Electronic Supplementary Material (ESI) for Chemical Communications.
This journal is © The Royal Society of Chemistry 2015

Ligation Driven ^{19}F Relaxation Enhancement in Self-Assembled Ln(III) Complexes

Gemma-Louise Davies,† Asha Brown, Octavia Blackburn, Manuel Tropiano, Stephen Faulkner, Paul D. Beer, Jason J. Davis*

Department of Chemistry, University of Oxford, South Parks Road, Oxford, OX1 3QR, UK.
E-mail: Jason.davis@chem.ox.ac.uk, Tel: +44 (0)1865 275 914, Fax:+44 (0)1865 272 690
† *Current address: Department of Chemistry, University of Warwick, Gibbet Hill, Coventry, CV4 7AL, UK.*

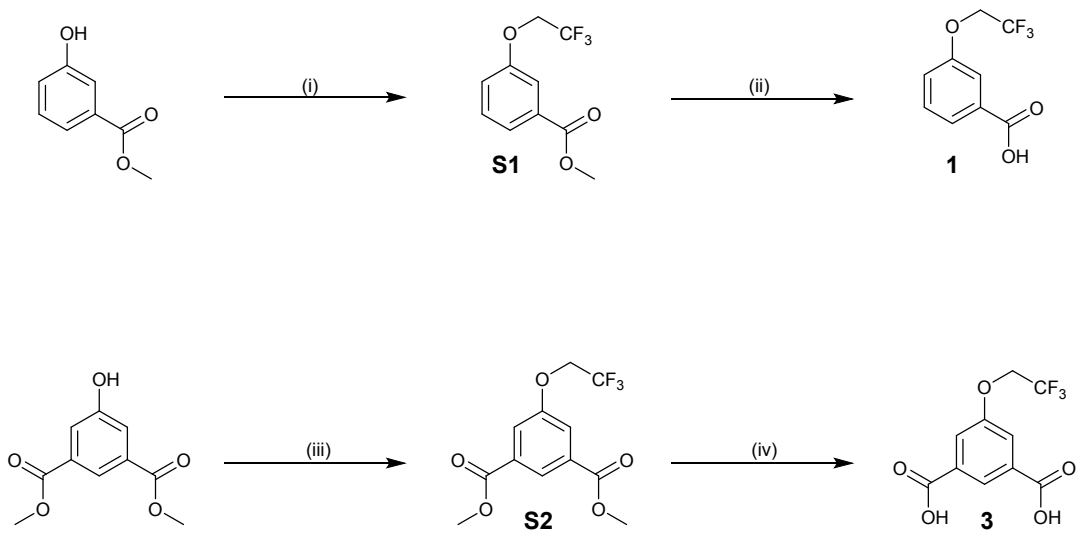
Supporting Information

Experimental

Synthetic Procedures and Characterisation Data

All reagents and solvents were purchased from commercial suppliers and used as received unless otherwise stated. Dry DMF was obtained by purging with N_2 and then passing through an MBraun MPSP-800 column. H_2O was de-ionised and micro-filtered using a Milli-Q ® Millipore machine. Petroleum ether refers to the fraction of boiling point 40–60ºC. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Varian Mercury-VX 300 spectrometer at 293 K. Chemical shifts are quoted in parts per million relative to the residual solvent peak. Electrospray mass spectra were obtained using a Micromass LCT Premier XE spectrometer or a Micromass GCT spectrometer.

The mononuclear[1] and binuclear[2] Ln-DO3A complexes were prepared according to previously reported procedures.



Scheme S1. Synthesis of the trifluoromethyl-functionalised carboxylic acid derivatives **1** and **3**. *Reagents and conditions*: (i) methanesulfonate 2,2,2-trifluoromethylester, Cs_2CO_3, DMF, 80 °C, 48 hours, 41%; (ii) NaOH, THF, MeOH, H_2O, r.t., 60 hours, 77%; (iii) methanesulfonate 2,2,2-trifluoromethylester, Cs_2CO_3, DMF, 80 °C, 72 hours, 53%; (iv) NaOH, THF, MeOH, H_2O, r.t., 48 hours, 88%.

Methyl 3-(2,2,2-trifluoroethoxy)benzoate S1

Methyl 3-hydroxybenzoate (0.50 g, 3.29 mmol) and methanesulfonate 2,2,2-trifluoromethylester (1.17 g, 6.57 mmol) were dissolved in dry, de-gassed DMF (20 mL) and Cs_2CO_3 (1.61 g, 4.93 mmol) was added. The reaction mixture was heated at 80 °C under nitrogen for 48 hours, then cooled to room temperature and filtered. After concentration of the filtrate on a rotary evaporator, the residue was dissolved in CH_2Cl_2 (30 mL). The solution was filtered and the filtrate concentrated on a rotary evaporator to give a yellow oil. Purification of this residue by column chromatography (petroleum ether:CH_2Cl_2 7:3) afforded the product as a colourless oil (0.32 g, 41%). **^{1}H NMR** (300 MHz; $CDCl_3$) δ: 7.75 (dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.2 Hz, 1 H, Ar*H*), 7.60–7.59 (m, 1 H, Ar*H*), 7.43–7.38 (m, 1 H, Ar*H*), 7.20–7.16 (m, 1 H, Ar*H*), 4.41 (quartet, $^3J_{HF}$ = 8.0 Hz, 2 H, O$CH_2$$CF_3$), 3.93 (s, 3 H, CO_2CH_3); **^{13}C NMR** (75 MHz; $CDCl_3$) δ: 166.3 (s), 157.2 (s), 131.7 (s), 129.7 (s), 123.7 (s),

123.2 (quartet, $^{1}J_{CF}$ = 278 Hz), 120.2 (s), 114.8 (s), 65.8 (quartet, $^{2}J_{CF}$ = 35.7 Hz), 52.2 (s); **^{19}F NMR** (282 MHz; $CDCl_3$) δ: −73.9 (t, $^{3}J_{HF}$ = 8.0 Hz); **ESMS** *m/z*: 235.1 ($[M + H]^+$; 257.0 ($[M + Na]^+$); **HRMS** (ES) *m/z*: 257.0406 ($[M + Na]^+$. $C_{10}H_9F_3NaO_3$ requires 257.0396).

3-(2,2,2-Trifluoroethoxy)benzoic acid 1

Methyl 3-(2,2,2-trifluoroethoxy)benzoate **S1** (0.15 g, 0.64 mmol) was dissolved in THF (3.5 mL) and MeOH (3.5 mL). A solution of NaOH (0.064 g, 1.60 mmol) in H_2O (3.5 mL) was added and the reaction mixture was stirred at room temperature under nitrogen for 60 hours, before being diluted with H_2O (2.5 mL). After removal of the organic solvents *in vacuo*, 1 M $HCl_{(aq)}$ was added to the remaining aqueous solution until the pH reached 1. The precipitate was collected by filtration, washed with H_2O (4 x 15 mL) and dried under high vacuum to yield the product as a white solid (0.11 g, 77%). **^{1}H NMR** (300 MHz; DMSO-d_6) δ: 13.1 (br s, 1 H, CO_2H), 7.63 (d, $^{3}J_{HH}$ = 7.6 Hz, 1 H, Ar*H*), 7.55–7.54 (m, 1 H, Ar*H*), 7.49–7.44 (m, 1 H, Ar*H*), 7.31 (dd, $^{3}J_{HH}$ = 8.2 Hz, $^{4}J_{HH}$ = 2.9 Hz, 1 H, Ar*H*), 4.85 (quartet, $^{3}J_{HF}$ = 8.8 Hz, 2 H, OCH_2CF_3); **^{13}C NMR** (75 MHz; DMSO-d_6) δ: 166.8 (s), 157.0 (s), 132.5 (s), 130.0 (s), 124.0 (quartet, $^{1}J_{CF}$ = 278 Hz), 123.1 (s), 119.8 (s), 115.0 (s), 64.7 (quartet, $^{2}J_{CF}$ = 34.1 Hz); **^{19}F NMR** (282 MHz; DMSO-d_6) δ: −72.5 (t, $^{3}J_{FH}$ = 8.8 Hz); **ESMS** *m/z*: 218.9 ($[M – H]^-$); 438.9 ($[2M − H]^-$); 461.0 ($[2M – 2H + Na]^-$); **HRMS** (ES) *m/z*: 219.0273 ($[M – H]^-$. $C_9H_6F_3O_3$ requires 219.0275).

