Is macrocycle a synonym for kinetic inertness in Gd(III) complexes? Effect of coordinating and non-coordinating substituents on inertness and relaxivity of Gd(III) chelates with DO3A-like ligands.

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Content:

Table S1. Parameters obtained from fits of variable temperature ^{17}O transverse relaxivity measurements of water in presence of Gd chelates. Data was fit to a 4-parameter model as described previously (Caravan et al. *Inorg. Chem.* **2007**, *46*, 6632-6639). The ^{17}O hyperfine coupling constant was assumed to be 3.8 x 10^6 rad/s (Powell et al. *J. Am. Chem. Soc.* **1996**, *118*, 9333-9346).

Compound	τ_M^{310} **[ns]**	T_{1e}^{310} **[ns]**	$\Delta H^{\ddagger}$ **[kJ]**	E_v **[kJ]**
[Gd(**L1**)(H_2O)]	2190 ± 170	117 ± 110	34.1 ± 1.9	-13.3 ± 13.6
[Gd(**L2**)(H_2O)]	3500 ± 90	ND	30.5 ± 0.9	ND
[Gd(**L3**)(H_2O)]	12.7 ± 3.8	90 ± 180	27.7 ± 4.3	5.8 ± 33.4

ND = not determined. Water exchange was in the slow exchange region over the temperature range studied, i.e. T_{1e} did not contribute to the O-17 T_2. The data were fit to a 2 parameter model (τ_M^{310} and $\Delta H^{\ddagger}$).

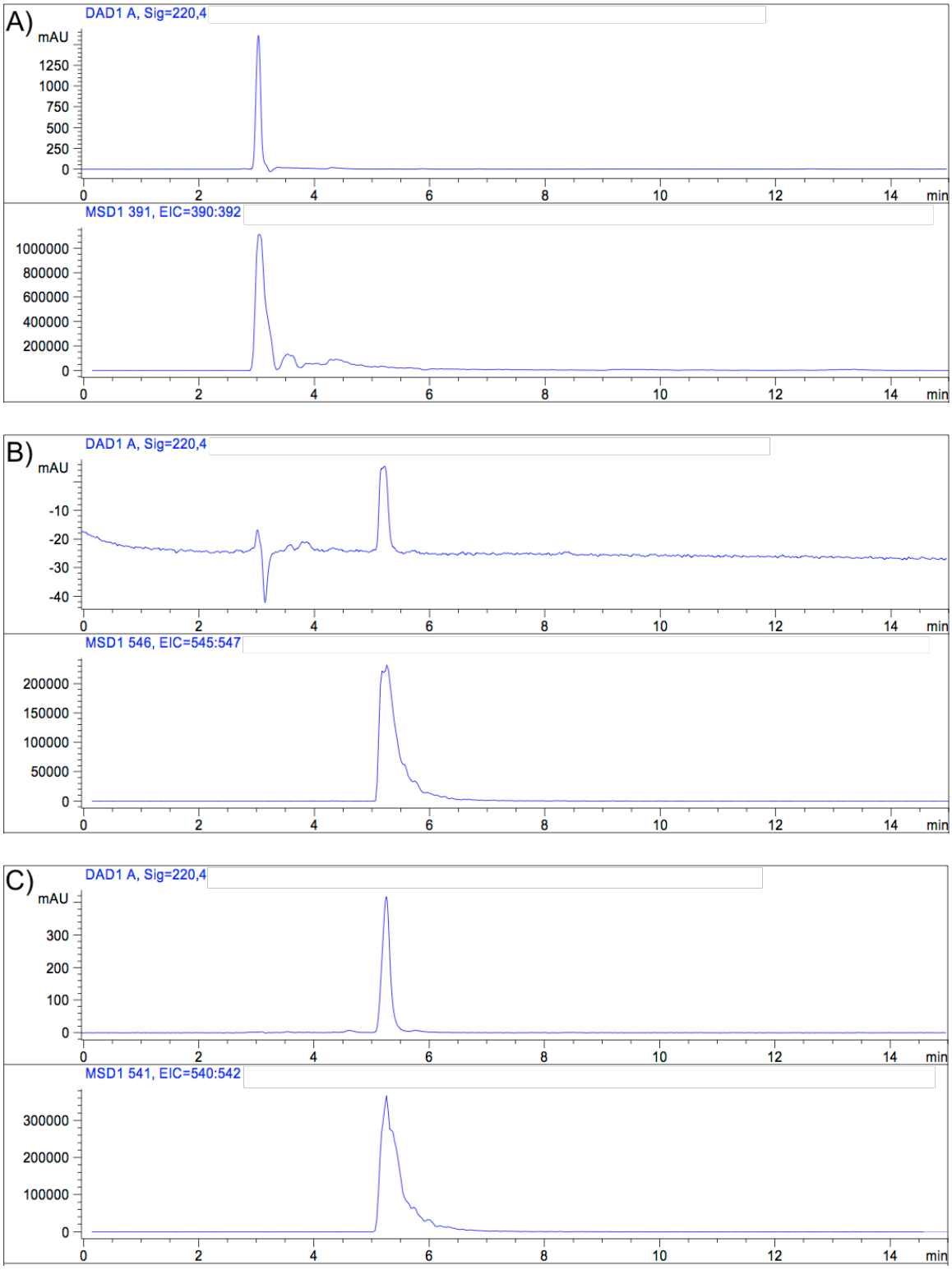
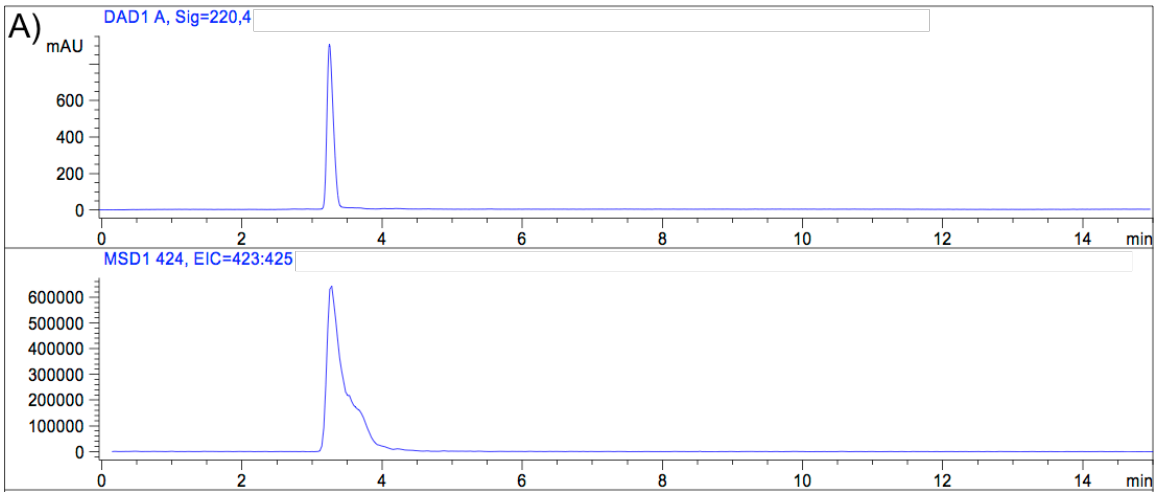
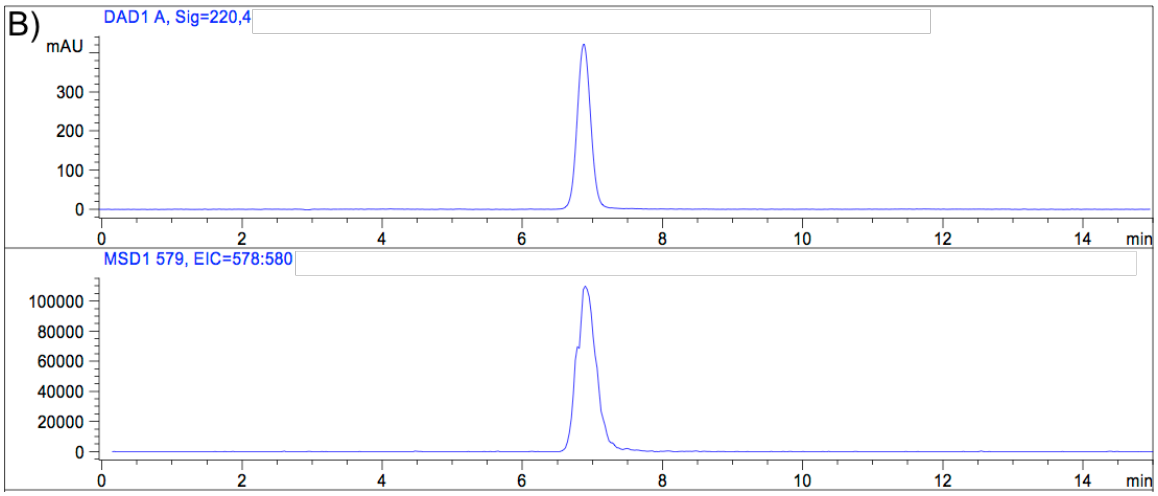


