Towards high relaxivity: a new series of gadolinium complexes with improved prototropic exchange effect for magnetic resonance imaging

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Magnetic Resonance Imaging (MRI) has become a prominent technique in diagnostic clinical medicine for detection, early diagnosis and evaluation of progression of tumor and diseases (e.g. Alzheimer's disease, rheumatoid arthritis). MRI can assess anatomy at excellent spatial resolution but the intrinsic contrast sometimes is not sufficient, thus the use of paramagnetic contrast agents (CAs) can be of great assistance.
Among these CAs, gadolinium-based contrast agents (GBCAs) are currently the most used worldwide for clinical applications (more than 40 million doses are given worldwide each year) and their effect in term of MRI signal enhancement can be predicted by the longitudinal relaxivity (r_1). Improvement of relaxometric properties of CAs (i.e. r_1) is still a need and the optimization of their chemical properties is certainly a suitable successful strategy in this respect [1].
In this work, a new series of Gd-complexes (*Fig. 1*, **1**-**3**) was designed to explore the role of intramolecular proton exchange catalysis in relaxivity enhancement [2,3]. The coordination cage of these complexes is the same of the commercial Gd-HP-DO3A with an additional phenol, aniline and benzoic moiety, respectively. In addition, the phenol moiety of **1** was further modulated to get more insight into the position and pKa value of the phenol group. The overall PhD project was focused on design, synthesis and relaxometric characterization of novel Gd-complexes in terms of relaxivity value as well as relaxation enhancement as a function of pH. In addition, protonation constants of alcoholic OH and phenol, aniline and benzoic moieties were determined for both ligands and Gd-complexes.
Moreover, results of the project carried out in collaboration with MR Neuroimaging Agents group of Max Planck Institute of Biological Cybernetics (Tubingen, Germany) will be presented. The project aimed to develop new Gd-complexes sensitive to zinc ion for MRI applications. Zinc imaging is suggested as a non-invasive technique to investigate zinc role in several pathological diseases such as type 2 diabetes, cancer and neurodegenerative diseases (e.g. Alzheimer`s disease) [4]. Ligands of these novel Gd-complexes were designed by introduction of a zinc sensitive function into the core scaffold of HP-DO3A. The relaxivity profile upon zinc addition will be presented and discussed in this talk as preliminary results, as well as the synthetic strategy.

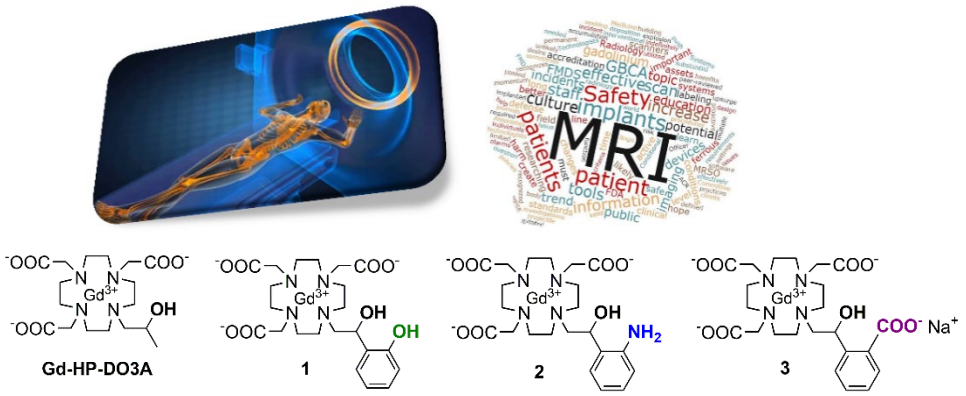

Fig. 1 Commercial Gd-HP-DO3A and three examples of novel Gd-complexes (**1**-**3**) developed in the PhD project.

[1] Zhou Z. *et al.*, *WIREs Nanomed. Nanobiotechnol.*, **2013**, *5*, 1–18.
[2] Fringuello Mingo A. *et al.*, *Magn. Reson. Med.*, **2017**, *78*, 1523-1532.
[3] Carnovale I.M. *et al.*, *Chem. Commun.*, **2018**, *54*, 10056-10059.
[4] Bonnet C.S., *Coord. Chem. Rev.*, **2018**, *369*, 91-104.