Dimethyl 5-(2,2,2-trifluoroethoxy)isophthalate S2[3]

5-Hydroxymethylisophthalate (1.00 g, 4.76 mmol) and methanesulfonate 2,2,2-trifluoromethylester (1.70 g, 9.52 mmol) were dissolved in dry, de-gassed DMF (20 mL). Cs_2CO_3 (2.33 g, 7.14 mmol) was added and the reaction mixture was heated at 80 °C under nitrogen for 72 hours. After being allowed to cool to room temperature, the reaction mixture

was filtered and the filtrate concentrated on a rotary evaporator. The residue was dissolved in CH_2Cl_2:MeOH 1:1, dry-loaded onto silica and purified by column chromatography, eluting with CH_2Cl_2:hexane 1:1, to afford the product as a white solid (0.74 g, 53%). **^{1}H NMR** (300 MHz; $CDCl_3$) δ: 8.39 ($^4J_{HH}$ = 1.4 Hz, 1 H, Ar*H*), 7.81 (d, $^4J_{HH}$ = 1.4 Hz, 2 H, Ar*H*), 4.46 (quartet, $^3J_{HF}$ = 7.9 Hz, O*C*H_2CF$_3$), 3.96 (s, 3 H, CO_2C*H*$_3$); **^{13}C NMR** (75 MHz; $CDCl_3$) δ: 165.4 (s), 157.2 (s), 132.1 (s), 124.5 (s), 123.0 (quartet, $^1J_{CF}$ = 278 Hz), 119.9 (s), 65.8 (quartet, $^2J_{CF}$ = 36.1 Hz), 52.4 (s); **^{19}F NMR** (282 MHz; $CDCl_3$) δ: −73.9 (t, $^3J_{FH}$ = 7.9 Hz); **ESMS** *m/z*: 293.1 ([M + H]$^+$; 310.1 ([M + NH_4]$^+$; 315.0 ([M + Na]$^+$); **HRMS** (ES) *m/z*: 315.0449 ([M + Na]$^+$. $C_{12}H_{11}F_3NaO_5$ requires 315.0451).

5-(2,2,2-Trifluoroethoxy)isophthalic acid 3

Dimethyl 5-(2,2,2-trifluoroethoxy)isophthalate **S2** (0.50 g, 1.71 mmol) was dissolved in THF (10 mL) and MeOH (10 mL). A solution of NaOH (0.342 g, 8.56 mmol) in H_2O (10 mL) was added and the reaction mixture was stirred at room temperature under nitrogen for 48 hours. The organic solvents were removed on a rotary evaporator and 1 M $HCl_{(aq)}$ was added to the remaining aqueous solution until the pH reached 1. The resulting precipitate was collected by filtration, washed with H_2O (4 x 15 mL) and dried under high vacuum to afford the product as a white solid (0.40 g, 88%). **^{1}H NMR** (300 MHz; CD_3OD) δ: 8.34 (t, $^4J_{HH}$ = 1.4 Hz, 1 H, Ar*H*), 7.84 (d, $^4J_{HH}$ = 1.4 Hz, 2 H, Ar*H*), 4.68 (quartet, $^3J_{HF}$ = 8.4 Hz, 2 H, CH_2); **^{13}C NMR** (75 MHz; CD_3OD) δ: 168.3 (s), 159.1 (s), 134.3 (s), 125.8 (s), 125.2 (quartet, $^1J_{CF}$ = 277 Hz), 121.2 (s), 66.9 (quartet, $^2J_{CF}$ = 35.7 Hz); **^{19}F NMR** (282 MHz; CD_3OD) δ: −71.8 (t, $^3J_{FH}$ = 8.4 Hz); **HRMS** (ES) *m/z*: 263.0171 ([M – H]$^-$. $C_{10}H_6F_3O_5$ requires 263.0173).

