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Supporting Information for

One-Pot Direct Synthesis for Multifunctional Ultrasmall Hybrid Silica Nanoparticles

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Experimental Section

S1. Materials

Hydrochloric acid (HCl, 37%) was purchased from VWR Chemicals BDH Prolabo (France). Sodium hydroxide pellets (NaOH, ≥ 98%) were purchased from Sigma-Aldrich Chemicals (France). Europium chloride hexahydrate ($EuCl_3 \cdot 6H_2O$, 99.9 %), lutetium chloride hexahydrate ($LuCl_3 \cdot 6H_2O$, 99.9 %), terbium chloride hexahydrate ($TbCl_3 \cdot 6H_2O$, 99.9 %), holmium chloride hexahydrate ($HoCl_3 \cdot 6H_2O$, 99.9 %), bismuth chloride ($BiCl_3$, ≥ 98 %), tetraethyl orthosilicate ($Si(OC_2H_5)_4$, TEOS, 98%), aminopropyltriethoxysilane ($H_2N(CH_2)_3$-$Si(OC_2H_5)_3$, APTES, 99%), anhydrous DMSO for the synthesis of the silane precursor, deuterium oxide D_2O for NMR experiments, glacial acetic acid for preparing buffer at pH 5 were purchased from Sigma-Aldrich Chemicals (France). 1,4,7,10-Tetraazacyclododecane-1-glutaric anhydride-4,7,10-triacetic acid (DOTAGA anhydride, 80%) and APTES-DOTAGA (≥ 80%) were provided by Chematech (France). Gadolinium chloride hexahydrate ($GdCl_3 \cdot 6H_2O$, 99.999 %) was purchased from Metall Rare Earth Limited (China). Milli-Q water (ρ > 18 MΩ) was used as

water source. Vivaspin® concentrators and Vivaflow® 200 cassettes (MWCO = 3 kDa or 5 kDa) were purchased from Sartorius Stedim Biotech (France).

S2. Synthesis of the chelating silane APTES-DOTAGA

S2.1. Synthesis of APTES-DOTAGA from butyl protected DOTAGA

APTES-DOTAGA can be synthesized starting from the t-butyl protected DOTAGA which was coupled to APTES through peptide coupling. This was followed by the deprotection of the intermediate to get the final compound. The reaction scheme is presented in (Figure 1-A).

S2.1.1. Synthesis protocol

DOTAGA(tBu)$_4$ (Chematech) (0.9g, 1.284 mmol) was weighed in 100 mL round bottom flask and was dissolved in 20 mL of DCM (dichloromethane, VWR) under the hood with stirring. DIPEA (N, N-diisopropylethylamine, Alfa Aesar) (1.14 mL, 6.55 mmol) was added into above solution followed by coupling agents namely HBTU (0.52 g, 1.37 mmol) and HOBt (Hydroxybenzotriazole, Fluorochem) (0.18 g, 1.37 mmol) and the solution was left for stirring at rt (room temperature) for 15 min. APTES (0.3 g 1.37 mmol) was added to the above solution directly using the 1mL syringe and solution was stirred further at rt for 60 min after which the product formation was confirmed through MS. The above solution was mixed with 50 mL of citric acid solution (pH:2.5-3) in a separating funnel and the organic layer was recovered. The organic layer was further mixed with 50mL of 5% $NaHCO_3$ in a separating funnel and the organic layer was recovered. The DCM solution was stirred with 5 g of $MgSO_4$ for 10 min and filtered using sintered funnel to receive the dry and clear DCM solution. Organic phase was evaporated under vaccum at 30°C to get a viscous brownish residue, as an intermediate product (1.05g, 78%). The intermediate formation was verified using HRMS, ^{1}H, ^{13}C NMR and elemental analysis.

DOTAGA(tBu)$_4$-APTES (1 g) was weighed into a 100 mL round bottom flask and was mixed with 5mL of concentrated HCl and stirred for 10min. Later, the acid was evaporated under vacuum at 35°C in 5-15min to get a dried residue. The above dried residue was dissolved in 10mL of water and lyophilized to get a light brown colored powder (850mg, 81%). The product was verified using HRMS, ^{1}H NMR and elemental analysis.

