Electronic Supporting Information

Magnetofluorescent micellar complexes of terbium(III) as potential bimodal contrast agents for magnetic resonance and optical imaging

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Contents

1 Experimental

1.1 Materials

Reagents and solvents were obtained from Sigma–Aldrich (Bornem, Belgium), Acros Organics (Geel, Belgium), ChemLab (Zedelgem, Belgium), Matrix Scientific (Columbia, USA) and BDH Prolabo (Leuven, Belgium), and were used without further purification. Terbium(III) chloride hexahydrate was obtained from Sigma–Aldrich (Bornem, Belgium).

1.2 Instrumentation

^{1}H and spectra were recorded by using a Bruker Avance 300 spectrometer (Bruker, Karlsruhe, Germany), operating at 300 MHz for ^{1}H.

IR spectra were measured by using a Bruker Vertex 70 FT-IR spectrometer (Bruker, Ettlingen, Germany).

Mass spectra were obtained by using a Thermo Finnigan LCQ Advantage mass spectrometer. Samples for the mass spectrometry were prepared by dissolving the product (2 mg) in methanol (1 mL), then adding 200 mL of this solution to a water/methanol mixture (50:50, 800 mL). The resulting solution was injected at a flow rate of 5 mL min^{-1}.

TXRF measurements were performed on a Bruker S2 Picofox (Bruker, Berlin, Germany) with a molybdenum source. Terbium(III) solutions of approximately 1000 ppm in milli-Q water were prepared and 500 µL of this solution was mixed with 500 µL of a 1000 ppm Chem-Lab gallium standard solution (1000 µg/mL, 2-5% HNO_3). 10 µL of this mixture with similar Tb(III)-Ga(III) concentrations was put on a Bruker AXS quartz glass sample plate for measurement.

Solutions were dispersed in a 180 W Bandelin Sonorex RK 510 H sonicator equipped with a thermostatic heating bath.

Absorption spectra were measured on a Varian Cary 5000 spectrophotometer on freshly prepared aqua solutions in quartz Suprasil cells (115F-QS) with an optical pathlength of 1 cm.

Emission spectra and luminescence decays of Tb^{III} micellar complexes were recorded on an Edinburgh Instruments FS920 steady state spectrofluorimeter. This instrument is equipped with a 450W xenon arc lamp, a high energy microsecond flashlamp mF900H and an extended red-sensitive photomultiplier (185–1010 nm, Hamamatsu R 2658P). All spectra are corrected for the instrumental functions. Luminescence decays were determined under ligand excitation (265 nm) monitoring emission of the $^5D_4 \rightarrow {}^7F_J$ (J = 6 - 3) transition for Tb^{III} complexes. Luminescence decays were analyzed using Edinburgh software; lifetimes are averages of at least three measurements. Quantum yields were determined by a comparative method with a standard reference; estimated experimental errors for quantum yield determination ±10%. Rhodamine 101 (Sigma) in ethanol (Q=100%) was used as a standard for the complexes. Solutions with a concentration of about 10^{-5} M were prepared to obtain an optical density lower than 0.05 at the excitation wavelength.

Relaxometry: ^{1}H T_1 and T_2 measurements were performed at 310 K at 0.47, 1.41, 7.05, and 11.75 T on Minispec mq-20, mq-60, Avance-300 and Avance-500 from Bruker, respectively.

DLS measurements: Photon correlation spectroscopy was performed at room temperature with a BIC multiangle laser light-scattering system with a 90° scattering angle (Brookhaven Instruments Corporation, Holtsville, USA). The intensity weighted micellar diameter was measured on 0.1 wt% diluted suspensions in Milli-Q water, sonicated for 15 mins, passed through a 200 nm PTFE filter before analysis and calculated by a non-negatively constrained least-squares (multiple pass) routine.

1.3 Synthesis and characterization of Ligands and Complexes

Chloroacetamides, cis-DOTA-BC_{12}PheA, cis-DOTA-BC_{14}PheA, trans-DOTA-BC_{12}PheA, and trans-DOTA-BC_{14}PheA and complexes.

2-chloro-N-(4-dodecylphenyl)acetamide and 2-chloro-N-(4-tetradecylphenyl)acetamide

4-dodecyaniline (1g, 3.82 mmol, 1 eq.) or 4-tetradecyaniline (1g, 3.45 mmol, 1 eq.) were dissolved in dichloromethane (10 mL) and potassium carbonate (1.32g or 1.19 g, 9.56 mmol or 8.64 mmol, 2.5 eq.) was added and the suspension was stirred for 30 minutes at ambient temperature. Chloroacetyl chloride (0.457 g or 0.429 g, 4.21 mmol or 3.80 mmol, 1.1 eq.) was slowly added and mixed for 10 minutes. The reaction was held at reflux for 4 hours then allowed to cool to ambient temperature, after which the filtrate was concentrated to obtain a residue which was recrystallized in hexane to afford the final product.

2-chloro-N-(4-dodecylphenyl)acetamide: Yield: 1.15 g, 89 %; ^{1}H NMR (300 MHz, CD_2Cl_2, 25 °C, TMS): δ = 0.91 (t, 3H, C***H***$_3$-$(CH_2)_9$-CH_2- CH_2-Ar), 1.30, 1.32 (m, 18H, CH_3-(C***H***$_2$)$_9$-CH_2-CH_2-Ar), 1.62 (m, 2H, CH_3-$(CH_2)_9$-C***H***$_2$-CH_2-Ar), 2.62 ppm (t, 2H, CH_3-$(CH_2)_9$-CH_2-C***H***$_2$-Ar), 4.21 (s, 2H, Cl-C***H***$_2$-CO), 7.19, 7.22 (d, 2H, phenyl C***H***), 7.45, 7.48 (d, 2H, phenyl C**H**), 8.16 ppm (s, 1H, amide N**H**). ESI-MS (+ve mode): *m/z*: calcd 360.9 $[M+Na]^+$, found 363.0 $[M+Na]^+$, 699.8 $[2M+Na]^+$.