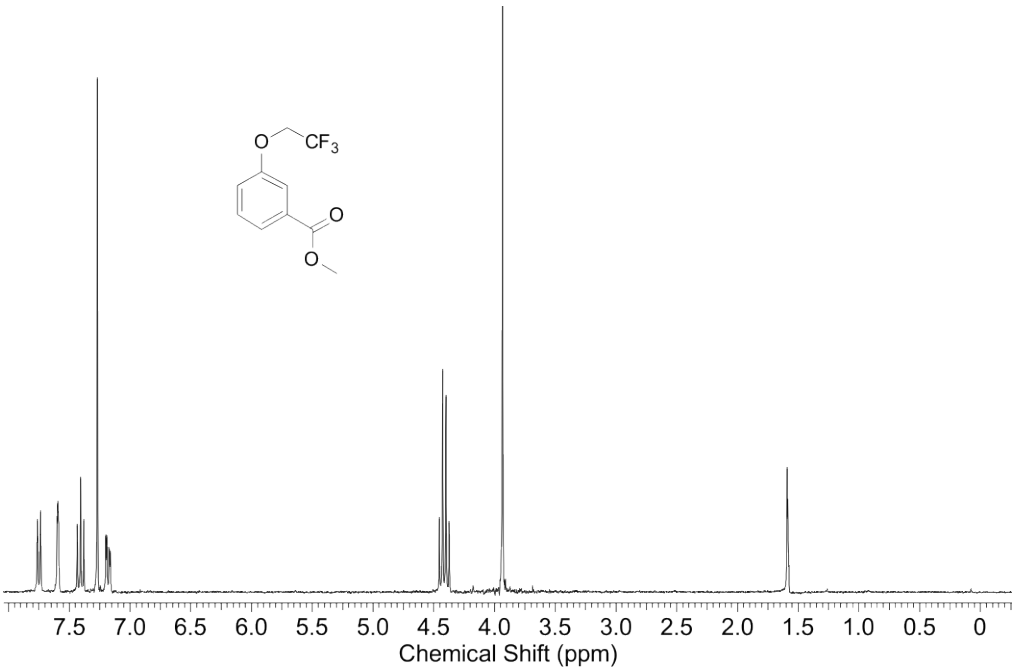


Figure S1. ^{1}H NMR spectrum (300 MHz; $CDCl_3$; 298 K) of compound **S1**

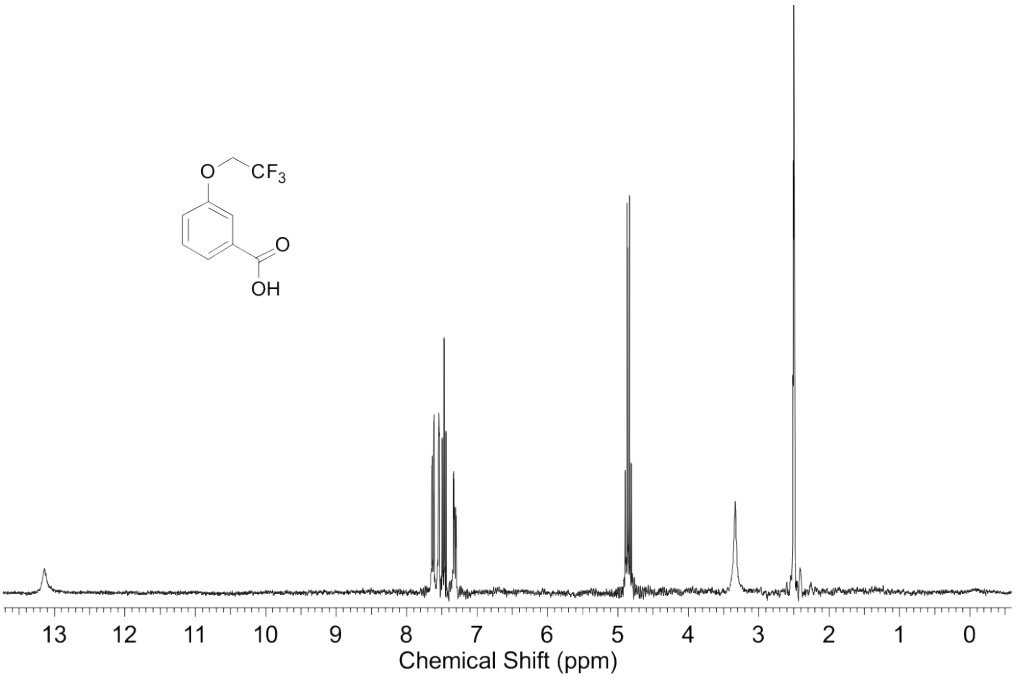


Figure S2. ^{1}H NMR spectrum (300 MHz; DMSO-d_6; 298 K) of compound **1**

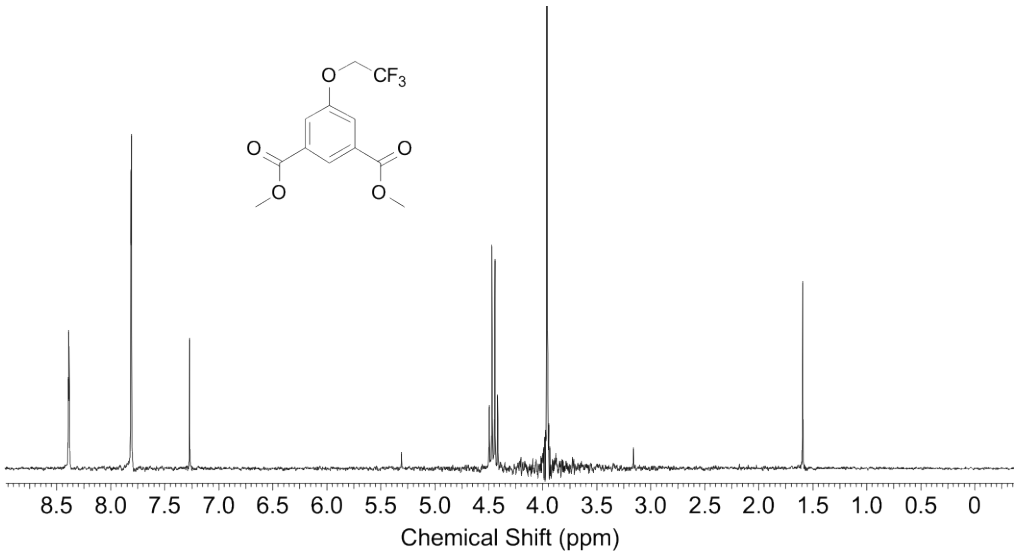


Figure S3. ^{1}H NMR spectrum (300 MHz; $CDCl_3$; 298 K) of compound **S2**

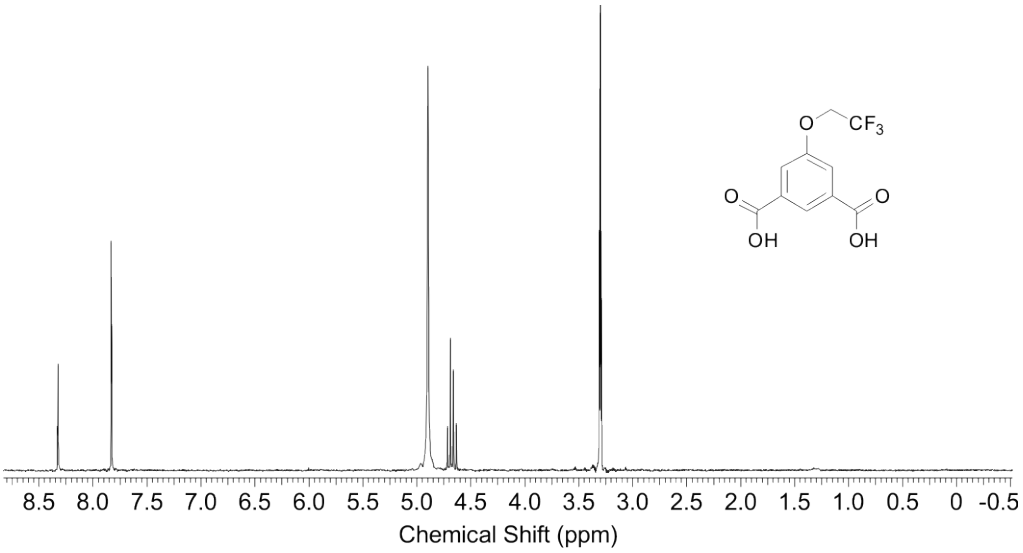


Figure S4. ^{1}H NMR spectrum (300 MHz; CD_3OD; 298 K) of compound **3**

Protocols for ^{19}F NMR Relaxation and Luminescence Titration Experiments

^{19}F relaxation experiments were carried out using an Agilent Mercury two-channel 300 MHz instrument equipped with a 5 mm z-gradient switchable 4-nucleus, tuned to ^{19}F and operated at 25 ^{o}C, 16 scan acquisitions were collected. Varian software was used; for measurement of R_1 and R_2 relaxation rates, the standard inversion-recovery or CPMG method was employed respectively with a typical 90^{o} pulse calibration. Samples were prepared by dissolving the fluorinated carboxylate species (2 μmol) and the Gd^{3+}-chelate (2 μmol) in a 50:40:10 methanol:water:D2O solution (2ml total volume) so that a 1:1 molar ratio was maintained. pH was adjusted using a concentrated NaOH solution.

Binding association constants were derived using titrations. Solutions containing the Eu^{3+}-chelate were prepared (10^{-4} M) in methanol. A 10 mM fluorinated isophthalic acid solution in methanol was prepared and pH adjusted using NaOH solution. The isophthalic acid solution was titrated into the Eu^{3+}-containing solution and fluorescence spectra were recorded. All measurements were performed in a Cary Eclipse spectrometer (with typical parameters: λ_{ex} 394 nm, 10 nm slits, 5 ms gate time, 0.1 ms delay time, 0.02 ms decay time). The titration was monitored by following changes in the emission spectrum of the lanthanide complexes in solution. At each point of the titration, an emission spectrum was recorded. Each band, corresponding to an excited state radiative transition, is integrated and linked with the titrant concentration.[4] The peak of each characteristic Eu^{3+} peak was used to determine the binding constant using Dynafit software, where data was fitted to a 1:1 binding model by least-squares iterative analysis.[5]

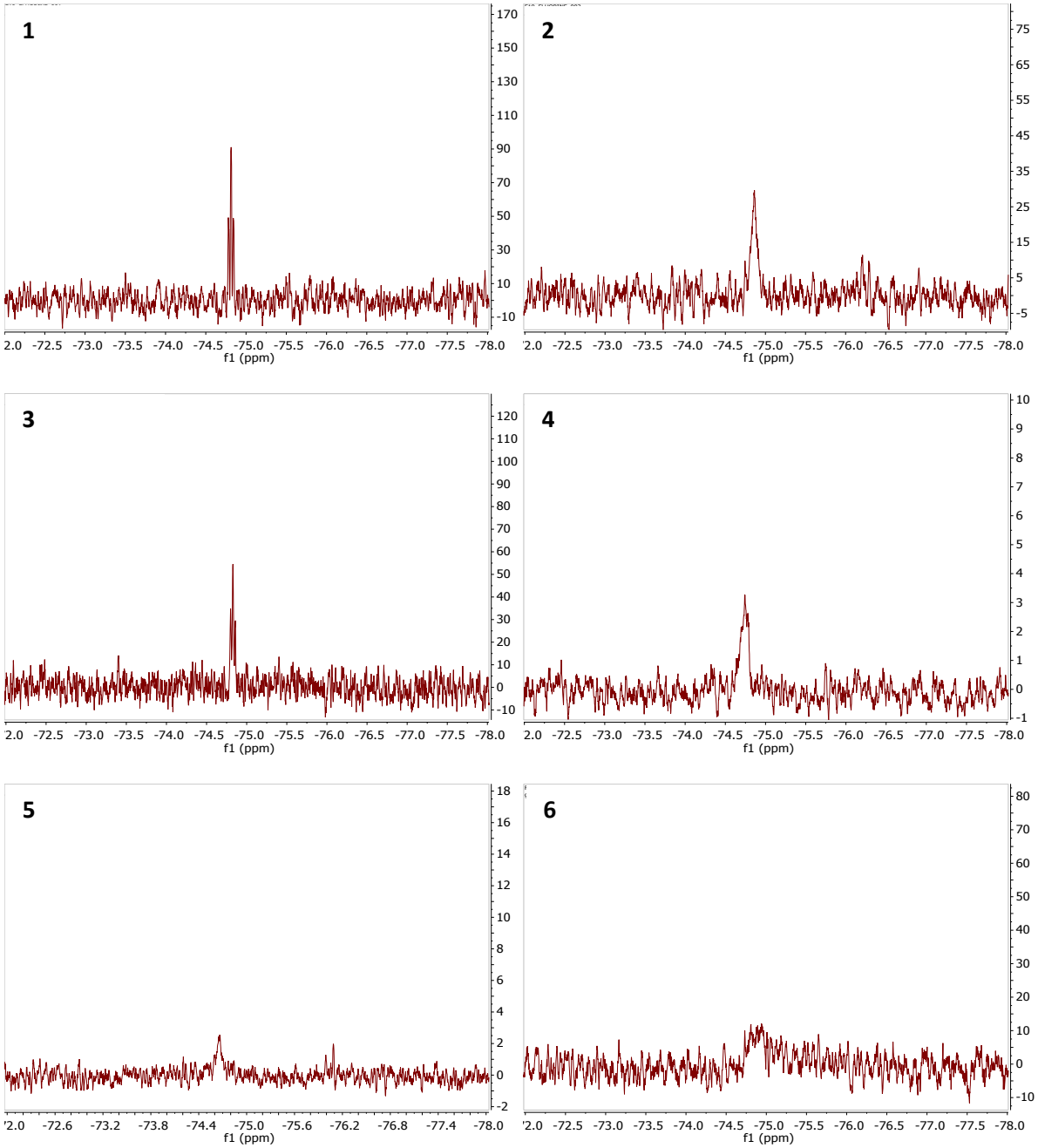


Figure S5. ^{19}F NMR spectra of compounds and complexes **1-6**, as labelled. Samples measured in 10% D_2O and 50/50 methanol/water solutions, 16 scan acquisition. Triplet peak resolution is reduced in Gd-chelate ligated species due to line broadening.