S2.1.2. Characterization

S2.1.2.1. Characterization of butyl protected APTES-DOTAGA

HRMS: Calculated for $C_{44}H_{85}N_5O_{12}Si$: 926.585 $[M+Na]^+$; Obtained: m/z = 926.584 $[M+Na]^+$ (Figure S2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.4 – 0.7 (m, 2H), 0.7 – 0.8 (m, 1H), 1.0 (dd, *J* = 9.0, 6.7 Hz, 1H), 1.1 – 1.2 (m, 9H), 1.3 – 1.5 (m, 32H), 1.5 (p, *J* = 7.8 Hz, 2H), 1.7 (d, 1H), 1.9 – 2.1 (m, 1H), 2.1 – 2.3 (m, 1H), 2.4 – 3.4 (m, 29H), 3.5 – 3.7 (m, 1H), 3.7 – 3.8 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 7.5, 7.8, 18.3, 20.4, 23.5, 25.9, 26.8, 27.8, 27.8, 27.9, 27.9, 27.9, 28.2, 28.3, 29.7, 33.0, 38.6, 42.1, 47.6, 49.8, 58.4, 63.6, 80.8, 82.3, 171.1, 173.2.

Elemental Analysis:

Calculated for $C_{44}H_{85}N_5O_{12}Si$**.** $0.9HPF_6$ (%): C: 51.03, H:8.36, N:6.76.

Observed (%): C: 51.86, H: 8.91, N: 8.38.

S2.1.2.2. Characterization of deprotected APTES-DOTAGA

HRMS: Calculated for $C_{22}H_{41}N_5O_{12}Si$: 596.259 $[M+H]^+$; Obtained: m/z = 596.261 $[M+H]^+$; 618.242 $[M+Na]^+$ (Figure S3).

^{1}H NMR (500 MHz, Deuterium Oxide) δ 0.5 – 0.8 (m, 2H), 1.2 – 1.3 (m, 1H), 1.4 – 1.6 (m, 1H), 1.6 – 1.8 (m, 1H), 1.8 – 2.2 (m, 1H), 2.3 – 4.5 (m, 26H).

Elemental Analysis:

Calculated for $C_{22}H_{41}N_5O_{12}Si$**.** HPF_6**.** 2HCl (%): C: 32.44, H:5.44, N:8.60.

Observed (%): C: 32.17, H: 6.54, N: 9.39.

S2.2. Synthesis of APTES-DOTAGA from DOTAGA anhydride

S2.2.1. Synthesis protocol

10.0 g (17.45 mmol) of DOTAGA anhydride (Chematech) was put in a 1 L round flask. Then, 530 mL of anhydrous DMSO (SigmaAldrich) and 2.062 mL (8.72 mmol) of APTES (SigmaAldrich) were added quickly. DOTAGA anhydride was used in excess to make sure all APTES will react (Figure S4). This allows the precise control of the composition of the final particles in the next step. The reaction was heated to 75°C under argon atmosphere overnight (18 h). The product formed as white precipitate. The product was fully precipitated by transferring to 5 L of acetone and kept at 4°C for 18 h. The precipitate was filtered through filter paper grade 42. Around 2.5 L of acetone was used to wash the precipitate to remove DMSO. The remaining acetone was removed by evaporating at 37°C overnight.

S2.2.2. Characterization of APTES-DOTAGA synthesized from DOTAGA anhydride

S2.2.2.1. IR spectra

DOTAGA and the mixture of APTES-DOTAGA were dissolved in water and adjusted to pH 2 to protonate carboxyl groups. This makes the peak at 1677 cm^{-1} of C=O amide distinguished from the one at 1713 cm^{-1} of C=O carboxyl. The 2 solutions were dried at 80°C for 4 days. IR spectra were acquired with dry powder.