2-chloro-N-(4-tetradecylphenyl)acetamide: Yield: 0.64 g, 51 %; ^{1}H NMR (300 MHz, CD_2Cl_2, 25 °C, TMS): δ = 0.91 (t, 3H, C***H***$_3$-$(CH_2)_{11}$-CH_2- CH_2-Ar), 1.29, 1.34 (m, 22H, CH_3-(C***H***$_2$)$_{11}$-CH_2-CH_2-Ar), 1.62 (m, 2H, CH_3-$(CH_2)_{11}$-C***H***$_2$-CH_2-Ar), 2.62 ppm (t, 2H, CH_3-$(CH_2)_{11}$-CH_2-C***H***$_2$-Ar), 4.21 (s, 2H, Cl-C***H***$_2$-CO), 7.19, 7.22 (d, 2H, phenyl C***H***), 7.45, 7.48 (d, 2H,

phenyl C***H***), 8.16 ppm (s, 1H, amide N***H***). ESI-MS (+ve mode): *m/z*: calcd 389.0 $[M+Na]^+$, found 391.1 $[M+Na]^+$, 754.1 $[2M+Na]^+$.

Cis-DOTA-BC$_{12/14}$PheA

Di-tert-butyl 2,2'-(1,4,7,10-tetraazacyclododecane-1,4-diyl)diacetate

1,4,7,10-tetraazacyclododecane (1 g, 5.63 mmol, 1 eq.) was dissolved in anhydrous chloroform (80 mL), placed under an argon atmosphere, DIPEA (1.819 g, 14.1 mmol, 2.5 eq.) was added, and the solution was mixed for 15 minutes. Tert-butyl bromoacetate (2.197 g, 11.3 mmol, 2 eq.) was added slowly for approximately 30 minutes and the reaction was allowed to continuously stir for a further 12 hours. The resulting solution was washed with water (3 x 60 mL) and the organic phase dried over Mg_2SO_4. The solvent was removed and crude product was purified by column chromatography (basic Al_2O_3, dicholoromethane/methanol, 98:2) to afford the final colourless oily compound (0.87 g, 39 %).

^{1}H NMR (300 MHZ, $CDCl_3$, 25 °C, TMS): δ = 1.46 (s, 18H, (C***H***$_3$)$_6$-O-CO), 2.7 (m, 4H, O-CO-N-(CH$_2$)$_2$-N-(C***H***$_2$)$_2$-N-(CH$_2$)$_2$-N-CO-O), 2.78 (m, 12H, O-CO-CH$_2$-N-(C***H***$_2$)$_4$-C***H***$_2$), 3.32 ppm (m, 4H, O-CO-C***H***$_2$-N). ESI-MS (+ve mode): *m/z*: calcd 401.6 $[M+H]^+$, found 401.6 $[M+H]^+$, 423.8 $[M+Na]^+$.

Di-tert-butyl 2,2'-(7,10-bis(2-((4-dodecylphenyl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4-diyl)diacetate (protected-cis-DOTA-BC$_{12}$PhenA) and di-tert-butyl 2,2'-(7,10-bis(2-oxo-2-((4-tetradecylphenyl)amino)ethyl)-1,4,7,10-tetraazacyclododecane-1,4-diyl)diacetate (protected-cis-DOTA-BC$_{14}$PheA)

Di-tert-butyl 2,2'-(1,4,7,10-tetraazacyclododecane-1,4-diyl)diacetate (0.23g, 0.57 mmol, 1 eq.) was dissolved in dry acetonitrile (15 mL) and potassium carbonate (0.397 g, 2.87 mmol, 5 eq.) was added with the suspension being heated to reflux. 2-chloro-N-(4-dodecylphenyl)acetamide (0.485 g, 1.44 mmol, 2.5 eq.) or 2-chloro-N-(4-tetradecylphenyl)acetamide (0.525 g, 1.44 mmol, 2.5 eq.) was dissolved in warm acetonitrile (50 mL), added drop-wise and the reaction was held at reflux for 48 hours. After allowing the suspension to cool to ambient temperature, the potassium carbonate was separated by filtration and the solvent was removed. The crude product was purified by column chromatography (neutral Al_2O_3, dichloromethane/methanol, 98:2) to afford the final colourless oily product.

Protected-cis-DOTA-BC$_{12}$PhenA: Yield: 0.31 g, 54 %; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.88 (t, 6H, C***H***$_3$-(CH$_2$)$_{10}$-CH$_2$-Ar), 1.26 (m, 38H, CH$_3$-(C***H***$_2$)$_{10}$-CH$_2$-Ar), 1.40 (s, 18H, (C***H***$_3$)$_6$-O-CO), 2.55 (t, 4H, CH$_3$-(CH$_2$)$_{10}$-C***H***$_2$-Ar), 2.77, 2.81, 2.87 (m, 12H, O-CO-N-(C***H***$_2$)$_2$-N-(CH$_2$)$_2$-N-(C***H***$_2$)$_2$-N-CO-O), 3.01 (m, 4H, O-CO-N-(C***H***$_2$)$_2$-N-CO-O), 3.18 (m, 4H, N-C***H***$_2$-CO-NH), 3.26 (m, 4H, N-C***H***$_2$-CO-O), 7.06, 7.09 (d, 4H, phenyl C***H***), 7.46, 7.49 (d, 4H, phenyl C***H***), 9.49 ppm (s, 2H, amide N**H**). ESI-MS (+ve mode): *m/z*: calcd 1026.5 $[M+Na]^+$, found 1026.4 $[M+Na]^+$.

Protected-cis-DOTA-BC$_{14}$PhenA: Yield: 0.35 g, 57 %; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.87 (t, 6H, C***H***$_3$-(CH$_2$)$_{12}$-CH$_2$-Ar), 1.26 (m, 44H, CH$_3$-(C***H***$_2$)$_{12}$-CH$_2$-Ar), 1.40 (s, 18H, (C***H***$_3$)$_6$-O-CO), 2.54 (t, 4H, CH$_3$-(CH$_2$)$_{12}$-C***H***$_2$-Ar), 2.77, 2.81, 2.87 (m, 12H, O-CO-N-(C***H***$_2$)$_2$-N-(CH$_2$)$_2$-N-(C***H***$_2$)$_2$-N-CO-O), 3.01 (m, 4H, O-CO-N-(C***H***$_2$)$_2$-N-CO-O), 3.18 (m, 4H, N-C***H***$_2$-CO-NH), 3.26 (m, 4H, N-C***H***$_2$-CO-O), 7.06, 7.09 (d, 4H, phenyl C***H***), 7.46, 7.49 (d, 4H, phenyl C***H***), 9.49 ppm (s, 2H, amide N***H***). ESI-MS (+ve mode): *m/z*: calcd 1082.6 $[M+Na]^+$, found 1084.1 $[M+Na]^+$.