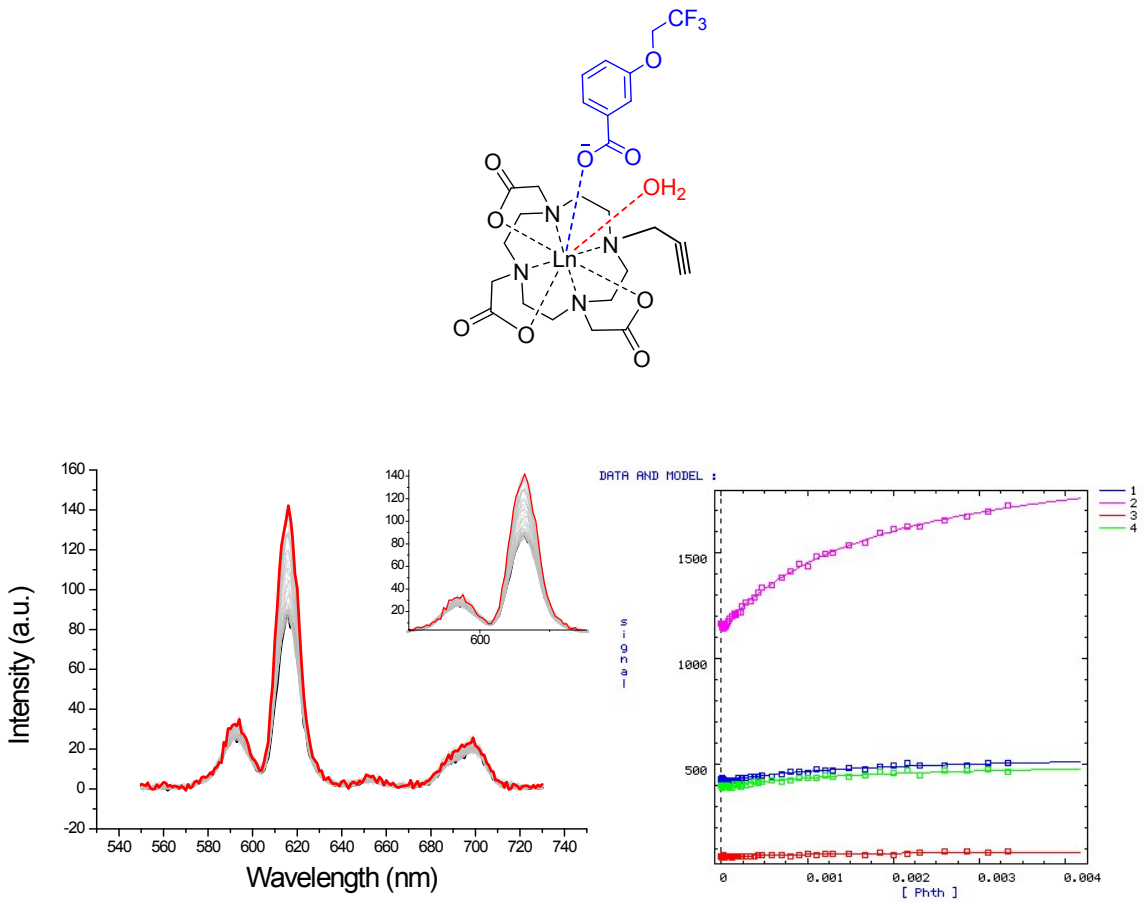


Figure S6. Schematic represents self-assembled complex. Normalised emission spectra (λ_{ex} 394 nm) of a mononuclear lanthanide DO3A chelate with increasing additions of **1** at pH 6-7 (left). Black line indicates spectrum before addition of **1**, red after saturating concentrations of **1** (0.005 M), with the intermediate concentrations shown in grey. The output from Dynafit from the fitting of the titration of a binuclear europium chelate with **1** showing data (squares) and fit (lines); the data is shown as a measure of varying emission intensity as a function of molar concentration of **1** (right). The increase in emission intensity with addition of **1** with a subsequent plateau in the behaviour is indicative of displacement of water from the coordination sphere of the chelate by **1** and hence removal of quenching hydroxyl groups. k_a values listed in Table S1.

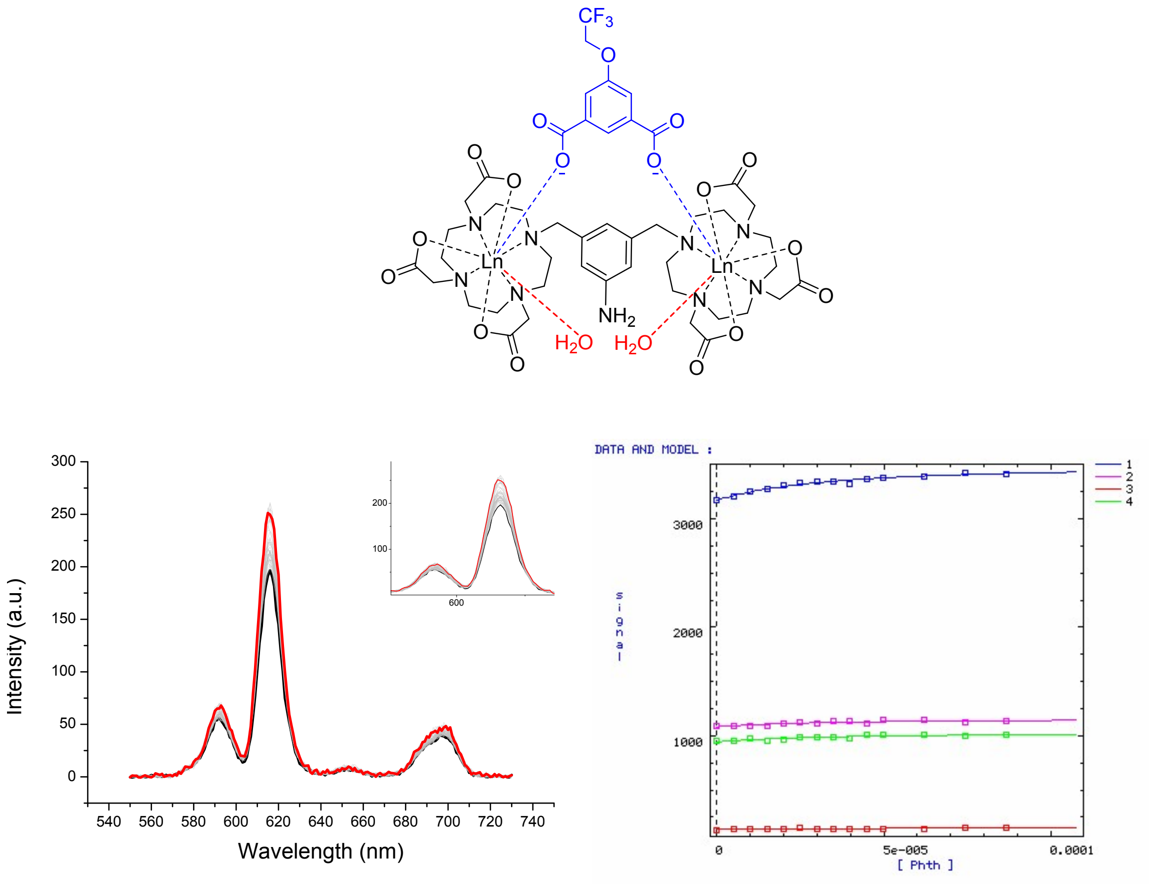
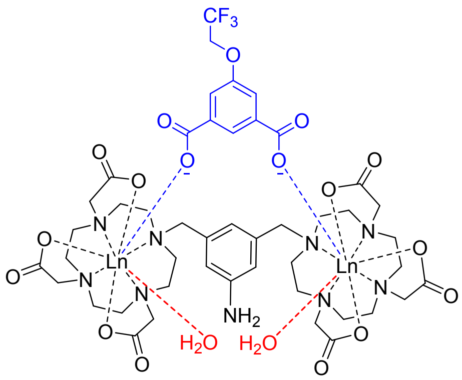
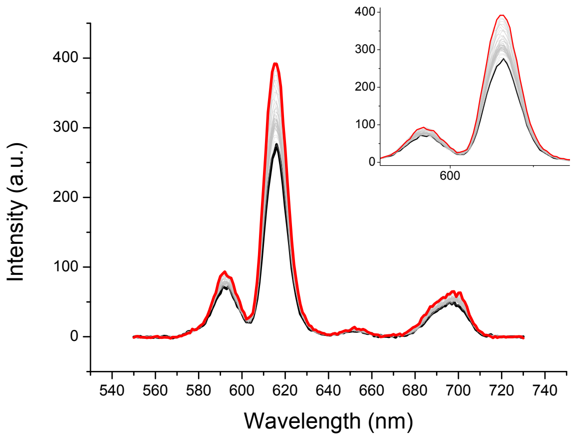