Figure S5 shows the IR spectrum of DOTAGA powder and APTES-DOTAGA synthesis mixture. The assignment for some important peaks is shown in Table S1.[1] The appearance of peak at 1677.0 cm^{-1}, and the decrease of peak intensity at 1712.7 cm^{-1} is an indication of the formation of the amide bond.[2]

S2.2.2.2. Mass spectrometry

MS spectrum was obtained in negative mode at the concentration of total DOTAGA around 0.1 mM. Figure S6 shows the overall spectrum which has 4 main peaks at 594, 475, 296.5 and 237 m/z. Figure S7 to show the zoomed region of each of the peak along with the proposed molecular formula and simulated spectrum. The agreement between the real spectra and simulated spectra as well as the co-presence of singly charged ions and doubly charged ions confirm the reliability of the proposed structures.

S2.2.2.3. Determination of the total contents of (reacted and unreacted) DOTAGA:

The first method to determine the contents of DOTAGA is colorimetric titration with Ca^{2+} using EBT (Eriochrome® Black T) as color indicator in ammonia buffer solution at pH 10 (Sigma-Aldrich Chemicals, France). The test gives a value around 1.70 µmol/mg. This result might be slightly overestimated due to the difficulty of recognizing the equivalent point indicated by the color change from pale blue to violet. However, it gives an approximate idea about the real value (Figure S8).

The second method is complexometric titration with europium salt ($EuCl_3$) (Figure S9). The test gives 1.47 ± 0.11 µmol/mg for the content of DOTAGA.

S2.2.2.4. Determination of the content of APTES-DOTAGA:

The next task is to determine the content of APTES-DOTAGA. Due to the similarity in chemical properties of DOTAGA and APTES-DOTAGA, it is difficult to determine their contents in a mixture. Therefore, a HPLC method was developed to separate them. Since silanes can react with the residual silanols on the surface of silica chromatographic columns when they are concentrated enough, in order to keep the surface of the column intact, the concentration of silanes should be kept as low as possible. DOTAGA was labeled with Gd^{3+} and the fluorescent emission was detected at 312 nm (λ_{ex} = 274 nm). In our case, the total concentration of silanes was kept lower than 0.2 mM without any observable distortions in peak shape or gradual increase of pressure.

HPLC setup:

The same system was used to analyze this sample with some modification (Figure S10). Only isocratic elution at 99% H_2O/TFA (99.9:0.1) and 1% ACN/TFA (99.9:0.1) was used since no NP is present. A longer C18 column (BDS-HYPERSIL-C18 250 mm x 4.6 mm, 5 µm, 130 Å, ThermoFisher Scientific) was used to offer higher separation capability. The flow was maintained for 15 min to elute all the expected peaks. After that, acetonitrile was raised to 90 % gradually to clean the column from unexpected organic impurities. Then, the system was re-equilibrated to the initial condition before a new analysis. Before the measurement of each sample, a baseline was obtained in the same manner by injecting Milli-Q water.

Calibration standards preparation: a 10 mL solution of 0.375 µmol $GdCl_3$ and 0.450 µmol DOTAGA was prepared from $GdCl_3.6H_2O$ salt and DOTAGA anhydride. pH was kept below 4 before mixing and adjusted at 5.5 after mixing by addition of NaOH solutions. The solution was incubated at 80°C during 48 h to allow the complexation to complete. Final pH is verified at the end. Solution was filled to 25 mL in a volumetric flask and the final concentrations of $GdCl_3$ and DOTAGA were 15 mM

and 18 mM respectively. From this stock solution, a series of samples with DOTAGA(Gd^{3+}) concentration from 0.01 mM to 0.15 mM were prepared by dilution in water. The calibration curve is fitted from the concentrations of DOTAGA(Gd^{3+}) solutions and the areas under the curve of their peaks.

Sample preparation: The dried powder was dissolved in water. This solution was mixed with an excess amount of $GdCl_3$ to achieve final concentration of 57.8 mg/L for the synthesis mixture and 0.2 mM Gd^{3+}. The pH is adjusted to around 5 and incubated at 80°C during 48 h to allow the complexation to complete. Final pH is verified at the end. The area of the DOTAGA(Gd^{3+}) peak was fitted to the calibration curve to give the concentration of unreacted DOTAGA in the sample and the content of APTES-DOTAGA in the powder was then deduced.