Figure S1. LC-MS chromatograms showing UV absorbance (220 nm) and extracted masses for $[M+H]^+$ ions.
A) ligand **L1**, analytical method G.
B) chelate [Gd(**L1**)], analytical method G.
C) chelate [Eu(**L1**)], analytical method G.





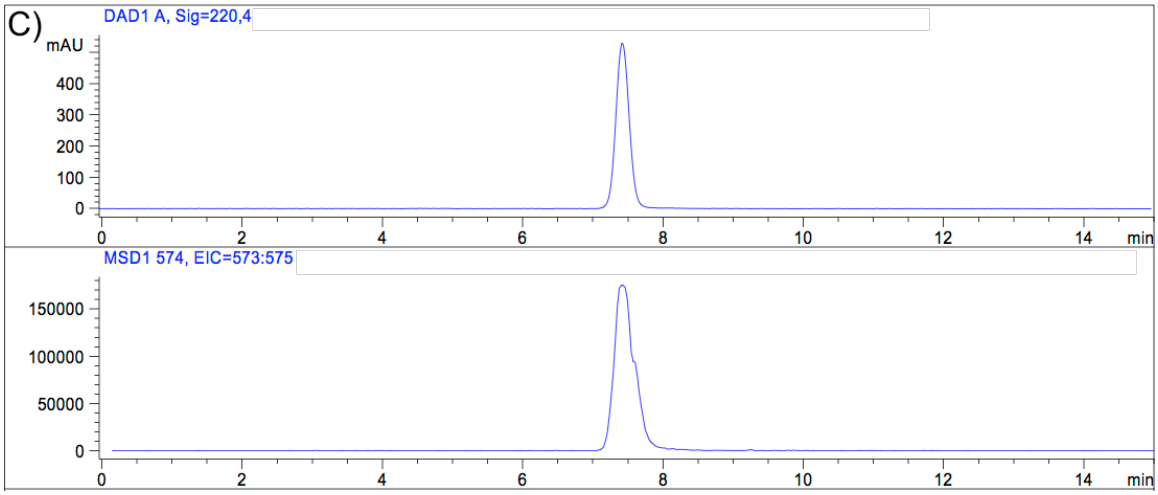


Figure S2. LC-MS chromatograms showing UV absorbance (220 nm) and extracted masses for $[M+H]^+$ ions.
A) ligand **L2**, analytical method G.
B) chelate [Gd(**L2**)], analytical method G.
C) chelate [Eu(**L2**)], analytical method G.