Figure S7. Schematic represents self-assembled complex. Normalised emission spectra (λ_{ex} 394 nm) of a binuclear bis-*m*-xylyl europium chelate with increasing additions of **3** at pH 3-4 (left). Black line indicates spectrum before addition of **3**, red after saturating concentrations of **3** (0.005 M), with the intermediate concentrations shown in grey. The output from Dynafit from the fitting of the titration of a binuclear europium chelate with **3** showing data (squares) and fit (lines); the data is shown as a measure of varying emission intensity as a function of molar concentration of **3** (right). The increase in emission intensity with addition of **3** with a subsequent plateau in the behaviour is indicative of displacement of water from the coordination sphere of the chelate by **3** and hence removal of quenching hydroxyl groups. k_a values listed in Table S1.





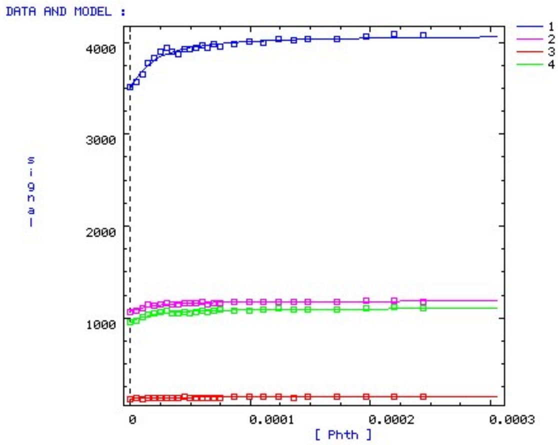


Figure S8. Schematic represents self-assembled complex. Normalised emission spectra (λ_{ex} 394 nm) of a binuclear bis-*m*-xylyl europium chelate with increasing additions of **3** at pH 6-7 (left). Black line indicates spectrum before addition of **3**, red after saturating concentrations of **3** (0.005 M), with the intermediate concentrations shown in grey. The output from Dynafit from the fitting of the titration of a binuclear europium chelate with **3** showing data (squares) and fit (lines); the data is shown as a measure of varying emission intensity as a function of molar concentration of **3** (right). The increase in emission intensity with addition of **3** with a subsequent plateau in the behaviour is indicative of displacement of water from the coordination sphere of the chelate by **3** and hence removal of quenching hydroxyl groups. k_a values listed in Table S1.

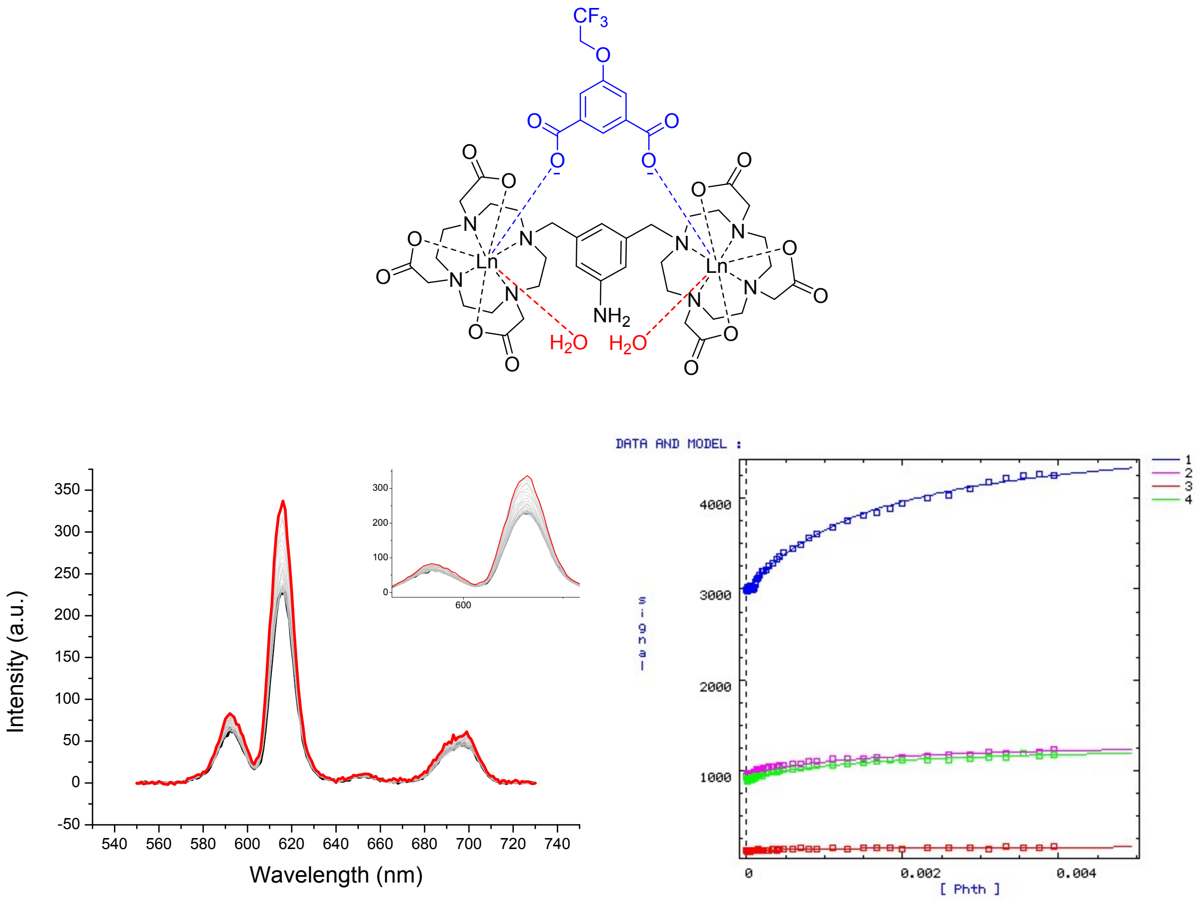


Figure S9. Schematic represents self-assembled complex. Normalised emission spectra (λ_{ex} 394 nm) of a binuclear bis-*m*-xylyl europium chelate with increasing additions of **3** at pH 9-10 (left). Black line indicates spectrum before addition of **3**, red after saturating concentrations of **3** (0.005 M), with the intermediate concentrations shown in grey. The output from Dynafit from the fitting of the titration of a binuclear europium chelate with **3** showing data (squares) and fit (lines); the data is shown as a measure of varying emission intensity as a function of molar concentration of **3** (right). The increase in emission intensity with addition of **3** with a subsequent plateau in the behaviour is indicative of displacement of water from the coordination sphere of the chelate by **3** and hence removal of quenching hydroxyl groups. k_a values listed in Table S1.

