Functionalized azamacrocyclic compounds as Ca^{2+} sensitive contrast agents for MR imaging

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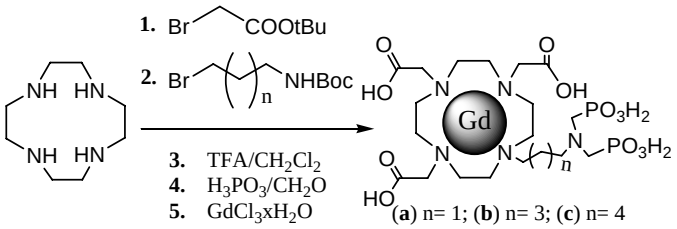
Introduction. The ability to non-invasively observe changes in Ca^{2+} concentration is important for neuroscience. We have therefore developed a series of gadolinium chelate complexes based on DO3A (Scheme 1), which is hypothesized to change relaxivity in magnetic resonance experiments dynamically with Ca^{2+} concentration. Different lengths of the phosphonate side chains are expected to lead to different binding constants of the phosphonate - gadolinium bonds. The latter property can be exploited for fine-tuning the sensitivity of the agent to calcium ion concentration.

Synthesis of ligands and complexes. Ligands were prepared in four steps from Cyclen including alkylation, deprotection and introduction of phosphonate groups (Scheme 1). Pure products were obtained as a white powders in total yield 74.2% (**a**), 69.5% (**b**) and 70.3% (**c**). Gadolinium complexes were obtained by treating of the ligands with 1.2 equivalent of $GdCl_3$ at pH 7.0 -7.5 and 60°C for 18h.



Scheme 1: Synthesis of Gd-DO3A-PAMP (**a**), Gd-DO3A-AAMP (**b**) and Gd-DO3A-HAMP(**c**)

Results and Discussion. MR relaxivity r_1 and r_2 was measured for four concentrations of each macrocyclic compound (0.1, 0.4, 0.7, 1.0 mM) at pH 7.2 in a KMOPS buffer and differentconcentrations of Ca^{2+}. The sensitivity of the contrast agents for changes in Ca^{2+} concentrations increased with the chain length of the phosphonate functions (See Fig.1). Specifically for compound **c** the range of Ca^{2+}concentration is compatible with extracellular physiological conditions.

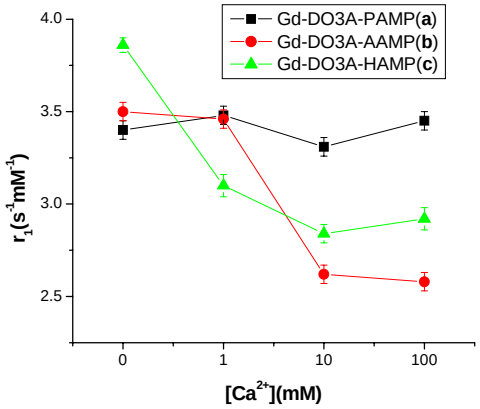


Figure 1. Dependence of the complexes relaxivity to the Ca^{2+}ions concentration

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