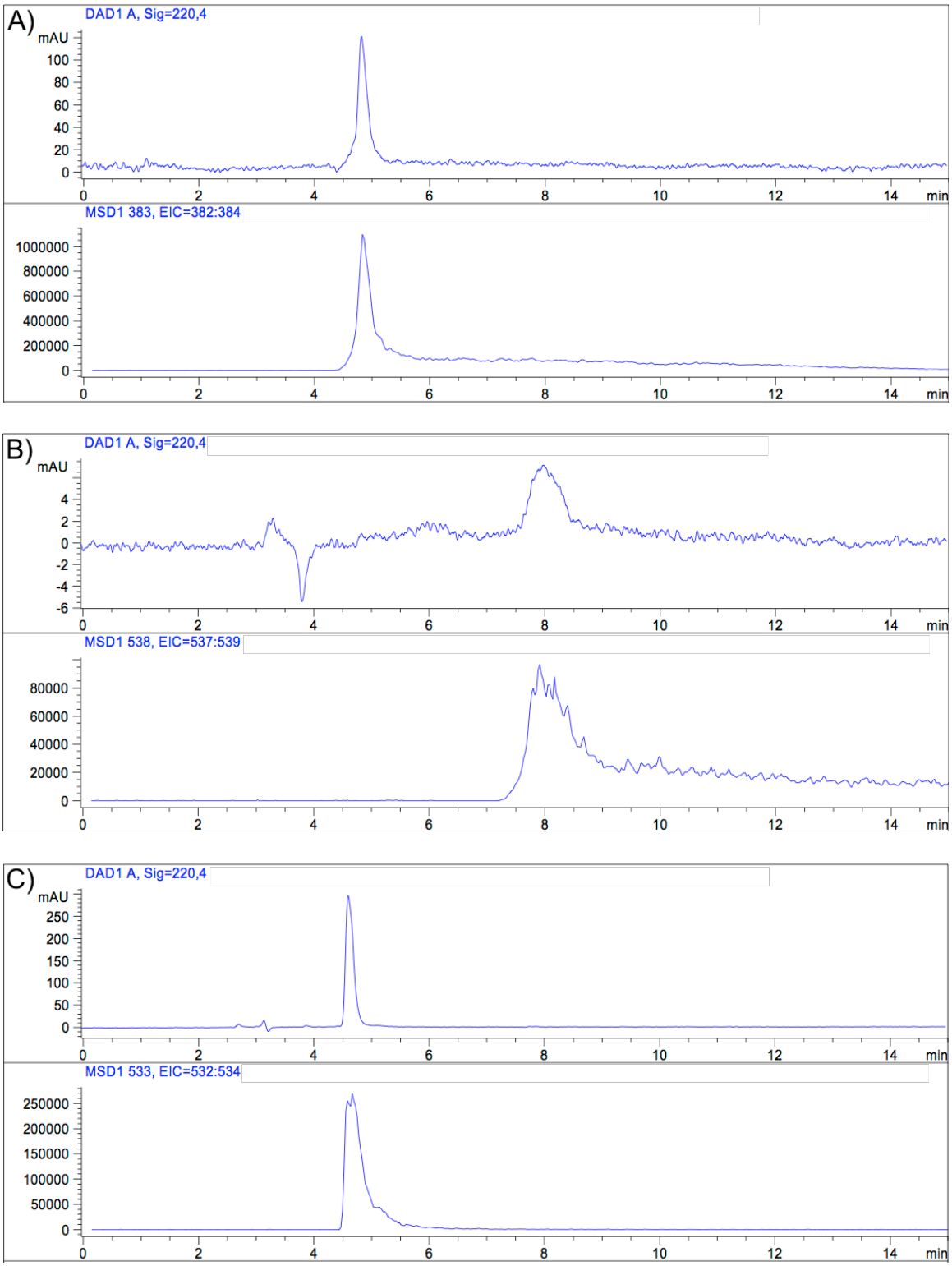


Figure S3. LC-MS chromatograms showing UV absorbance (220 nm) and extracted masses for $[M+H]^+$ ions.
A) ligand **L3**, analytical method H.
B) chelate [Gd(**L3**)], analytical method I.
C) chelate [Eu(**L3**)], analytical method G.

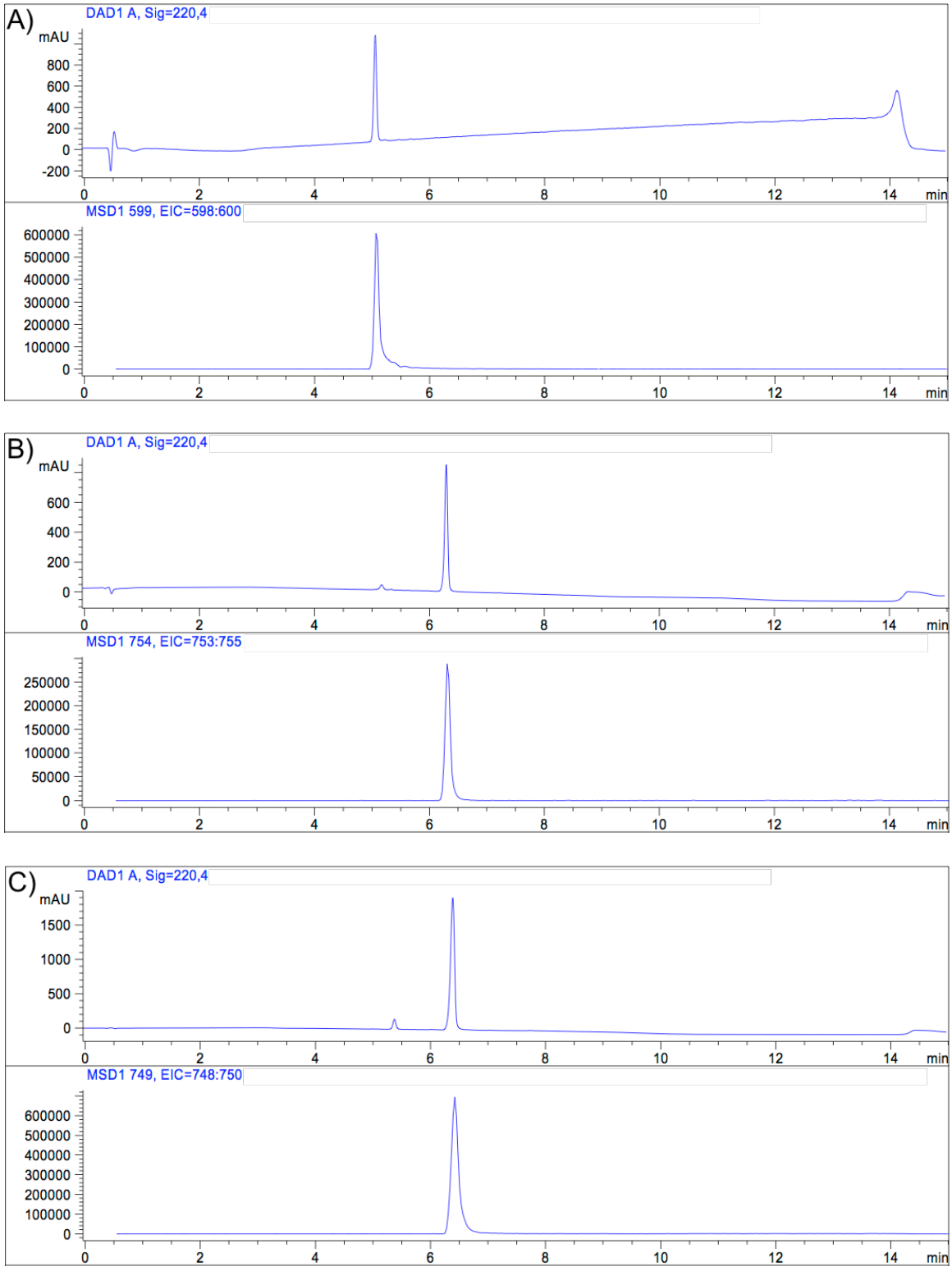


Figure S4. LC-MS chromatograms showing UV absorbance (220 nm) and extracted masses for $[M+H]^+$ ions.
A) ligand **L4**, analytical method J.
B) chelate [Gd(**L4**)], analytical method K.
C) chelate [Eu(**L4**)], analytical method K.