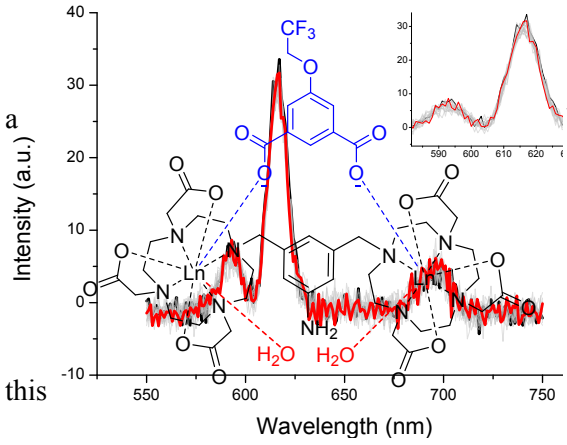


Figure S10. Schematic represents self-assembled complex. Normalised emission spectra (λ_{ex} 394 nm) of binuclear bis-*m*-xylyl europium chelate with increasing additions of **3** at pH 11-12. Black line indicates spectrum before addition of **3**, red after saturating concentrations of **3** (0.005 M), with the intermediate concentrations shown in grey. Emission intensity does not appear to vary dramatically indicating very weak binding or a lack of binding in strong alkaline environment.

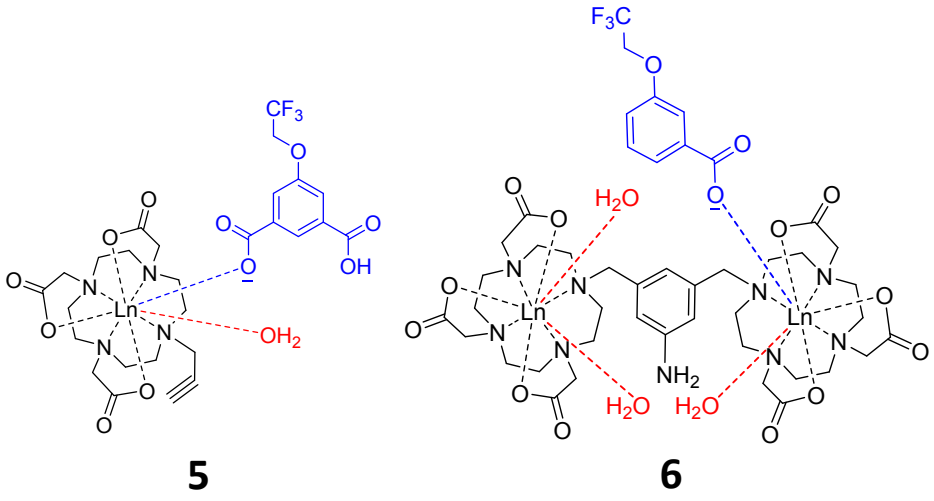


Figure S11. Coordination compounds formed through ligation of fluorinated carboxylate species with mono- and binuclear lanthanide DO3A species (control samples).

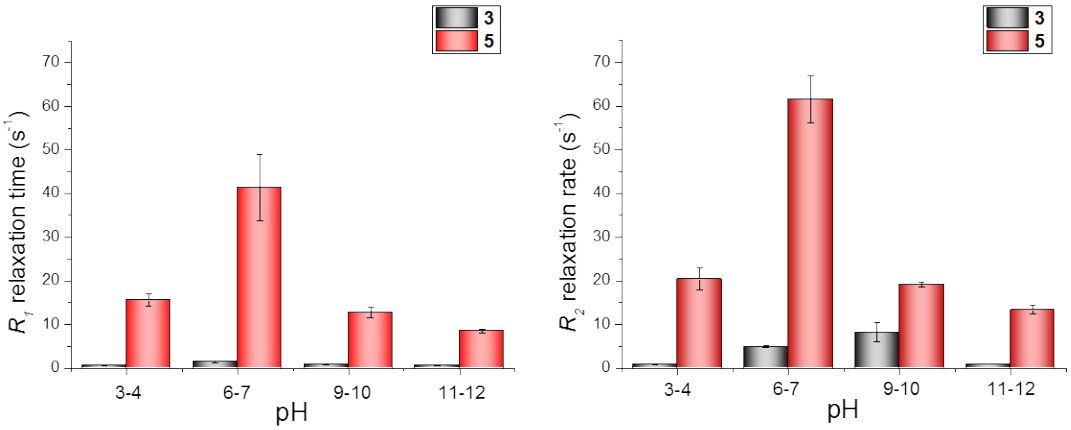


Figure S12. Binding of the fluorinated isophthalic acid derivative, **3**, with a mononuclear DO3A lanthanide chelate to yield the complex, **5**, and the ^{19}F relaxation rate (R_1 and R_2) behaviour of the complexes at different pHs, measured at 7 T and 25 ^{o}C. Error bars represent cumulative errors arising from triplicate repetitions of relaxation rate assessment.

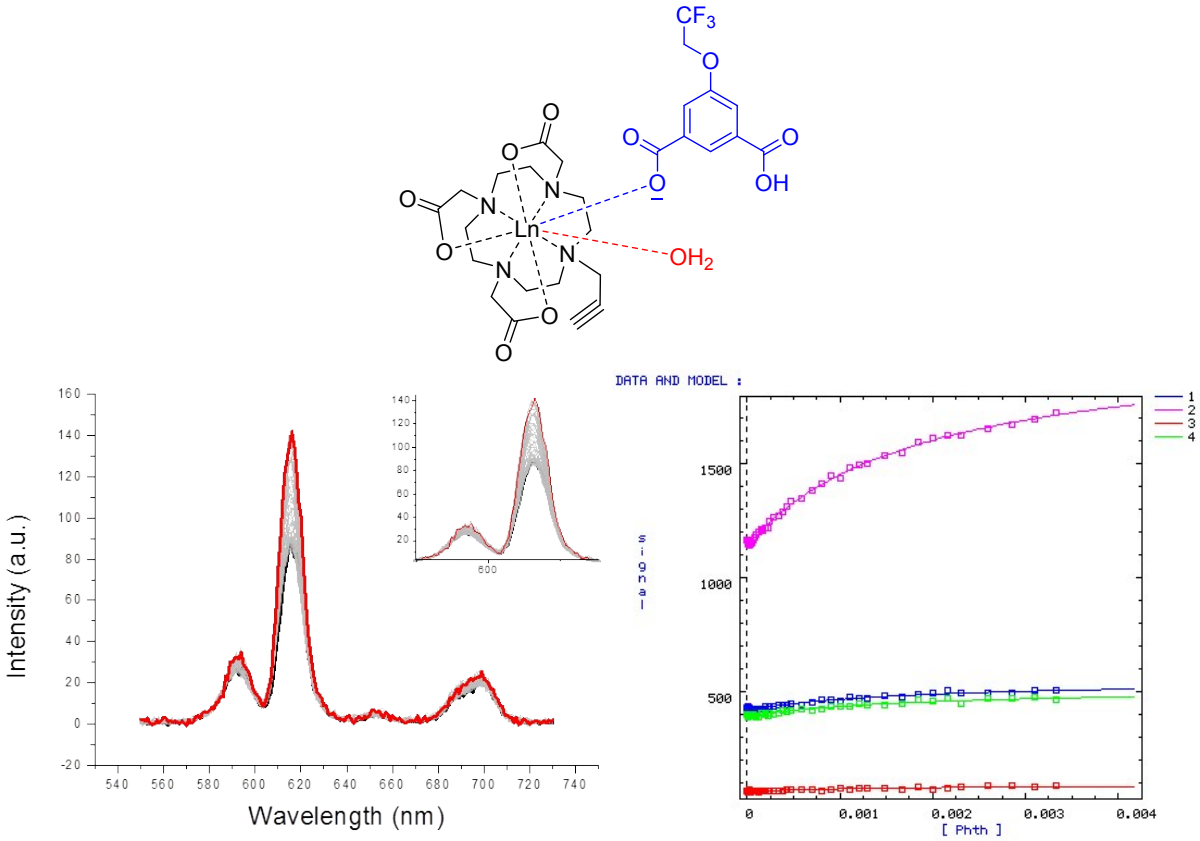
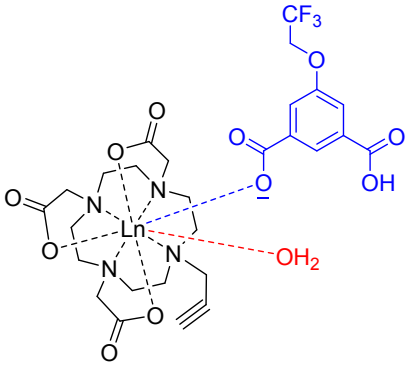


Figure S13. Schematic represents self-assembled complex. Normalised emission spectra (λ_{ex} 394 nm) of a mononuclear lanthanide DO3A chelate with increasing additions of **3** at pH 3-4. Black line indicates spectrum before addition of **3**, red after saturating concentrations of **3** (0.005 M), with the intermediate concentrations shown in grey. The output from Dynafit from the fitting of the titration with **3** showing data (squares) and fit (lines); the data is shown as a measure of varying emission intensity as a function of molar concentration of **3** (right). The increase in emission intensity with addition of **3** with a subsequent plateau in the behaviour is indicative of displacement of water from the coordination sphere of the chelate by **3** and hence removal of quenching hydroxyl groups. k_a values listed in Table S1.