2,2'-(7,10-bis(2-((4-dodecylphenyl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4-diyl)diacetic acid (cis-DOTA-BC$_{12}$PhenA) and 2,2'-(7,10-bis(2-((4-tetradecylphenyl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4-diyl)diacetic acid (cis-DOTA-BC$_{14}$PhenA)

Di-tert-butyl 2,2'-(7,10-bis(2-((4-dodecylphenyl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4-diyl)diacetate (0.3 g, 0.3 mmol) or di-tert-butyl 2,2'-(7,10-bis(2-oxo-2-((4-tetradecylphenyl)amino)ethyl)-1,4,7,10-tetraazacyclododecane-1,4-diyl)diacetate (0.3 g, 0.28 mmol) was dissolved in dichloromethane (5 mL), trifluoroacetic acid (5 mL) was added and mixed at ambient temperature for 12 hours. Dichloromethane (5 mL) was added and the solvents removed, followed by adding at additional amount of dichloromethane (5 mL) and solvents removed a second time affording the final colourless oily product.

Cis-DOTA-BC$_{12}$PhenA: Yield: quantitative; ^{1}H NMR (300 MHz, pyridine-D5, 25 °C, TMS): δ = 0.89 (t, 6H, C***H***$_3$-(CH$_2$)$_9$-CH$_2$- CH$_2$-Ar), 1.27 (m, 36H, CH$_3$-(C***H***$_2$)$_9$-CH$_2$-Ar), 1.58 (m, 4H, CH$_3$-(CH$_2$)$_9$-C***H***$_2$-CH$_2$-Ar), 2.55 (t, 4H, CH$_3$-(CH$_2$)$_9$-CH$_2$-C***H***$_2$-Ar), 3.38 (m, 16H, DOTA C***H***$_2$), 4.12 (m, 4H, N-C***H***$_2$-CO-NH), 4.27 (m, 4H, N-C***H***$_2$-CO-O), 7.16, 7.19 (d, 4H, phenyl C***H***), 8.09, 8.06 (d, 4H, phenyl C***H***), 11.42 ppm (s, 2H, amide N***H***). IR: $\tilde{\nu}_{max}$ = 1635 (C=O free acid), 1558 cm^{-1} (C=O amide). ESI-MS (+ve mode): *m/z*: calcd 914.3 $[M+Na]^+$, found 914.2 $[M+Na]^+$.

Cis-DOTA-BC$_{14}$PhenA: Yield: quantative; ^{1}H NMR (300 MHz, pyridine-D5, 25 °C, TMS): δ = 0.88 (t, 6H, C***H***$_3$-(CH$_2$)$_{11}$-CH$_2$-CH$_2$-Ar), 1.29 (m, 42H, CH$_3$-(C***H***$_2$)$_{11}$-CH$_2$-Ar), 1.59 (m, 4H, CH$_3$-(CH$_2$)$_{11}$-C***H***$_2$-CH$_2$-Ar), 2.55 (t, 4H, CH$_3$-(CH$_2$)$_{11}$-CH$_2$-C***H***$_2$-Ar), 3.36 (m, 16H, DOTA C***H***$_2$), 4.11 (m, 4H, N-C***H***$_2$-CO-NH), 4.25 (m, 4H, N-C***H***$_2$-CO-O), 7.17, 7.20 (d, 4H, phenyl C***H***), 8.07, 8.09 (d, 4H, phenyl C***H***), 11.40 ppm (s, 2H, amide N***H***). IR: $\tilde{\nu}_{max}$ = 1636 (C=O free acid), 1559 cm^{-1} (C=O amide). ESI-MS (+ve mode): m/z: calcd 970.4 [M+Na]+, found 971.4 [M+Na]+.

Trans-DOTA-BC$_{12/14}$PheA

4,10-Bis((benzyloxy)carbonyl)-4,10-diaza-1,7-diazoniacyclododecane-1,7-diium chloride

1,4,7,10-tetraazacyclododecane (1 g, 5.8 mmol, 1 eq.) was dissolved in chloroform (40 mL) in an ice-bath and benzyl chloroformate (1.98 g, 11.61 mmol, 2 eq.) in chloroform (10 mL) was added drop-wise. The solution was allowed to warm to ambient temperature and mixing continued for 24 hours. The solvent was evaporated and the product suspended in diethyl ether (10 mL), filtered and washed with diethyl ether (2 x 10 mL). The solid was dried to afford a white powder (quantitative yield).

^{1}H NMR (300 MHZ, D_2O, 25 °C, TMS): δ = 3.07 (m, 8H, C***H***$_2$-N-C***H***$_2$), 3.50 (m, 8H, C***H***$_2$-NCO_2-C***H***$_2$), 5.07 (s, 4H, O-C***H***$_2$-phenyl), 7.33 ppm (m, 10H, phenyl C***H***). ESI-MS (+ve mode): *m/z*: calcd 441.5 $[M+H]^+$, found 441.8 $[M+H]^+$.

Dibenzyl 4,10-bis(2-(tert-butoxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,7-dicarboxylate

4,10-Bis((benzyloxy)carbonyl)-4,10-diaza-1,7-diazoniacyclododecane-1,7-diium chloride (1 g, 1.95 mmol, 1 eq.) was suspended in acetonitrile (20 mL) and DIPEA (1.259 g, 9.74 mmol, 5 eq.) mixed in acetonitrile (8 mL) was added turning the solution clear. Tert-butyl bromoacetate (1.14 g, 5.84 mmol, 3 eq.) was mixed in acetonitrile (4 mL) and added. The solution was heated at 60 °C for 12 hours and then allowed to cool to ambient temperature. The solvent was evaporated and the residue extracted with diethyl ether (20 mL) and water (20 mL). The organic layer was washed further with water (10 mL), sodium hydroxide solution (0.5 g/ 10 mL) and water (10 mL). The organic layer was dried over Mg_2SO_4 and solvent evaporated. The crude product was purified by column chromatography (neutral Al_2O_3, dichloromethane/methanol, 98:2) to afford the final colourless oily compound (1.1 g, 84 %).