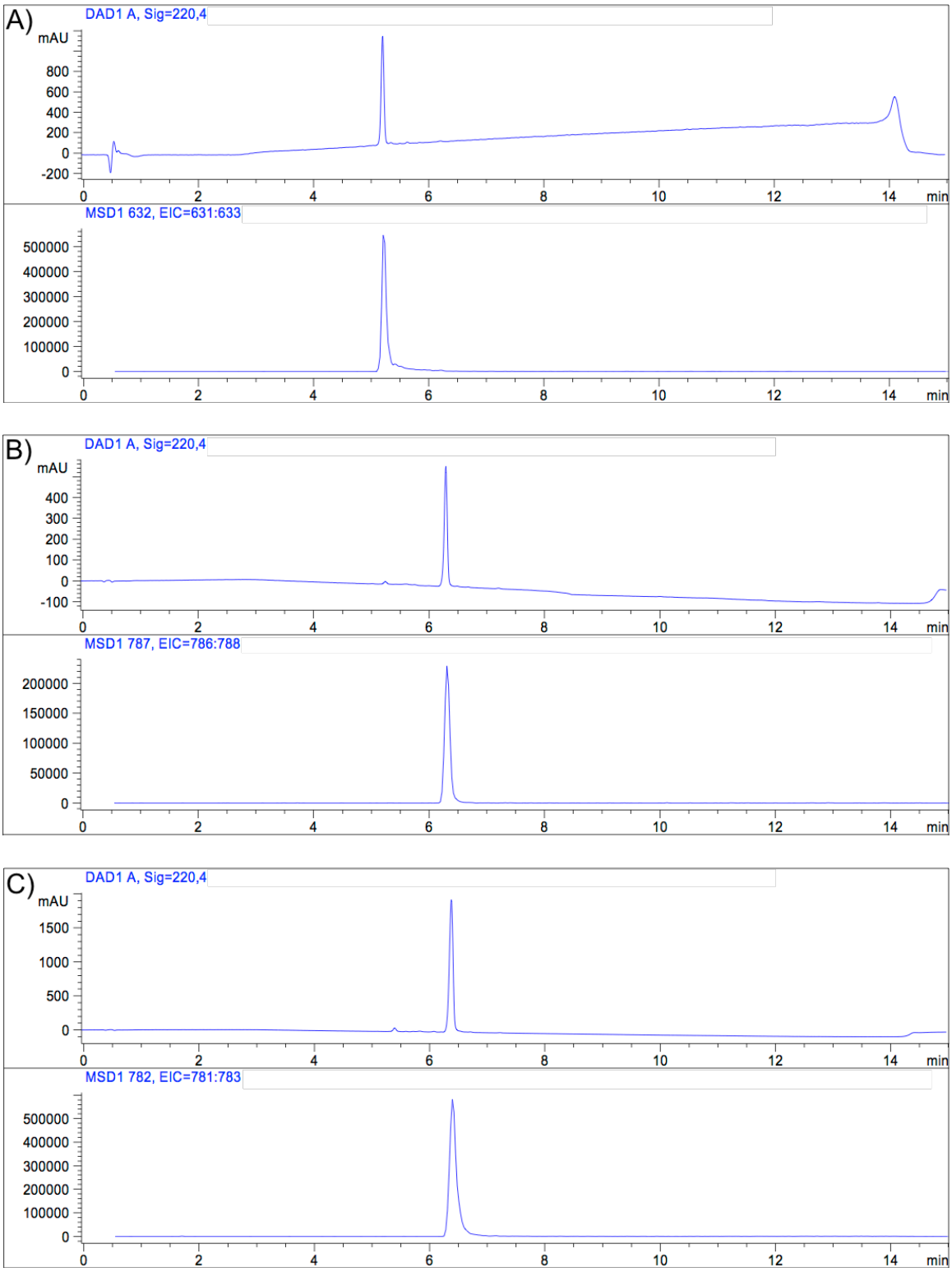
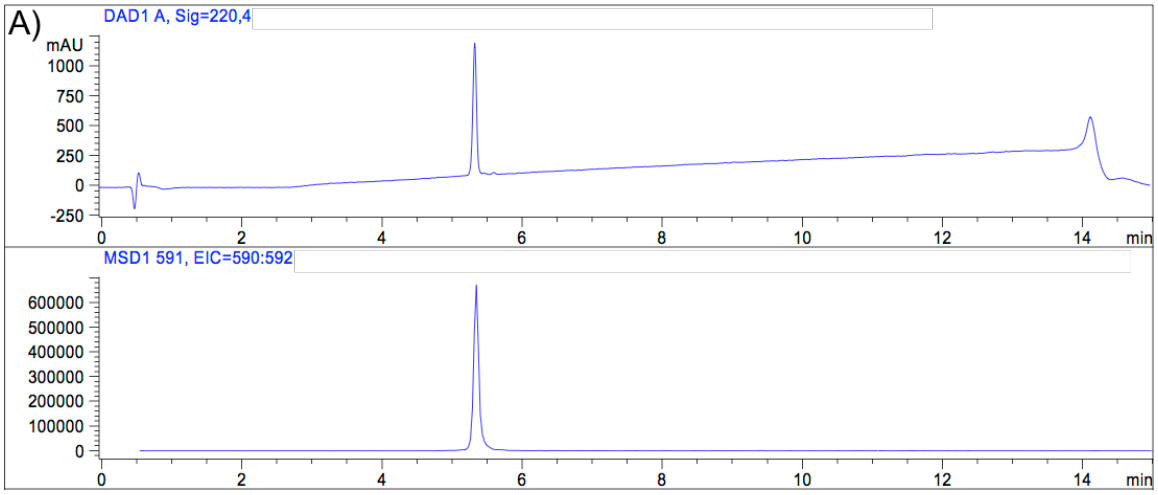
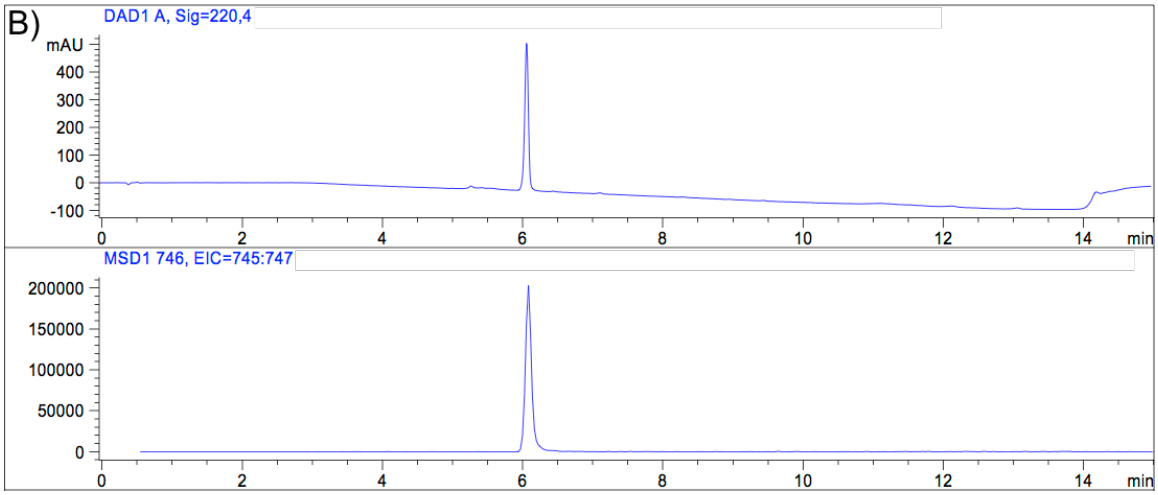


Figure S5. LC-MS chromatograms showing UV absorbance (220 nm) and extracted masses for $[M+H]^+$ ions.
A) ligand **L5**, analytical method J.
B) chelate [Gd(**L5**)], analytical method K.
C) chelate [Eu(**L5**)], analytical method K.