Figure S10-A shows the chromatograms of the analytes. By superimposing the chromatogram of the synthesis mixture (red) with the one of $GdCl_3$ (black) and DOTAGA(Gd^{3+}) (blue), we can identify the expected peaks. The first peak corresponds to free Gd^{3+}. The third peak should correspond to DOTAGA(Gd^{3+}). Finally, the second peak should correspond to the product of the reaction APTES-DOTAGA(Gd^{3+}). So, the chromatography helped in clearly separating 3 components from each other. Using a calibration curve of the peak area and concentration of DOTAGA(Gd^{3+}) (Figure S10-B), we can determine the concentration of DOTAGA(Gd^{3+}) in the sample and then determine its initial contents in the powder which is around 0.74 µmol/mg.

Table S2 shows the summary of the above results. IR and MS spectra as well as HPLC chromatograms show that the precursor has been formed after the reaction. The quantifications proved that the reaction was complete and half of the DOTAGA anhydride has reacted with APTES. After the whole process, we obtained the yield of 37 % of APTES-DOTAGA compared to the introduced DOTAGA anhydride or 74 % compared to the expected amount of APTES-DOTAGA. It is worth reminding that, in this case, the starting molar ratio DOTAGA : APTES was 2 : 1.

S3. Synthesis of USNP

pH of the solutions during the syntheses was adjusted by adding HCl or NaOH at appropriate concentration.

S3.1. Synthesis of USNPr and USNPr@Gd* with ready-to-use chelating silane

For HPLC, 2 samples were prepared: 1) The filtered solution was diluted 2 times to reach a theoretical concentration of APTES-DOTAGA equivalent to 5 mM before being injected to the column, The absorption was followed at 295 nm. 2) 200 µL of this solution was mixed with 5 µL of CuSO4 506 mM, an excess amount compared to the theoretical concentration of chelating agents in the solution at pH 3, 80°C for 2 h. The product was diluted to a theoretical concentration of 5 g/L right before being injected to HPLC system. The absorption was followed at 700 nm.

S3.2. Synthesis of USNPi-1, 2, 3, 4 using *in situ* formed chelating silane in DMSO/H_2O

For HPLC, a small sample of each purified solution was diluted 40 times in HCl 10^{-2} M right before being injected to HPLC for analysis at 295 nm.

A small quantity of 4 samples was redispersed in water at 80 – 100 g/L and pH 7. These stock solutions were quickly diluted to 10 g/L with water before being measured in DLS.

A small quantity of 3 samples USNPi-2, 3, 4 was redispersed in water at 150 - 200 g/L or 120 – 150 mM in DOTAGA according to the results found by Eu titration. Their pHs were adjusted to 5.5. Then an amount of $GdCl_3$ 50 mM in HCl 0.1 mM (molar ratio DOTAGA : Gd = 10 : 1) was added. Their pHs were readjusted to 5.5 before being incubated at 80°C for 2 nights. Water was filled to achieve 50 mM in DOTAGA, 5 mM in Gd for each sample right before their relaxation times were measured. The amount of Gd in the samples were quantified precisely again with ICP-OES. Their relaxivities can be calculated using common method shown below.

S3.3. Synthesis of USNPi-5 using *in situ* formed chelating silanes in DEG/H_2O

For DLS measurement, a small amount of sample after the reaction between APTES and DOTAGA anhydride was taken and diluted 10 times in water and filtered to obtain homogeneous solutions instead of initial suspensions before its D_H was measured in DLS. Similarly, a small amount of sample after adding TEOS was taken and diluted 10 times in water to measure D_H in DLS. A small sample of purified solution was diluted 10 times in water right before being analyzed by DLS or in aqueous solution of TFA 0.1% before being analyzed by HPLC at 295 nm.

S4. Complexation of metals in USNP

S4.1. Complexation of Gd and Lu on USNPr to create USNPr@Gd and USNPr@Lu

Solution after the complexation was diluted to reach the concentration of DOTAGA equivalent to 5 mM before being injected to the HPLC column.

S4.2. Complexation of USNPi-5 with different metals (Gd, Ho, Tb and Bi)
The lyophilized powders of these NPs was redispersed in water and diluted to 5 g/L in aqueous solution of TFA 0.1% before being analyzed by HPLC at 295 nm.

