Supplementary Material (ESI) for Organic & Biomolecular Chemistry

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ELECTRONIC SUPPLEMENTARY INFORMATION

for

AAZTA-based bifunctional chelating agents for the synthesis of multimeric/dendrimeric MRI contrast agents

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1) General experimental conditions

All reactants were used as supplied from commercial sources unless stated otherwise. Reactions requiring exclusion of moisture were carried out under an argon atmosphere. Water refers to high purity water with conductivity of 0.04 μScm^{-1}, obtained from the "MILLI-Q" purification system.

Thin-layer chromatography was carried out on silica plates (Merck 5554) and visualized by UV lamp (254 nm). Preparative column chromatography was carried out using silica gel (Merck Silica Gel 60, 230 ± 400 mesh) pre-soaked in the starting eluent.

^{1}H and ^{13}C NMR spectra were recorded on JEOL ECP 400 (^{1}H at 399.968, ^{13}C at 100.572 MHz) spectrometer. Chemical shifts are reported relative to TMS and were referenced using the residual proton solvent resonances. Chemical shifts are reported in ppm and coupling constants in Hz. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m).

Mass spectra with electrospray ionization (ES) were recorded on a SQD 3100 Mass Detector (Waters), operating in positive or negative ion mode, with methanol as the carrier solvent.

Measurements of pH were performed using a Hanna 211 pH meter and Aldrich Chemical Company micro-pH combination electrode, calibrated using pH 4, pH 7 and pH 10 buffer solutions.

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The HPLC-MS analysis was carried out on a Waters system equipped of Waters 1525 binary HPLC Pump and Waters 2489 UV/vis and Waters SQD 3100 detectors. The stationary phase used was the Waters XTerra RPC18 150x4.6 mm column (5μm) (flow rate 1ml/min).

Size exclusion HPLC were carried out on Sephadex G25 columns on Amersham Akta Purifier chromatographic system equipped with two pumps, a UV–vis triple wavelength detector (set at 215, 230 and 254 nm), and on-line pH, conductivity, and temperature monitors. Water was used as eluent at a flow of 2 mL/min.

The water proton longitudinal relaxation rates of aqueous solutions of Gd_8L3 and Gd_8L4 were measured by using a Stelar Spinmaster spectrometer (Mede, Italy) operating at 0.5 T and 298 K. The concentration of Gd^{III} in the solution was determined by Evans experiment. For the measurement of the relaxation rates, the standard inversion-recovery method was employed (16 experiments, 2 scans) with a typical 90° pulse width of 3.5 ms, and the reproducibility of the T_1 data was ± 0.5%. The temperature was controlled with a Stelar VTC-91 airflow heater equipped with a copper-constantan thermocouple (uncertainty of ± 0.1 °C).

Infrared (IR) spectra were recorded in the range 4000–400 cm^{-1} at 4 cm^{-1} resolution using a Bruker Equinox 55 spectrometer.

Elemental analysis were performed on a EuroVector EA 3000 instrument.

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2) HPLC method and retention times

Method 1:

Solvent A: H_2O-TFA 0.1%; Solvent B: MeCN-TFA 0.1%; Flow: 1 mL/min

HPLC gradient conditions

Time (min)	Solvent A (%)	Solvent B (%)
0	90	10
2.5	90	10
15	30	70
17.5	0	100
25	0	100

Method 2:

Solvent A: H_2O-TFA 0.1%; Solvent B: MeOH-TFA 0.1%; Flow: 1 mL/min

HPLC gradient conditions

Time (min)	Solvent A (%)	Solvent B (%)
0	98	2

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2.5	98	2
15	50	50
17.5	0	100
25	0	100