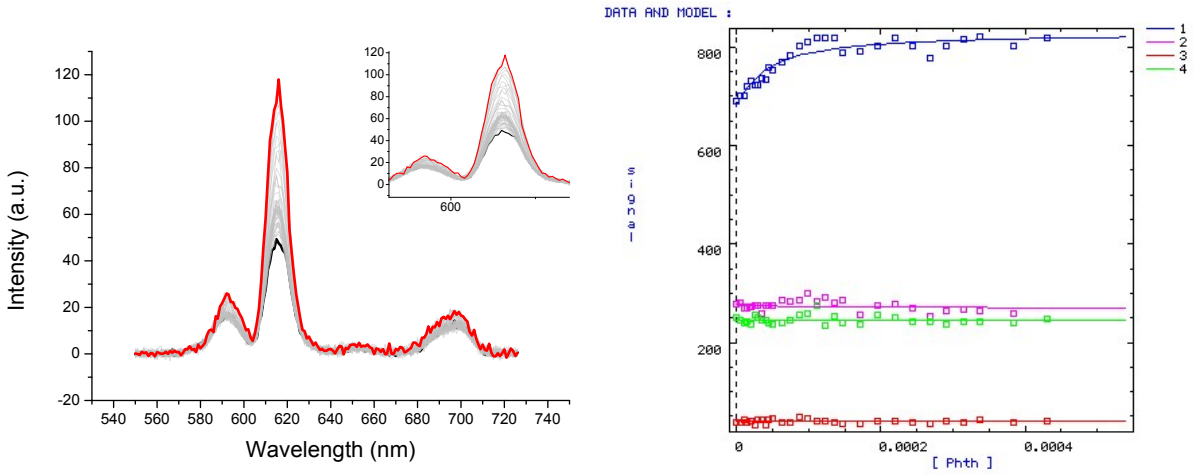
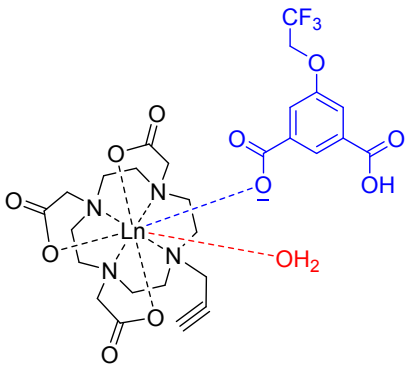


Figure S14. Schematic represents self-assembled complex. Normalised emission spectra (λ_{ex} 394 nm) of a mononuclear lanthanide DO3A chelate with increasing additions of **3** at pH 6-7. Black line indicates spectrum before addition of **3**, red after saturating concentrations of 3 (0.005 M), with the intermediate concentrations shown in grey. The output from Dynafit from the fitting of the titration with **3** showing data (squares) and fit (lines); the data is shown as a measure of varying emission intensity as a function of molar concentration of **3** (right). The increase in emission intensity with addition of **3** with a subsequent plateau in the behaviour is indicative of displacement of water from the coordination sphere of the chelate by **3** and hence removal of quenching hydroxyl groups. k_a values listed in Table S1.



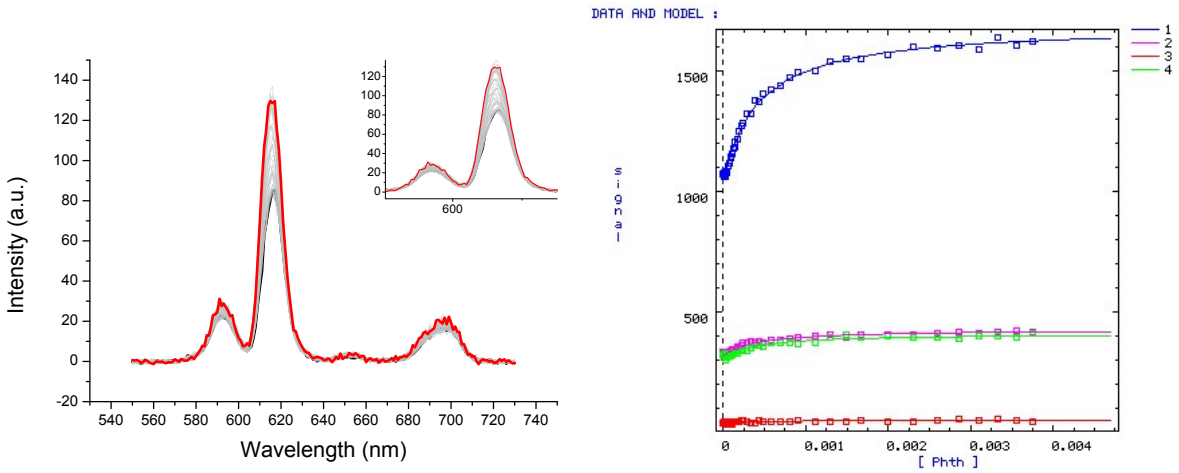
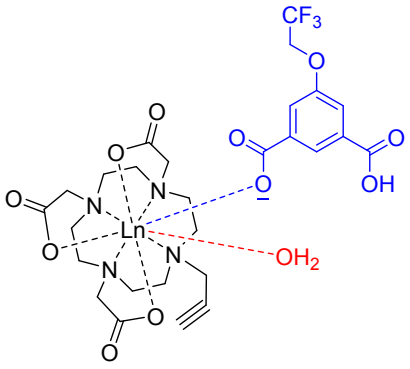


Figure S15. Schematic represents self-assembled complex. Normalised emission spectra (λ_{ex} 394 nm) of a mononuclear lanthanide DO3A chelate with increasing additions of **3** at pH 9-10. Black line indicates spectrum before addition of **3**, red after saturating concentrations of **3** (0.005 M), with the intermediate concentrations shown in grey. The output from Dynafit from the fitting of the titration with **3** showing data (squares) and fit (lines); the data is shown as a measure of varying emission intensity as a function of molar concentration of **3** (right). The increase in emission intensity with addition of **3** with a subsequent plateau in the behaviour is indicative of displacement of water from the coordination sphere of the chelate by **3** and hence removal of quenching hydroxyl groups. k_a values listed in Table S1.



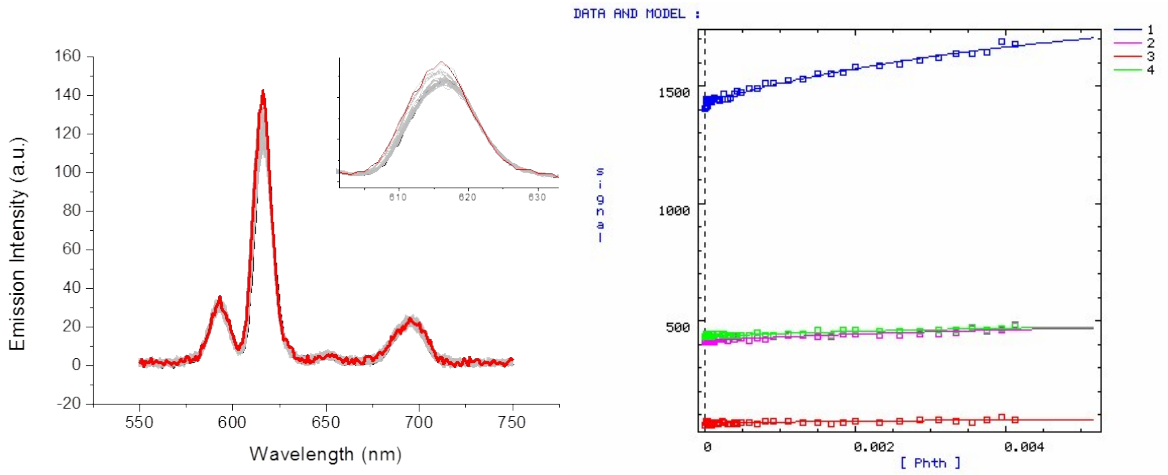
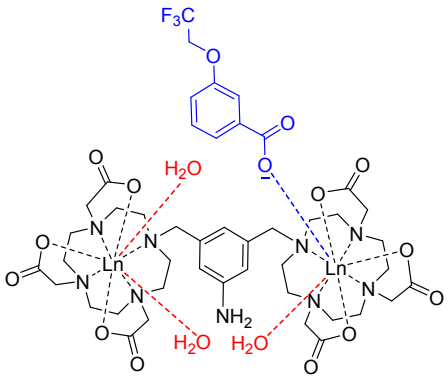


Figure S16. Schematic represents self-assembled complex. Normalised emission spectra (λ_{ex} 394 nm) of a mononuclear lanthanide DO3A chelate with increasing additions of **3** at pH 11-12. Black line indicates spectrum before addition of **3**, red after saturating concentrations of **3** (0.005 M), with the intermediate concentrations shown in grey. The output from Dynafit from the fitting of the titration with **3** showing data (squares) and fit (lines); the data is shown as a measure of varying emission intensity as a function of molar concentration of **3** (right). The increase in emission intensity with addition of **3** with a subsequent plateau in the behaviour is indicative of displacement of water from the coordination sphere of the chelate by **3** and hence removal of quenching hydroxyl groups. k_a values listed in Table S1.