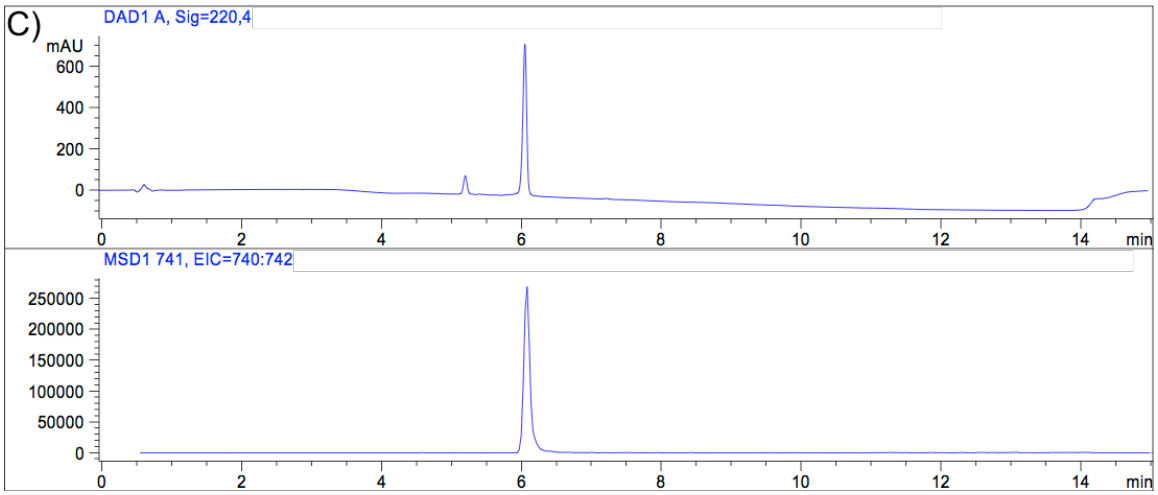


Figure S6. LC-MS chromatograms showing UV absorbance (220 nm) and extracted masses for $[M+H]^+$ ions.
A) ligand **L6**, analytical method J.
B) chelate [Gd(**L6**)], analytical method K.
C) chelate [Eu(**L6**)], analytical method K.

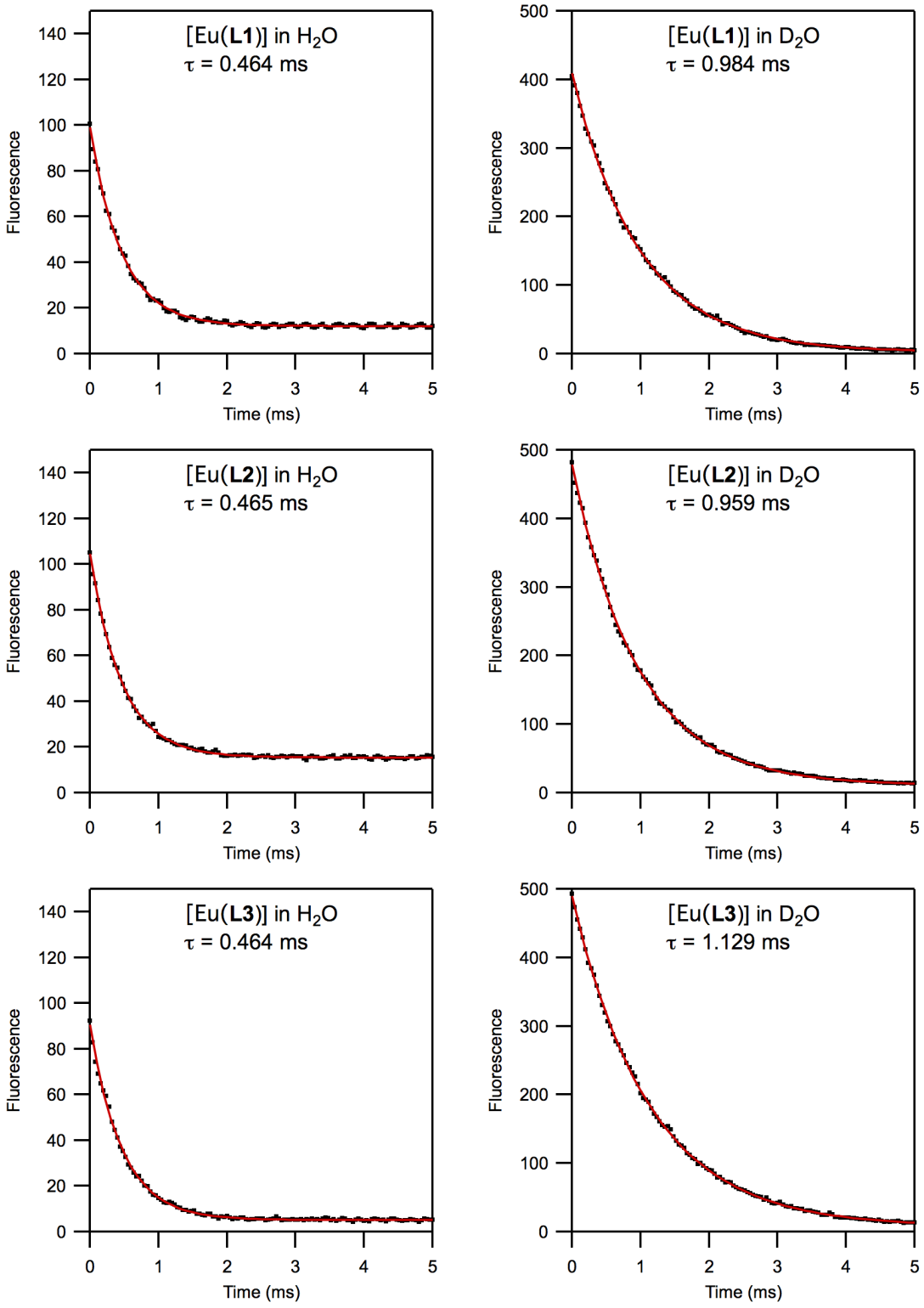


Figure S7. Time-dependent luminescence of Eu complexes of ligands **L1** − **L3** measured in H_2O and D_2O. Solid line represents monoexponential fit of the data.