^{1}H NMR (300 MHZ, $CDCl_3$, 25 °C, TMS): δ = 1.43 (s, 18H, CO-O-C-(C***H***$_3$)$_3$), 2.87 (m, 8H, C***H***$_2$-N-C***H***$_2$), 3.13 (s, 4H, N-C***H***$_2$-CO-O), 3.42 (m, 8H, C***H***$_2$-NCOO-C***H***$_2$), 5.13 (s, 4H, CO-O-C***H***$_2$-Ar), 10.02 ppm (m, 10H, phenyl C***H***). ESI-MS (+ve mode): *m/z*: calcd 669.8 $[M+H]^+$, found 669.7 $[M+H]^+$.

Di-tert-butyl 2,2'-(1,4,7,10-tetraazacyclododecane-1,7-diyl)diacetate

Dibenzyl 4,10-bis(2-(tert-butoxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,7-dicarboxylate (1.1 g, 1.64 mmol) was dissolved in dry methanol (10 mL) in a high pressure vessel and Pd-C catalyst (5 % Pd, 20 wt%, 0.218 g) was added. The vessel was placed on a Parr-aparatus, pressurised with hydrogen gas (40 p.s.i) and mixed for 12 hours. The solvents and by-products were removed under reduced pressure to afford the final oily colourless compound (quantitative yield).

^{1}H NMR (300 MHZ, $CDCl_3$, 25 °C, TMS): δ = 1.46 (s, 18H, CO-O-C-(C***H***$_3$)$_3$), 2.68 (m, 8H, C***H***$_2$-NH-C***H***$_2$), 2.87 (m, 8H, C***H***$_2$-NCH_2-C***H***$_2$), 3.35 ppm (s, 4H, N-C***H***$_2$-CO-O), ESI-MS (+ve mode): *m/z*: calcd 401.6 $[M+H]^+$, found 401.6 $[M+H]^+$, 423.8 $[M+Na]^+$.

Di-tert-butyl 2,2'-(4,10-bis(2-((4-dodecylphenyl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,7-diyl)diacetate (protected-trans-DOTA-BC$_{12}$PhenA) and di-tert-butyl 2,2'-(4,10-bis(2-oxo-2-((4-tetradecylphenyl)amino)ethyl)-1,4,7,10-tetraazacyclododecane-1,7-diyl)diacetate (protected-trans-DOTA-BC$_{14}$PhenA)

Di-tert-butyl 2,2'-(1,4,7,10-tetraazacyclododecane-1,7-diyl)diacetate (0.171 /0.13 g, 0.428/0.325 mmol, 1 eq.) was dissolved in dry acetonitrile (15 mL) and potassium carbonate (0.296 g, 2.138 mmol, 5 eq.) was added with the suspension being heated to reflux. 2-chloro-N-(4-dodecylphenyl)acetamide (0.361 g, 1.07 mmol, 2.5 eq.) or 2-chloro-N-(4-tetradecylphenyl)acetamide (0.297 g, 0.812 mmol, 2.5 eq.) was dissolved in warm acetonitrile (50 mL), added drop-wise and the reaction was held at reflux for 48 hours. After allowing the suspension to cool to ambient temperature, the potassium carbonate was separated by filtration and the solvent was removed. The crude product was purified by column chromatography (neutral Al_2O_3, dichloromethane/methanol, 98:2) to afford the final colourless oily product.

Protected-trans-DOTA-BC$_{12}$PhenA: Yield: 0.203 g, 47 %. ^{1}H NMR (300 MHZ, $CDCl_3$, 25 °C, TMS): δ = 0.88 (t, 6H, C***H***$_3$-$(CH_2)_9$-CH_2-CH_2-Ar), 1.25 (m, 38H, CH_3-(C***H***$_2$)$_9$-CH_2-CH_2-Ar), 1.36 (s, 18H, (C***H***$_3$)$_6$-O-CO), 1.62 (m, 4H, CH_3-$(CH_2)_9$-C***H***$_2$-CH_2-Ar), 2.54 (t, 4H, CH_3-$(CH_2)_9$-CH_2-C***H***$_2$-Ar), 2.81 (m, 4H, O-CO-N-$(CH_2)_2$-N-(C***H***$_2$)$_2$-N-$(CH_2)_2$-N-CO-O), 2.93 (m, 8H, O-CO-N-(C***H***$_2$)$_2$-N-$(CH_2)_2$-N-(C***H***$_2$)$_2$-N-CO-O), 3.19 (m, 4H, N-C***H***$_2$-CO-NH), 3.21 (m, 4H, N-C***H***$_2$-CO-O), 7.08, 7.11 (d, 4H, phenyl C***H***), 7.44, 7.47 ppm (d, 4H, phenyl C**H**). ESI-MS (+ve mode): *m/z*: calcd 1026.5 $[M+Na]^+$, found 1026.4 $[M+Na]^+$.

Protected-trans-DOTA-BC$_{14}$PhenA: Yield: 0.297 g, 49 %. ^{1}H NMR (300 MHZ, $CDCl_3$, 25 °C, TMS): δ = 0.88 (t, 6H, C***H***$_3$-$(CH_2)_{11}$-CH_2-CH_2-Ar), 1.25 (m, 42H, CH_3-(C***H***$_2$)$_{11}$-CH_2-CH_2-Ar), 1.36 (s, 18H, (C***H***$_3$)$_6$-O-CO), 1.62 (m, 4H, CH_3-$(CH_2)_{11}$-C***H***$_2$-CH_2-Ar), 2.54 (t, 4H, CH_3-$(CH_2)_{11}$-CH_2-C***H***$_2$-Ar), 2.81 (m, 4H, O-CO-N-$(CH_2)_2$-N-(C***H***$_2$)$_2$-N-$(CH_2)_2$-N-CO-O), 2.93 (m, 8H, O-CO-N-(C***H***$_2$)$_2$-N-$(CH_2)_2$-N-(C***H***$_2$)$_2$-N-CO-O), 3.19 (m, 4H, N-C***H***$_2$-CO-NH), 3.21 (m, 4H, N-C***H***$_2$-CO-O), 7.08, 7.11 (d, 4H, phenyl C***H***), 7.44, 7.47 ppm (d, 4H, phenyl C**H**). ESI-MS (+ve mode): *m/z*: calcd 1082.6 $[M+Na]^+$, found 1084.1 $[M+Na]^+$.