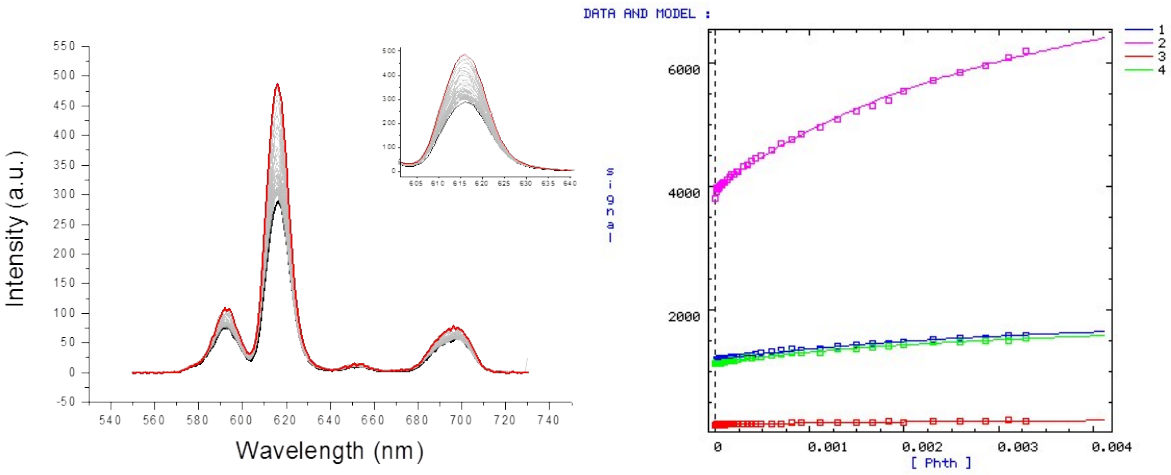


Figure S17. Schematic represents self-assembled complex. Normalised emission spectra (λ_{ex} 394 nm) of a binuclear bis-*m*-xylyl europium chelate with increasing additions of **1** at pH 6-7. Black line indicates spectrum before addition of **1**, red after saturating concentrations of **1** (0.005 M), with the intermediate concentrations shown in grey. The output from Dynafit from the fitting of the titration of a binuclear europium chelate with **1** showing data (squares) and fit (lines); the data is shown as a measure of varying emission intensity as a function of molar concentration of **1** (right). The increase in emission intensity with addition of **1** with a subsequent plateau in the behaviour is indicative of displacement of water from the coordination sphere of the chelate by **1** and hence removal of quenching hydroxyl groups. k_a values listed in Table S1.

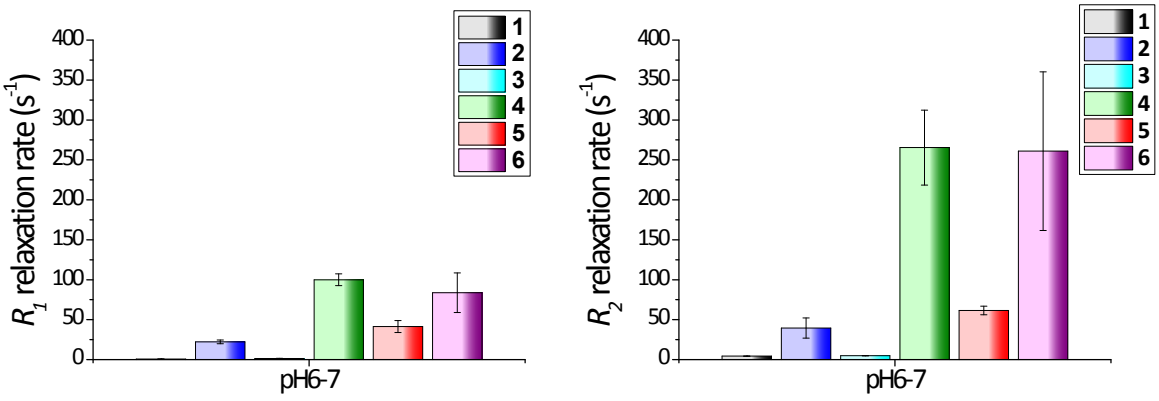


Figure S18. ^{19}F relaxation rate (R_1 and R_2) behaviour of the compounds and complexes as labelled, measured at pH 6-7 in 10% D_2O and 50/50 water/methanol solutions, 7 T and 25 ^{o}C. Error bars represent cumulative errors arising from triplicated repetitions of relaxation rate assessment.

Table S1. Longitudinal and transverse ^{19}F NMR relaxation rates (R_1 and R_2), the relative enhancement upon binding and binding association values (k_a) of fluorinated species and coordination compounds prepared, as labelled, at varying pHs conditions.

Sample	**pH**	R_1 **(s^{-1})**	R_2 **(s^{-1})**	R_1/R_2	k_a **(M^{-1}) [log k_a]**[a]	**^{19}F NMR Line Broadening (ppm)**[b]
1	6-7	0.72±0.06	4.39±0.17	0.16	n/a	0.113
2	6-7	22.26±2.36	39.56±12.7	0.56	527-565 [2.74±0.02]	0.223
3	3-4	0.68±0.04	0.93±0.06	0.73	n/a	0.100
	6-7	1.47±0.27	4.89±0.19	0.30	n/a	
	9-10	0.97±0.10	8.21±2.14	0.12	n/a	
	11-12	0.65±0.01	0.97±0.01	0.67	n/a	
4	3-4	43.02±6.41	91.27±20.34	0.47	32770-47960 [4.60±0.08]	0.307
	6-7	99.95±7.33	265.40±46.82	0.38	69859-83283 [4.89±0.04]	
	9-10	9.25±0.59	25.04±3.43	0.37	574-615 [2.78±0.02]	
	11-12	1.90 ±0.14	26.78±1.17	0.07	n/a	

5	3-4	15.57±1.38	20.36±2.52	0.77	475-892 [2.82±0.14]	0.179
	6-7	41.42±7.57	61.56±5.43	0.67	21000-33000 [4.42±0.10]	
	9-10	12.74±1.17	19.20±0.51	0.66	2400-2500 [3.39±0.01]	
	11-12	8.57±0.43	13.34±1.03	0.64	122-167 [2.16±0.07]	
6	6-7	83.79±24.75	260.95±99.23	0.32	245-269 [2.41±0.02]	0.502

[a] Binding data were fitted to a 1:1 binding model of mono- or bi-nuclear compounds titrated with 10 mM **1** or **3** (see Experimental section) by least-squares iterative analysis using Dynafit software; [b] Line breadth was measured using MestraNova software by measuring the widest part of the -74.7 ppm peak in the ^{19}F NMR spectrum, acquired using 16 scans.

References

1 M. Tropiano, N. L. Kilah, M. Morten, H. Rahman, J. J. Davis, P. D. Beer and S. Faulkner, *J. Am. Chem. Soc.*, 2011, **133**, 11847.

2 M. P. Placidi, L. S. Natrajan, D. Sykes, A. M. Kenwright and S. Faulkner, *Helv. Chim. Acta*, 2009, **92**, 2427.

3 Procedure adapted from P. Tang, Q. Wu, X. Wu, Z. Zheng, W. Ji, PCT Int. Appl., 2012019428, 16 February 2012

4 M. Tropiano, O. A. Blackburn, J. A. Tilney, L. R. Hill, M. P. Placidi, R. J. Aarons, D. Sykes, M. W. Jones, A. M. Kenwright, J. S. Snaith, T. J. Sorensen and S. Faulkner, *Chem. Eur. J.*, 2013, **19**, 16566.

5 J. A. Tilney, T. J. Sorensen, B. P. Burton-Pye and S. Faulkner, *Dalton T.*, 2011, **40**, 12063.