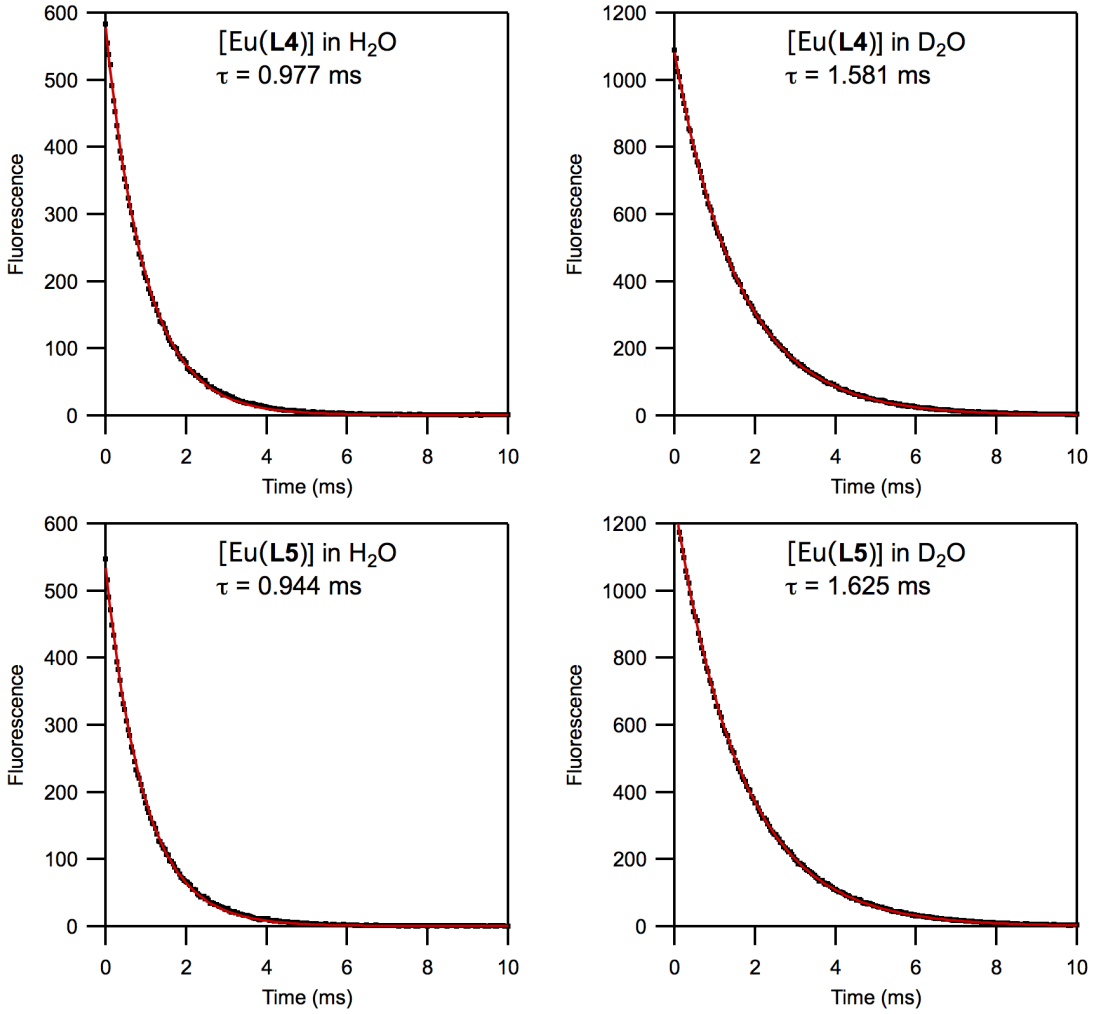


Figure S8. Time-dependent luminescence of Eu complexes of ligands **L4** and **L5** measured in H_2O and D_2O. Solid line represents monoexponential fit of the data.

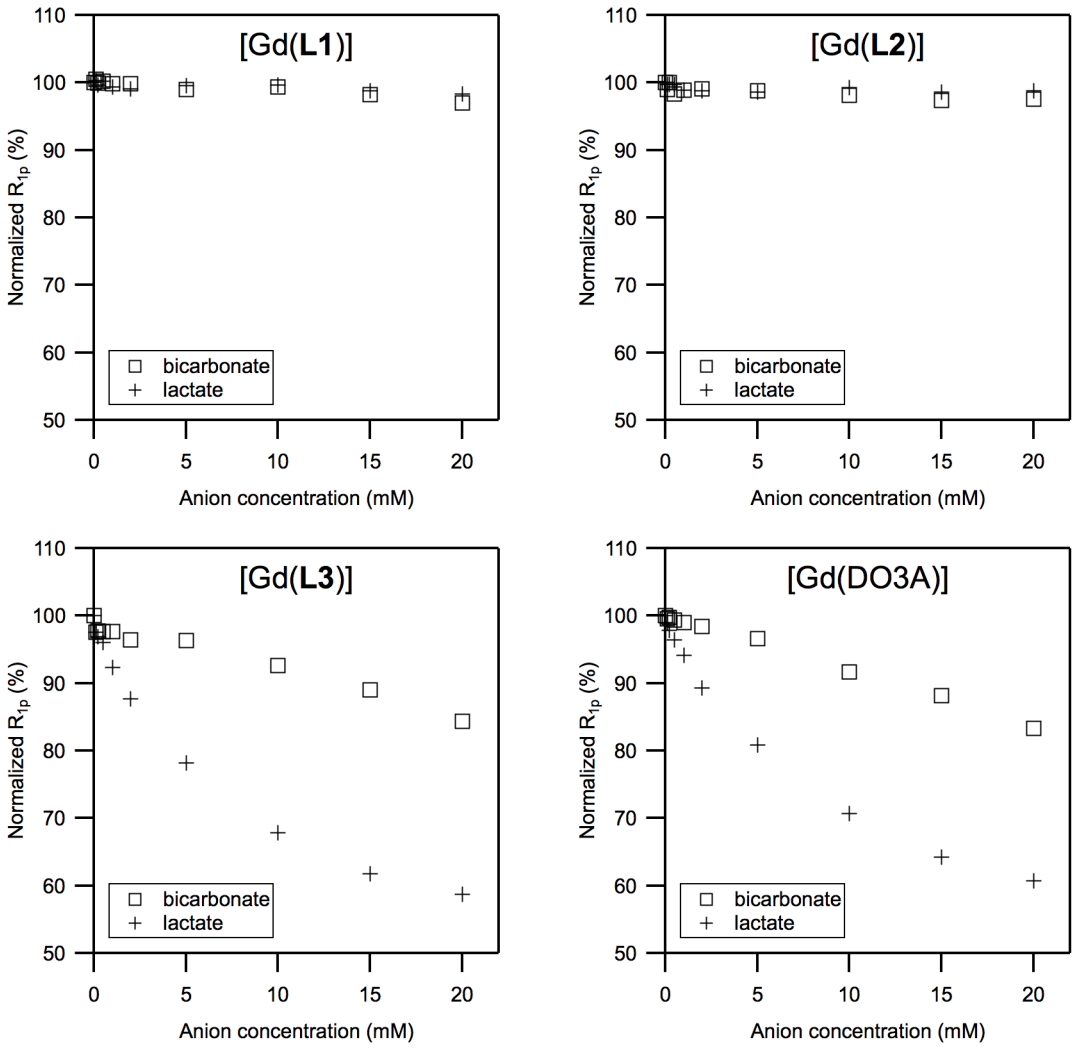


Figure S9. Relative change in relaxation rates of 1 mM solutions of gadolinium complexes in 50 mM HEPES buffer pH = 7.4 as a function of added bicarbonate or lactate.

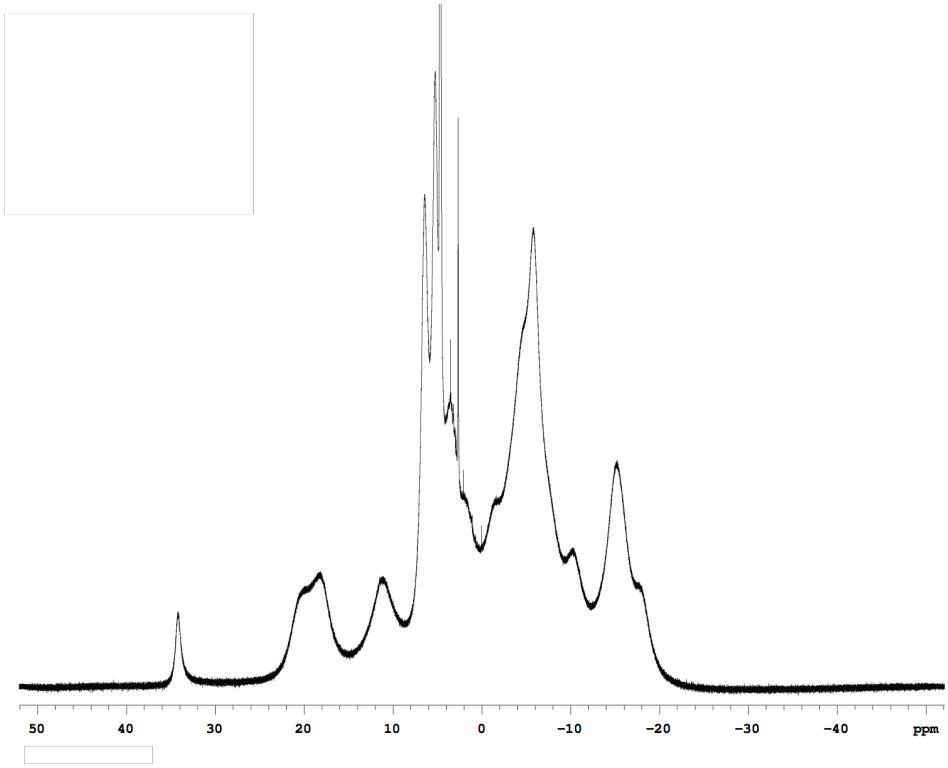


Figure S10. ^{1}H NMR spectrum of [Eu(**L1**)] in D_2O at 25 °C.

