity in tumor delineation compared to that of gadodiamide. As a control, a normal rat was infused bilaterally with 15 µl 0.0131 mM $Gd_3N@C_{80}[DiPEG_{5000}(OH)_x]$ and 0.5 mM gadodiamide at a rate of 0.2 µl/min for 75 min. Sequential T_1-weighted images were collected with a 2.4-T imager through the 75-min infusion phase and 100 min after infusion, which demonstrated a much slower diffusion of $Gd_3N@C_{80}[DiPEG_{5000}(OH)_x]$ in the healthy brain tissue compared with the diffusion of gadodiamide.

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

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