2,2'-(4,10-bis(2-((4-dodecylphenyl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,7-diyl)diacetic acid (trans-DOTA-BC$_{12}$PhenA) and 2,2'-(4,10-bis(2-((4-tetradecylphenyl)amino)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,7-diyl)diacetic acid (trans-DOTA-BC$_{14}$PhenA)

di-tert-butyl-2,2'-(4,10-bis(3-((4-dodecylphenyl)amino)-2-oxopropyl)-1,4,7,10-tetraazacyclododecane-1,7-diyl)diacetate (0.203 g, 0.197 mmol) or 2,2'-(4,10-bis(2-oxo-3-((4-tetradecylphenyl)amino)propyl)-1,4,7,10-tetraazacyclododecane-1,7-diyl)diacetic acid (0.169 g, 0.156 mmol) was dissolved in was dissolved in dichloromethane (5 mL), trifluoroacetic acid (5 mL) was added and mixed at ambient temperature for 12 hours. Dichloromethane (5 mL) was added and the solvents removed, followed by adding at additional amount of dichloromethane (5 mL) and solvents removed a second time affording the final colourless oily product.

Trans-DOTA-BC$_{12}$PhenA: Yield: quantitative; ^{1}H NMR (300 MHz, pyridine-D5, 25 °C, TMS): δ = 0.91 (t, 6H, C***H***$_3$-(CH$_2$)$_9$-CH$_2$-CH$_2$-Ar), 1.32 (m, 38H, CH$_3$-(C***H***$_2$)$_9$-CH$_2$-Ar), 1.58 (m, 4H, CH$_3$-(CH$_2$)$_9$-C***H***$_2$-CH$_2$-Ar), 2.54 (t, 4H, CH$_3$-(CH$_2$)$_9$-CH$_2$-C***H***$_2$-Ar), 3.12, 3.38 (m, 16H,DOTA C***H***$_2$), 4.07 (m, 4H, N-C***H***$_2$-CO-NH), 4.32 (m, 4H, N-C***H***$_2$-CO-O), 7.12, 7.15 (d, 4H, phenyl C***H***), 8.04, 8.07 (d, 4H, phenyl C***H***). IR: $\tilde{\nu}_{max}$ = 1635 (C=O free acid), 1522 cm^{-1} (C=O amide). ESI-MS (+ve mode): *m/z*: calcd 942.3 [M+Na]$^+$, found 942.2 [M+Na]$^+$.

Trans-DOTA-BC$_{14}$PhenA: Yield: quantative; ^{1}H NMR (300 MHz, pyridine-D5, 25 °C, TMS): δ = 0.91 (t, 6H, C***H***$_3$-(CH$_2$)$_{11}$-CH$_2$-CH$_2$-Ar), 1.32 (m, 42H, CH$_3$-(C***H***$_2$)$_{11}$-CH$_2$-Ar), 1.58 (m, 4H, CH$_3$-(CH$_2$)$_{11}$-C***H***$_2$-CH$_2$-Ar), 2.54 (t, 4H, CH$_3$-(CH$_2$)$_{11}$-CH$_2$-C***H***$_2$-Ar), 3.12, 3.38 (m, 16H,DOTA C***H***$_2$), 4.07 (m, 4H, N-C***H***$_2$-CO-NH), 4.32 (m, 4H, N-C***H***$_2$-CO-O), 7.12, 7.15 (d, 4H, phenyl C***H***), 8.04, 8.07 (d, 4H, phenyl C***H***). IR: $\tilde{\nu}_{max}$ = 1637 (C=O free acid), 1524 cm^{-1} (C=O amide). ESI-MS (+ve mode): m/z: calcd 998.4 [M+H]+, found 998.1 [M+Na]+.

Terbium(III) Cis-DOTA-BC$_{12}$PhenA, cis-DOTA-BC$_{14}$PhenA, trans-DOTA-BC$_{12}$PhenA, trans-DOTA-BC$_{14}$PhenA complexes

The ligand (0.1 g, ±0.1 mmol, 1 eq.) was dissolved in pyridine (5 mL) and a solution of hydrated $TbCl_3$ hexahydrate salt (0.11 mmol, 1.1 eq.) in H_2O (0.2 mL) was added. The mixture was brought to 70 °C for 3 hours after which the solvents were evaporated. The crude product was suspended in acetone (10 mL) and filtered over a Büchner. The solid was washed with an acetone/water 50:50 mixture (2 x 5 mL) to remove any free Tb(III) ions, rinsed again with acetone (2 x 10 mL) and dried in vacuo. The absence of free lanthanide ions was checked with an arsenazo indicator.

Tb(III)-cis-DOTA-BC$_{12}$PhenA: Yield: 43 %; IR: $\tilde{\nu}_{max}$ = 1603 (COO$^-$ asym. stretch), 1515 (amide II), 1387 cm^{-1} (COO$^-$ sym. stretch); ESI-MS (+ve mode): *m/z*: calcd 1049.2 [M+H]+, found 1047.6 [M+H]+.

Tb(III)-cis-DOTA-BC$_{14}$PhenA: Yield: 73 %; IR: $\tilde{\nu}_{max}$ = 1609 (COO$^-$ asym. stretch), 1508 (amide II), 1396 cm^{-1} (COO$^-$ sym. stretch); ESI-MS (+ve mode): *m/z*: calcd 1105.3 [M+H]+, found 1105.0 [M+H]+.

Tb(III)-trans-DOTA-BC$_{12}$PhenA: Yield: 66 %; IR: $\tilde{\nu}_{max}$ = 1608 (COO$^-$ asym. stretch), 1508 (amide II), 1396 cm^{-1} (COO$^-$ sym. stretch); ESI-MS (+ve mode): *m/z*: calcd 1049.2 [M+H]+, found 1049.5 [M+H]+.

Tb(III)-trans-DOTA-BC$_{14}$PhenA: Yield: 63 %; IR: $\tilde{\nu}_{max}$ = 1608 (COO$^-$ asym. stretch), 1514 (amide II), 1396 cm^{-1} (COO$^-$ sym. stretch); ESI-MS (+ve mode): *m/z*: calcd 1105.3 [M+H]+, found 1103.9 [M+H]+.