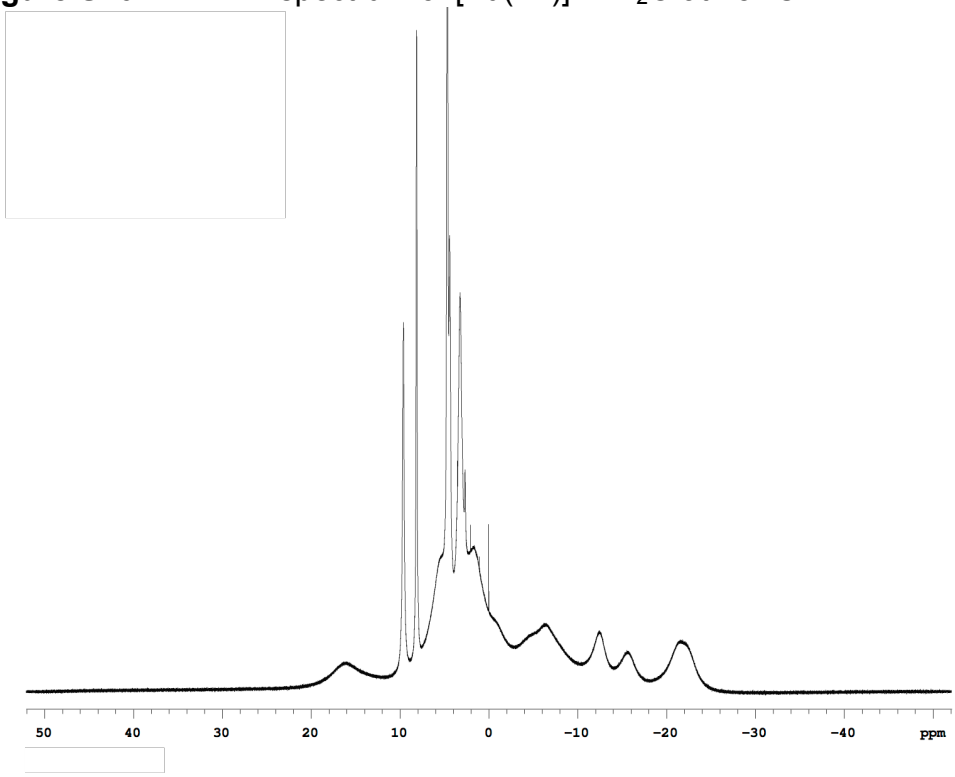


Figure S11. ^{1}H NMR spectra of [Eu(**L2**)] in D_2O at 25 °C.

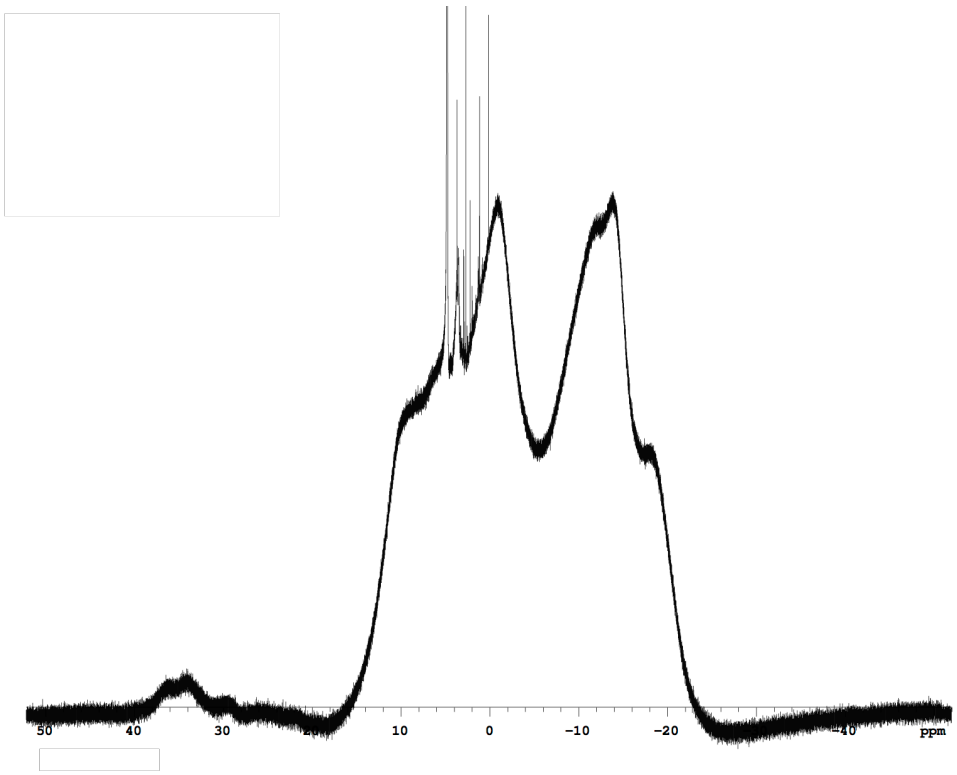


Figure S12. ^{1}H NMR spectra of [Eu(**L3**)] in D_2O at 25 °C.

