

New family of dendrimeric ligands as MRI contrast agents

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Introduction

Even though Magnetic Resonance Imaging (MRI) methods inherently provide high intrinsic tissue contrast, the use of extrinsic contrast agents (CAs) has become a routine in many diagnostic imaging procedures (1). The paramagnetic lanthanide Gd(III) is used to increase locally the longitudinal relaxation rate of surrounding tissue water, highlighting the intensity of specific tissue areas in T1 weighted images (2). However, free Gd(III) is toxic *in vivo* and *in vitro* and Gd(III) chelates must be used in the clinic for safety reasons (3,4). The first generation of Gd(III) ligands was derived from linear polyaminopolycarboxylates such as diethylenetriaminepentaacetic acid (DTPA) or from macrocycles such as 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) (5). The corresponding Gd(III) complexes depicted very high thermodynamic and kinetic stability (6). Nevertheless, their capacity to induce water relaxation, termed relaxivity (r_1), remained 4–5 $\text{s}^{-1}\text{mM}^{-1}$, well below the optimal values of approximately 100 $\text{s}^{-1}\text{mM}^{-1}$ predicted by theory (7). Reduced relaxivity imposed the use of large doses of these agents, limiting the possibilities to successfully visualize low concentration of molecular targets such as cell surface antigens, receptors, enzymes or even genes (8).

Aims

In this work we checked the ability of a new family of Gd(III) chelating derivatives to be used as contrast agents in MRI.

Methods

Synthesis: The compounds **1–3** were prepared according to the synthetic approach briefly depicted in figure 1 (9). **MR studies:** Water solutions of the new compounds were used to make relaxivity measurements at two magnetic fields. The low field studies were made in a 0.5 T, Minispect Bruker®. The high field evaluation were done in a PharmaScan Bruker® systems using a 7.0 T horizontal-bore superconducting magnet, equipped with a ^1H selective birdcage resonator of 38 mm and a Bruker gradient insert with 90 mm of diameter (maximum intensity 300 mT/m). T1 values of **1–3** were calculated at different Gd concentrations (from 0.1 to 0.6 mM) employing either an inversion-recovery method acquiring a FID (low field) or a sequence based in a magnetization saturation experiment acquiring using an echo-spin sequence. The high field data were analyzed in a Linux platform with home made software based on IDL (Iterative Data Language, Research System, Boulder, CO).

Results

Relaxivity values of the new compounds at clinical (6.9 for **1**, 3.7 for **2** and 4.6 $\text{s}^{-1}\text{mM}^{-1}$ for **3**, figure 2) and high field (results not shown) are higher than those reported in the literature for commercial CAs, like Magnevist® or Dotarem®. From a T₁-weighted image of a phantom containing **1–3** studies it can be clearly appreciated an increase in the signal intensity from **3** to **1** and its behaviour with the variation of Gd concentration (Figure 3).

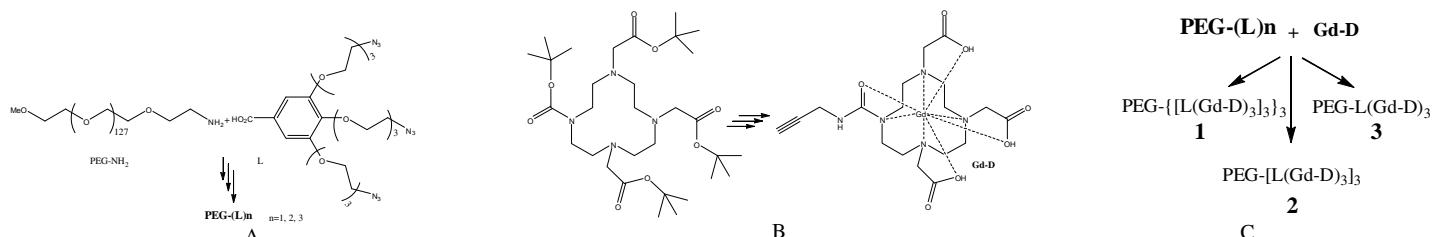


Figure 1: Synthesis of **1–3**. A, preparation of PEG-(L)n; B, synthesis of the Gd-DOTPA derivative; C, functionalization of the dendrimeric structures

Conclusion

We have optimized the synthesis of a new family of macrocycles derived from Gd-DOTA able to be used as MRI CAs. The new compounds show a remarkable improvement in the relaxation properties as MRI contrast agents related to the classical ones employed in clinical studies. This fact is probably due to the higher number of Gd atoms per molecule and the higher size of the molecules that restricts the rotation movement of it. This implies an enormous advantage to use them *in vivo* studies because of the lower dose necessary to obtain a high enhancement in the water tissue signals in T1 weighted images.

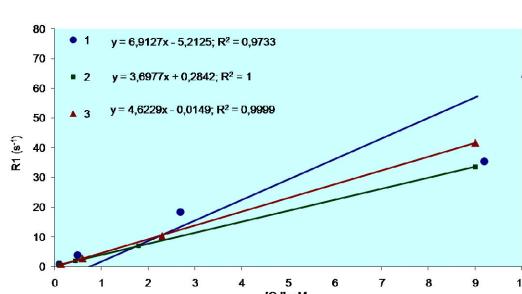


Figure 2: Relaxivity values of compounds **1–3** at clinical field (0.5 T)

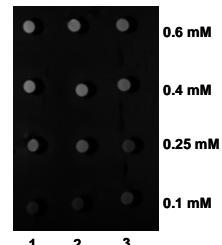


Figure 3: T1W image (7T) of **1–3** at different [Gd]

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