1.4 Preparation of micelles

1,2-Dipalmitoyl-sn-glycero-3-phosphocholine (DPPC, 80 mg, 0.109 mmol, 12 equiv.) and the amphiphilic complex (10 mg, ±0.091 mmol, 1 equiv.) were dissolved in a 1:1 chloroform/methanol solution (2 mL). After evaporation of the solvents in from flask with septum and needle fitted in a vacuum oven at 50 °C, a thin film was obtained which was rehydrated with hot water (2 mL, 70 °C). To improve the solubility, the suspension was sonicated in a 180 W sonicator with a thermostatic bath at 65 °C for 15 min. Polyoxyethylene sorbitan monooleate or Tween 80® (77 mg, 0.06 mmol, 6.5 equiv.) was added as a surfactant followed by another 15 min of sonication to fulfil the process of micelle formation. Water was evaporated in a flask with septum and needle fitted in a vacuum oven overnight at 50 °C leaving a thin film. A small amount of sample was removed for DLS measurements. For preparation of samples for relaxometry measurements, the thin film was rehydrated with Milli-Q water (1 mL), sonicated for 15 mins and passed through a 200 nm PTFE filter. The concentration of terbium(III) was analysed by TXRF before relaxometric measurements.

3 Supplementary Figures

Absorption and excitation spectra

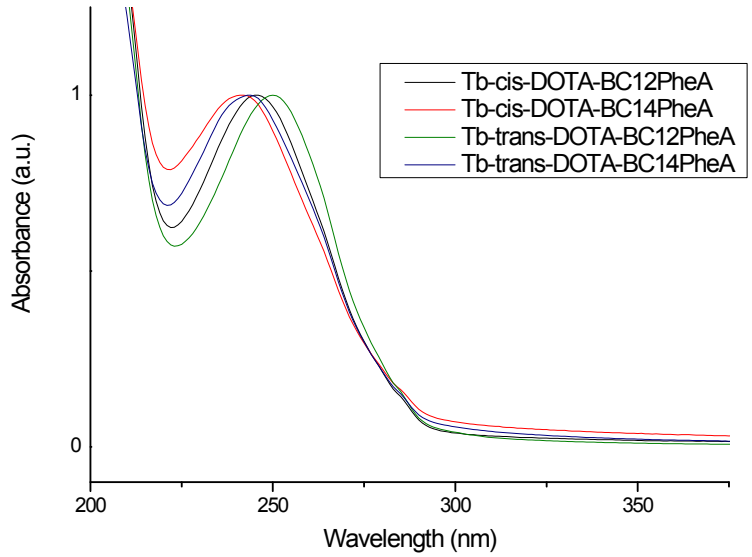

Fig. S1. Normalized absorbance spectrum of Tb^{III} complexes.

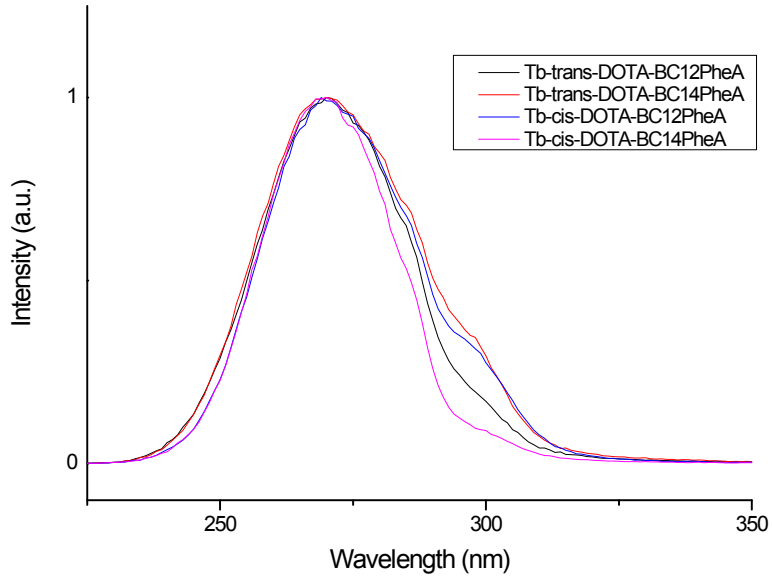

Fig. S2. Corrected and normalized excitation spectrum of Tb^{III} complexes.