S5. Analytical methods

S5.1. Dynamic light scattering (DLS) and zeta potential
Measurement was taken on 1 mL or 0.5 mL of the solution with a single use PMMA cuvette (Carl Roth GmbH, Germany) at 20 °C. Attenuator and position were optimized by the device. Fast mode was enabled to enhance the precision for the measurement of particles with hydrodynamic diameter less than 10 nm. For most of samples, lyophilized powder was redispersed in water to achieve 100 mg/mL solution and diluted to 10 mg/mL in an aqueous solution just before each measurement.

Zeta potential measurements were recorded at 20 °C within a DTS 1061 folded capillary cell (Malvern Instruments Ltd, USA). The zeta potential (ζ) was automatically calculated from electrophoretic mobility based on the Smoluchowski equation, $\nu = (\varepsilon\varepsilon_0\zeta/\eta)\zeta$, where ν is the measured electrophoretic mobility, η is the viscosity, ε is the dielectric constant of the electrolytic solution, $\varepsilon_0 \approx 8.854 \times 10^{-12}$ $C^2N^{-1}m^{-2}$ is the vacuum permittivity. Lyophilized powder was redispersed in water to achieve 100 mg/mL solution and diluted to 10 mg/mL in an aqueous solution containing 5 mM NaCl and adjusted to the desired pH just before each measurement.

S5.2. High Performance Liquid Chromatography (HPLC)

General system:
For UV−vis detector, the detecting wavelength was set at 295 nm where organic chelators can highly absorb for characterizing empty NP and at 700 nm where copper (Cu) complex of DOTAGA specifically absorb for characterizing Cu incorporated NP. Fluorescence detector (λ_{ex} = 274 nm, λ_{em} = 312 nm) was used to when characterizing Gd incorporated NP. The column temperature was maintained at 30 °C. Linear gradient LC elution was carried out with two mobile phases: (A) Milli-Q water/TFA 99.9:0.1 v/v and (B) acetonitrile (CH_3CN)/TFA 99.9:0.1 v/v. Each time, an amount of 20 µL of sample was loaded to an injection valve and injected into a Jupiter C4 column (150 mm × 4.60 mm, 5 µm, 300 Å, Phenomenex) at a flow rate of 1 mL/min. Then the elution was programmed as follows: 1% of solvent B in 7 min to elute the reactive and fragments, then a gradient from 1% to 90% in 15 min to elute the nanoparticle. The concentration of B was maintained over 7 min. Then, the concentration of solvent B was decreased to 1% over 1 min and maintained during 8 min to re-equilibrate the system for a new analysis. Before the measurement of each sample, a baseline was obtained under the same conditions by injecting Milli-Q water. The purity is calculated by dividing the area under the peak of the particle to the total area under the peaks of the particle and the reactive.

Quantification of DOTAGA on USNPr with Cu^{2+}:
For this analysis, samples were prepared as following. Ultrapure water was added to the lyophilized powder of USNPr to obtain a solution at 286 g/L. pH of this solution was adjusted to 3 by adding few drops of HCl in appropriate concentrations. An excess of $CuSO_4$ solution at pH 3 was added to the solution of USNP to achieve the final concentration of 143 g/L of USNP and 200 mM of Cu^{2+}. The complexation could probably reduce the pH of the solution. Therefore, pH should be readjusted to be nearly stable at 3 before being incubated at 80°C for at least 2 h. Detector was set at 700 nm to detect specifically the absorption of copper complexes which are free or grafted on the NPs. The concentration of Cu^{2+} and DOTAGA(Cu^{2+}) was determined by comparing peak area with their calibration curves at different concentrations (4 mM – 32 mM for Cu^{2+} and 0.1 mM – 15 mM for DOTAGA(Cu^{2+})). The total concentration of free Cu^{2+} and DOTAGA(Cu^{2+}) can be summed up to verify with the introduced amount. The content (mol/g) of free DOTAGA can be calculated from their molar concentrations (mol/L) determined by the assay and the mass concentration (mg/L) of the analyzed samples.