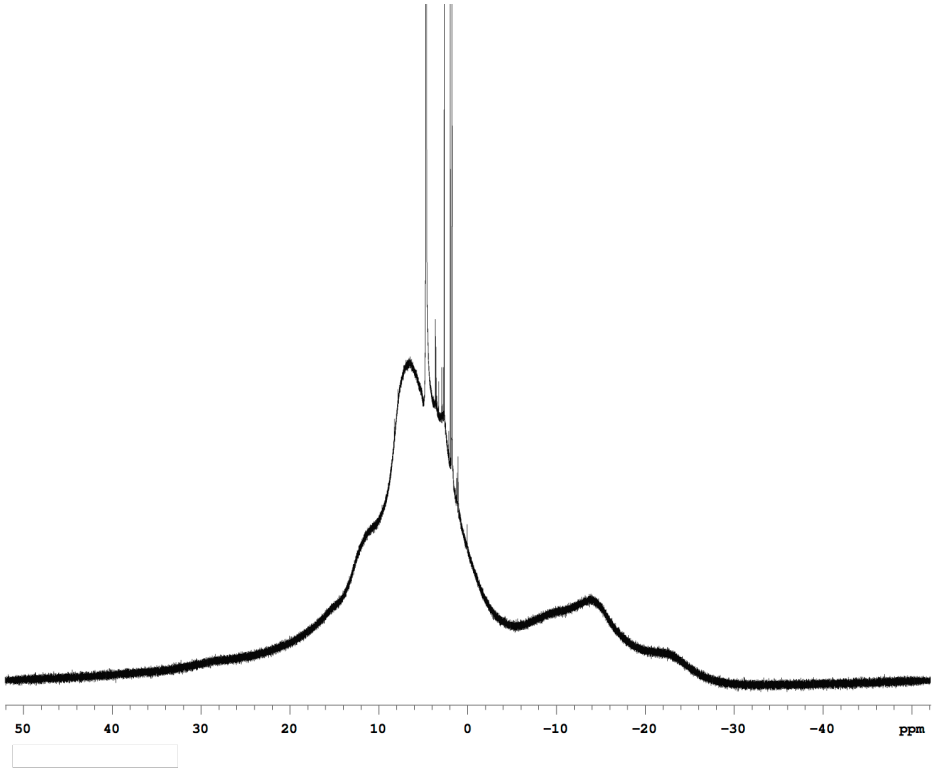


Figure S13. ^{1}H NMR spectra of [Eu(**L4**)] in D_2O at 25 °C.

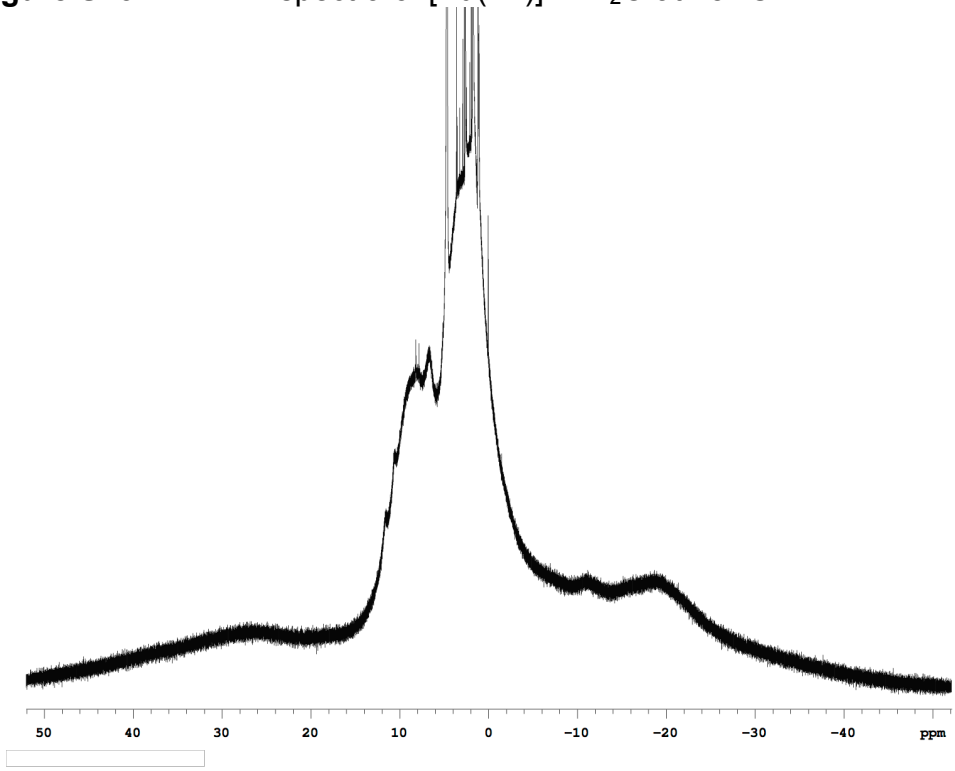


Figure S14. ^{1}H NMR spectra of [Eu(**L5**)] in D_2O at 25 °C.

List of HPLC methods:

Preparative:

(A) Preparative column Kromasil C18 20 x 250 mm, solvent A = H_2O + 0.1% TFA, solvent B = MeCN + 0.1% TFA. Gradient (% B): 5 for 2 min., 5 − 20 in 1 min., 20 − 80 in 12 min., 80 − 100 in 1 min., 100 for 4 min., 100 − 5 in 1 min., 5 for 4 min. Flow rate 20 mL/min. Detection at 220 nm.

(B) Preparative column Phenomenex Luna C5 20 x 250 mm, solvent A = H_2O + 0.1% TFA, solvent B = MeCN + 0.1% TFA. Gradient (% B): 5 for 2 min., 5 − 40 in 1 min., 40 − 80 in 12 min., 80 − 100 in 1 min., 100 for 4 min., 100 − 5 in 1 min., 5 for 4 min. Flow rate 20 mL/min. Detection at 220 nm.

(C) Preparative column Kromasil C18 20 x 250 mm, solvent A = H_2O + 0.1% TFA, solvent B = MeCN + 0.1% TFA. Gradient (% B): 5 for 1 min., 5 − 50 in 1 min., 50 − 80 in 8 min., 80 − 100 in 0.5 min., 100 for 1.5 min., 100 − 5 in 1 min., 5 for 4 min. Flow rate 20 mL/min. Detection at 220 nm.

(D) Same as (A) except for the main gradient being 30 − 60 in 12 min.

(E) Preparative column Kromasil C18 20 x 250 mm, solvent A = H_2O + 0.1% TFA, solvent B = MeCN + 0.1% TFA. Gradient (% B): 5 for 1 min., 5 − 50 in 1 min., 50 − 80 in 10 min., 80 − 100 in 1 min., 100 for 3 min., 100 − 5 in 0.5 min., 5 for 4.5 min. Flow rate 20 mL/min. Detection at 220 nm.

(F) Preparative column Kromasil C18 20 x 250 mm, isocratic 2% MeCN in H_2O for 10 min. Flow rate 20 mL/min. Detection at 220 nm.

Analytical:

(G) Analytical column Kromasil C18 4.6 x 250 mm, solvent A = 10 mM ammonium acetate pH = 7, solvent B = MeCN / 10 mM ammonium acetate (90:10). Isocratic 2% B for 15 min. Flow rate 0.8 mL/min.

(H) Analytical column Restek C18 Ultraaqueous 4.6 x 250 mm, solvent A = H_2O + 0.1% formic acid, solvent B = MeCN + 0.1% formic acid. Isocratic 2% B for 15 min. Flow rate 0.8 mL/min.

(I) Same as method G with analytical column Restek C18 Ultraaqueous 4.6 x 250 mm.

(J) Analytical column Luna C8(2) 2 x 100 mm, solvent A = H_2O + 0.1% formic acid, solvent B = MeCN + 0.1% formic acid. Gradient (% B): 5 for 2 min., 5 − 95 in 9 min., 95 for 1 min., 95 − 5 in 0.5 min., 5 for 2.5 min. Flow rate 0.8 mL/min.

(K) Analytical column Luna C8(2) 2 x 100 mm, solvent A = 10 mM ammonium acetate pH = 7, solvent B = MeCN / 10 mM ammonium acetate (90:10). Gradient (% B): 5 for 2 min., 5 − 95 in 9 min., 95 for 1 min., 95 − 5 in 0.5 min., 5 for 2.5 min. Flow rate 0.8 mL/min.