ESI-MS Spectra

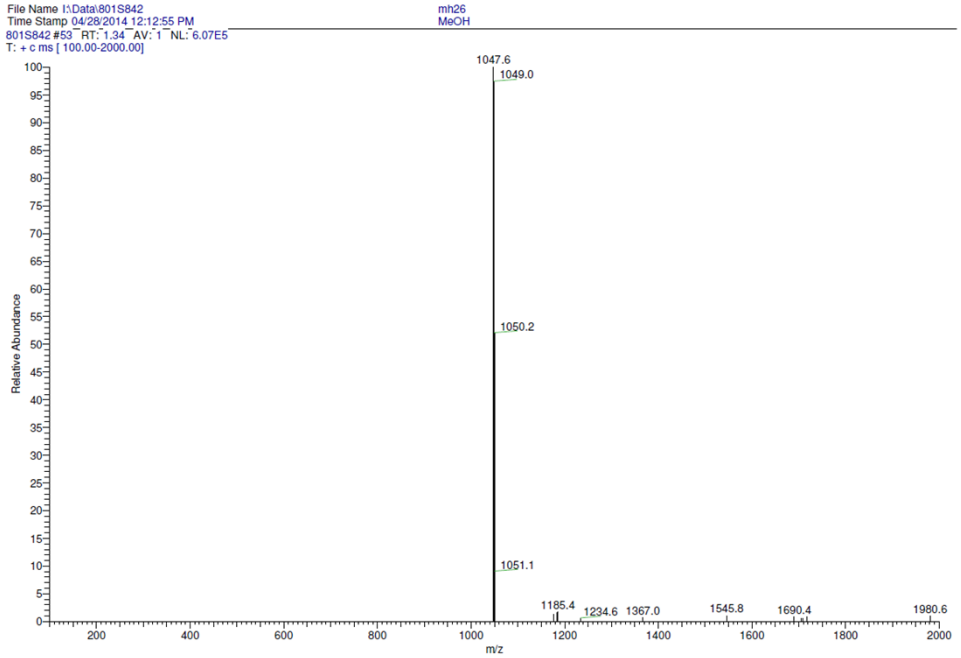

Fig. S3. ESI-MS Tb(III)-cis-DOTA-BC_{12}PheA

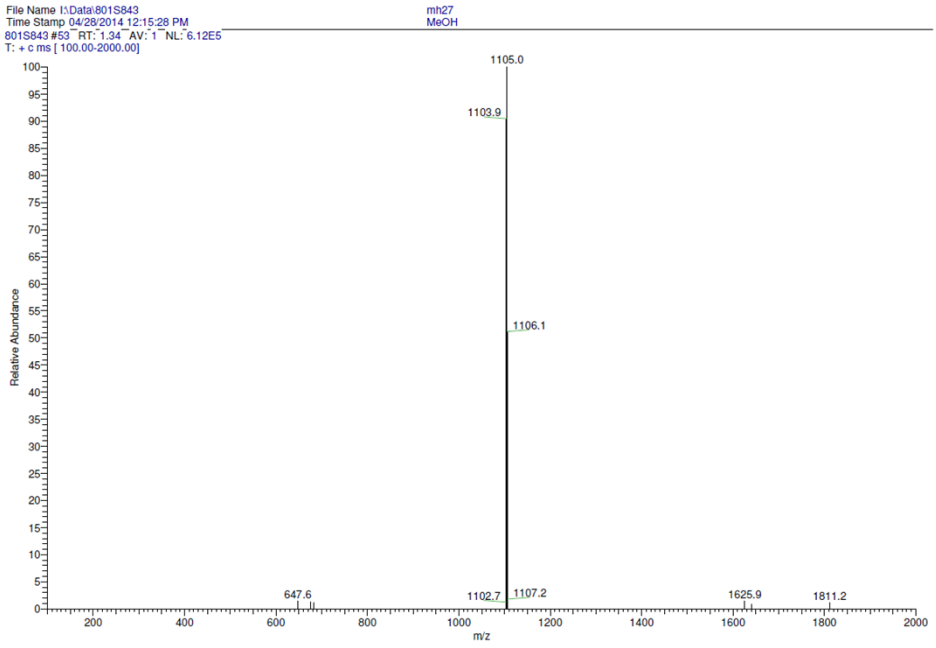

Fig S4. ESI-MS Tb(III)-cis-DOTA-BC_{14}PheA

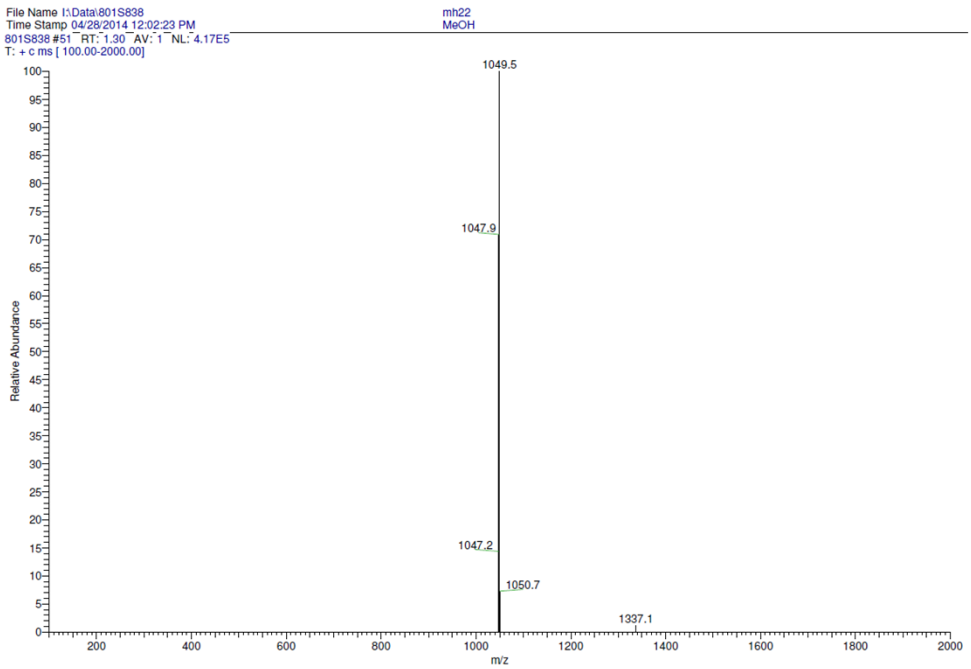

Fig. S5. ESI-MS Tb(III)-trans-DOTA-BC_{12}PheA

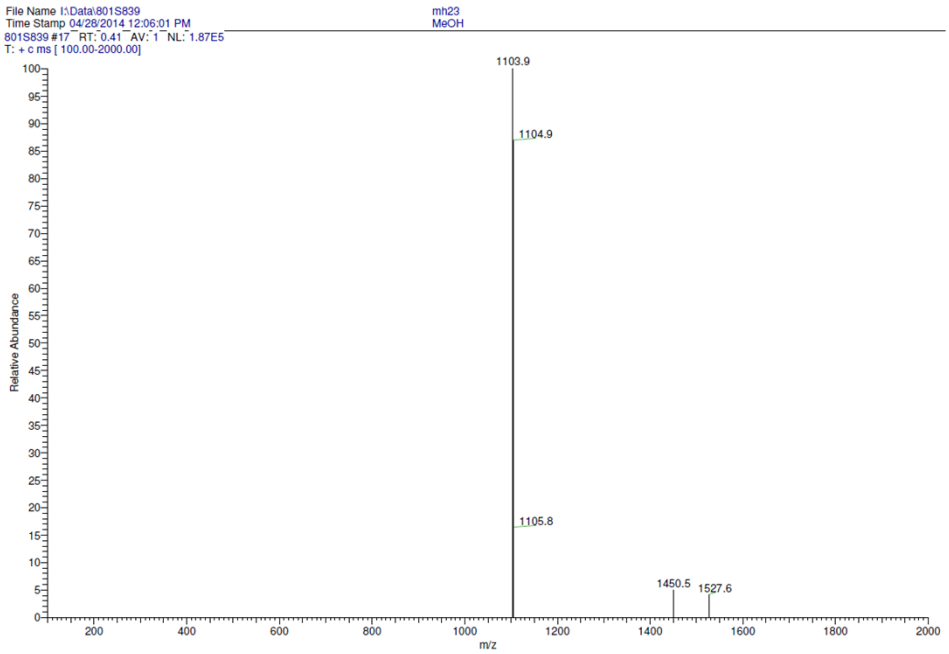

Fig. S6. ESI-MS Tb(III)-trans-DOTA-BC_{14}PheA

