Synthesis, *in vitro* and *in vivo* characterization of new chelator DO3AAHA and its derivate $DO3AAHA_{PEG750}$

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Over the past years, a wide number of chelators has been synthetized in order to complex a diversity of metal ions useful in medical imaging. DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), is an adequate chelator for Gd(III) and Ga(III) due to the high kinetic and thermodynamic stabilities of the metal complexes (for MRI (magnetic resonance imaging) and PET (positron emission tomography) respectively) [1].

In this work, the DOTA-based chelator DO3AAHA (1,4,7,10-tetraazacyclododecane-1-(6-amino)hexanoic-4,7,10-triacetic acid – Figure 1a) was synthesized and characterized. DO3AAHA acts as a bifunctional chelator due to the pendant free amino group. This group can be easily conjugated to biomolecules such as peptides or anti-bodies [2]. The Gd(III) and Ga(III) complexes of these conjugates do not compromise the kinetic and thermodynamic stabilities in relation to those of the analogous DOTA chelates.

In our first attempt to demonstrate the versatility and the advantages of DO3AAHA as a bifunctional chelator, it was attached to an activated PEG (polyethylene glycol) with Mn = 750, which afforded $DO3AAHA_{PEG750}$ (1,4,7,10-tetraazacyclododecane-1-(6-amino(PEG750))hexanoic-4,7,10-triacetic acid – Figure 1b). Adding PEG units to chelating frameworks is known to improve the pharmacokinetic properties of the resulting chelates [3].

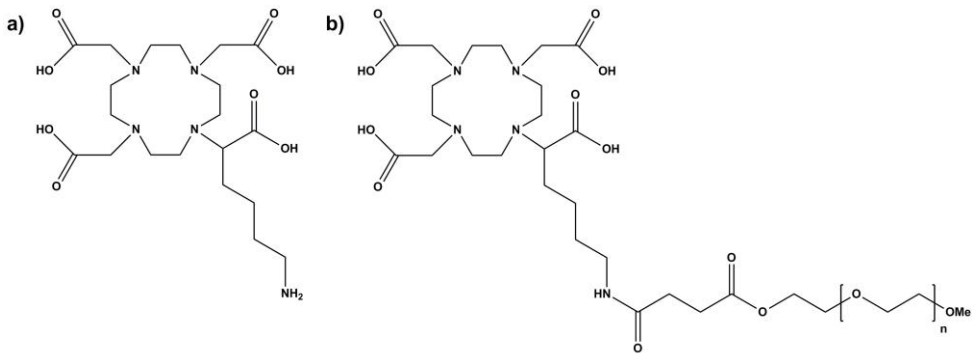

Figure 1 - Structure of a) DO3AAHA and b) $DO3AAHA_{PEG750}$.

The relaxivity (r_1 and r_2) of the Gd(III) chelates of both ligands was measured at 20 MHz at 25 and 37 °C. The dependence of $1/T_1$ on the temperature and pH was also studied. The kinetic stability of $[Gd(DO3AAHA)]^-$ was confirmed performing a competition experiment with Zn^{2+}.

The biodistribution of the ^{67}Ga-labeled chelates was investigated in Wistar rats.

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We include our contribution on topic: “Metal-based drugs: therapy and diagnosis.”