

Contrast agents with chelated lanthanoid ions for 19F MR imaging

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Target audience

Researchers in the area of X-nuclei, contrast enhanced MRI, cell tracking and cell-based therapies

Purpose

¹⁹F MRI represents potentially an interesting tool for cell tracking. Fluorine has a resonance frequency close to hydrogen one, therefore standard commercial scanners can be used for fluorine probe detection after only minor hardware and software changes. Due to zero concentration of fluorine in living organisms, there is no background in fluorine-based images. Generally long relaxation times of ¹⁹F nuclei require long repetition times leading to increase in total acquisition time. Relaxation times can be substantially shortened by a paramagnetic ion. The aim of our study was to synthesize molecular ¹⁹F probes based on DOTP-TFE with chelated lanthanoid ions, optimize imaging sequence timing and test the probes both *in vitro* and *in vivo*.

Subjects and Methods

DOTP-TFE containing twelve equivalent fluorine nuclei (see Fig. 1) was synthesized with chelated Ce, Dy, Tm, Yb, and Ho ions. MR images were acquired and relaxation times measured at 4.7T Bruker imager with a ¹H/¹⁹F homemade single-loop surface coil. T1 was measured by a saturation recovery sequence, T2 by a CPMG sequence, T2* was determined from the spectral linewidth.

In vitro experiments: gradient and turbo spin echo sequences were used with a matrix 32x32, voxel size 1.5x1.5x2 mm³. *In vivo* experiments on rats: after intraperitoneal injection of DOTP-TFE-Yb a turbo spin echo sequence (TE=8 ms, TR=200 ms, turbofactor 16, matrix 64x32, voxel size 1x1x10 mm³, AC=2048, scan time 13 minutes) was used to acquire ¹⁹F MR images.

Results

¹⁹F relaxation times of the chelates with different lanthanoids are summarized in the Table. According to acquired values, following imaging sequences were proposed for MRI: Turbo spin echo (TE=8ms) with 16 echoes for Ce (TR=500ms) and Yb (TR=200ms) chelates, gradient echo (TE/TR=3/15ms) for Dy, Tm, and Ho. All complexes in combination with optimized sequences provide *in vitro* sufficient signal at conditions mimicking experiments *in vivo* (concentration 1.25mM, number of acquisitions set for a 15-minute scan). *In vivo* application of the contrast agent into the abdomen of a rat confirmed visibility of the contrast agent in the application site (see Fig. 2).

Discussion

Although sensitivity of ¹⁹F MR signal is comparable to that of hydrogen, due to substantially lower concentration, higher number of acquisitions is necessary to obtain a sufficient signal. Therefore, shortening of the sequences is necessary. Relaxation times of complexes with Ce and Yb enable TR reduction in a spin echo based sequence down to 500 or 200ms resp., and use a turbofactor up to 16. Short relaxations in complexes carrying Dy, Tm, or Ho require a gradient echo sequence and permit TR reduction down to 15 ms which enables to acquire substantially more acquisitions (up to 2000 acquisitions in a 15-minute sequence), thus to make up for lost signal due to short T₂/T₂*. Based on initial *in vivo* experiments we presume that the probes will be suitable as blood pool contrast agents for *in vivo* applications as well as labels for cell tracking.

Conclusion

We have synthesized and successfully tested both *in vitro* and *in vivo* novel ¹⁹F contrast agents based on DOTP with 12 equivalent fluorine ions. We optimized imaging sequences for *in vivo* applications with respect to their actual relaxation times.

Acknowledgement

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Table: Relaxation times of fluorine complexes with chelated cerium (Ce), dysprosium (Dy), thulium (Tm), ytterbium (Yb), and holmium (Ho).

Reference:

Srinivas M.et al.2010,*Trends Biotechnol*,28(7):363–370.

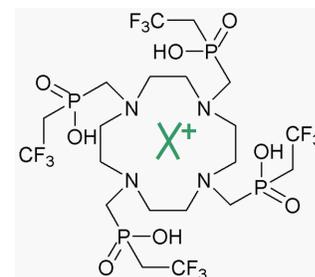


Fig. 1: Scheme of a DOTP-TFE molecule

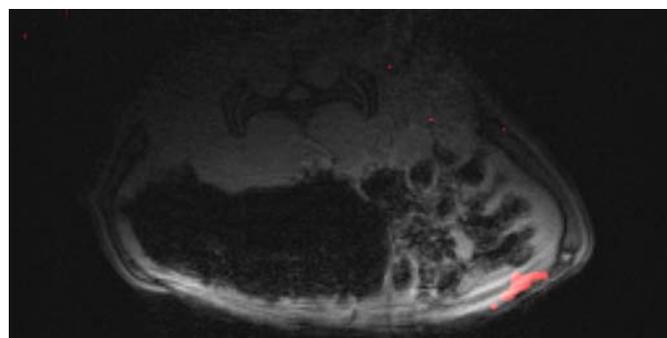


Fig. 2: ¹⁹F MR signal (red) over a ¹H MRI of a rat abdomen

	T1 (ms)	T2 (ms)	T2* (ms)
DOTP-TFE-Ce	243.8	84.5	4.28
DOTP-TFE-Dy	10.9	5.7	5.45
DOTP-TFE-Tm	10.8	9.1	5.12
DOTP-TFE-Yb	106.9	73.9	4.36
DOTP-TFE-Ho	10.9	7.3	4.08