DLS Profiles

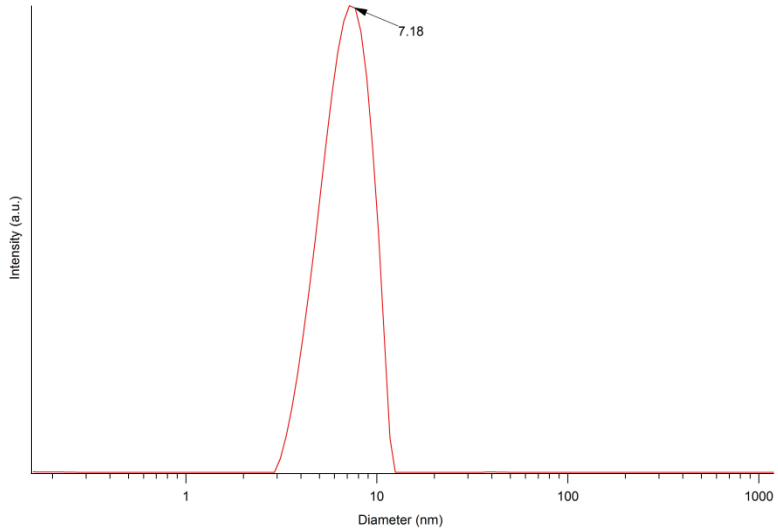

Fig. S7. DLS Tb-cis-DOTA-BC_{12}PheA: 7.18 nm

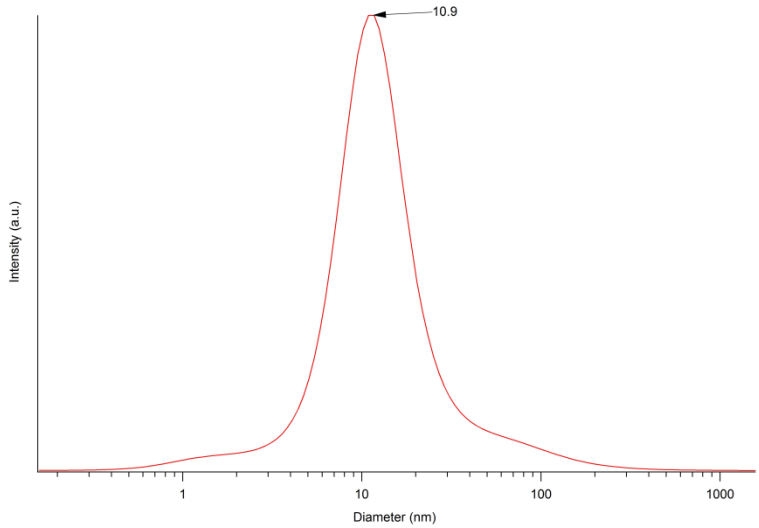

Fig. S8. DLS Tb-cis-DOTA-BC_{14}PheA: 10.9 nm

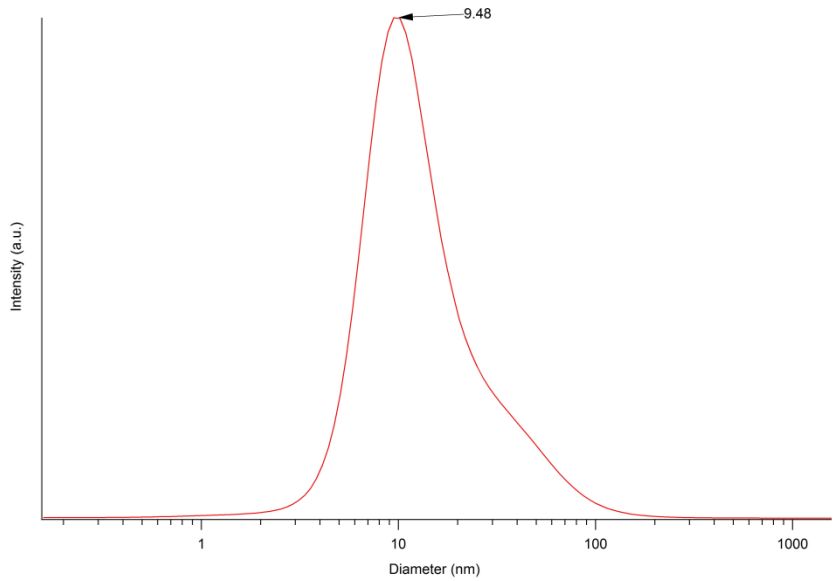

Fig. S9. DLS Tb-trans-DOTA-BC_{12}PheA: 9.48 nm

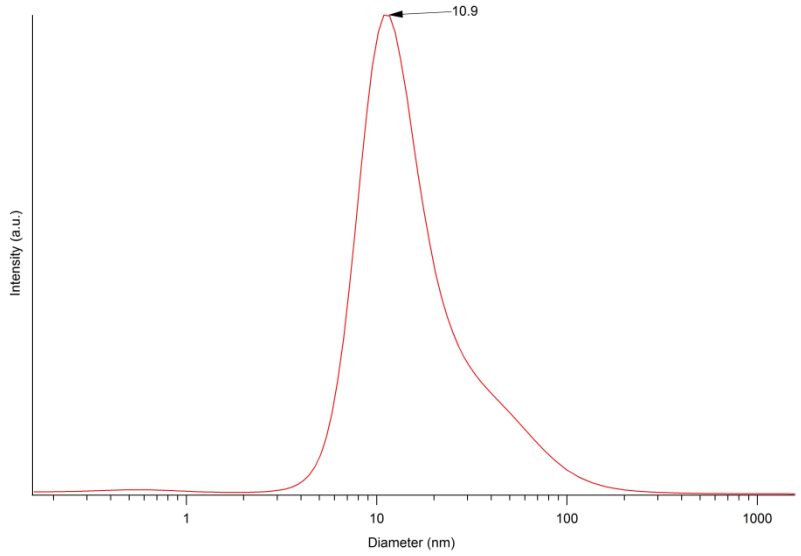

Fig. S10. DLS Tb-trans-DOTA-BC_{14}PheA: 10.9 nm