S5.3. Phosphorescence spectroscopy
Common parameters were: excitation slit 20 nm, emission slit 10 nm, averaging time 0.1 s, data interval 1 nm, total decay time 3 ms, number of flash 1, delay time 0.1 ms, gate time 2 ms, 800 V voltage.

Quantification of DOTAGA on USNP with Eu^{3+}:
Lyophilized particles were redispersed in water. A series of samples with a certain amount of this solution and an increasing amount of $EuCl_3$ was prepared in acetate buffer pH 5. These series of samples were incubated at 80°C for 48 h before the measurement. Samples were excited at 395 nm an emission at 594 nm and 616 nm, which are characteristic for Eu^{3+} ions, were chosen to follow the titration. The endpoint was determined when the luminescence intensity no longer increased linearly with the added amount of Eu^{3+}. The content (µmol/mg) of free DOTAGA can be calculated as in HPLC method.

Excitation and emission spectra of USNPi-5@Gd and USNPi-5@Tb:

Solutions of USNPi-5@Gd and USNPi-5@Tb at 0.06 g/L were measured. For USNPi-5@Gd, excitation spectrum was recorded between 210 nm and 300 nm at λ_{em} = 313 nm, emission spectrum was recorded between 300 nm and 400 nm at λ_{ex} = 273 nm. For USNPi-5@Tb, excitation spectrum was recorded between 210 nm and 400 nm at λ_{em} = 546 nm, emission spectrum was recorded between 400 nm and 650 nm at λ_{ex} = 221 nm. Appropriate filters were selected to remove Raman or second harmonic peaks when necessary.

S5.4. ^{1}H nuclear magnetic resonance (NMR) and diffusion ordered spectroscopy (DOSY)

S5.4.1. Parameters for measurements conducted on APTES-DOTAGA

The ^{1}H and ^{13}C NMR spectra were recorded at rt or at 330K. NMR spectra were run on Bruker Avance 300 and/or 500 spectrometers using pre-deuterated solvents as internal standard.

S5.4.2. Parameters for experiments conducted on USNP

Sample preparation:

For the empty USNPr sample, the lyophilized powder was redispersed in water. The pH of the solution was adjusted to 7.4 before water was added to have a final concentration at 127 g/L or 100 mM in DOTAGA.

For the USNPr@Lu sample, the lyophilized powder was redispersed in water. Using the content of DOTAGA calculated from Eu titration, 32.5 µL of $LuCl_3$ solution at 1.98 M (molar ratio DOTAGA : Lu = 1 : 0.9) was added slowly in 4 times. Between each time, pH was carefully increased to 4 – 5 by adding NaOH solutions before adding the next one. After 4 additions, pH was at 5. This solution was incubated at 80°C for 48 h. Finally, pH was increased to 7.4 and water was added to have a final concentration at 127 g/L or 100 mM in DOTAGA.

The two solutions were lyophilized and redispersed in D_2O at the same concentration. 470 – 500 µL of each sample was added to the NMR tubes for the measurement.

For USNPi-5 sample, the lyophilized powder was redispersed in D_2O at 100 g/L.

S5.5. Relaxivity measurement

300 µL of samples were measured at a specific Gd^{3+} concentration (mM), measured from ICP-OES. The longitudinal relaxation time T_1 and the transverse relaxation time T_2 (s) were measured. Then the relaxivities r_i (s^{-1} .mM^{-1}) (i = 1, 2) were obtained according to the following formula:

$$\left(\frac{1}{T_i}\right)measured = \left(\frac{1}{T_i}\right)water + r_i[Gd^{3+}]$$

$$\left(\frac{1}{T_i}\right)water \approx 0.2816\ (s^{-1})$$

$$i = 1\ or\ 2$$

S5.6. Elemental analysis

S5.6.1. Parameters for measurements conducted on APTES-DOTAGA

Elemental analyses were obtained on EA 1108 CHNS Fisons Instrument.

S5.6.2. Parameters for experiments conducted on USNP

Sample preparation for ICP-OES: The solution of particles at an estimated concentration in metal (Gd, Tb, Ho or Bi) of 10 ppm was digested for 3h in 4-5 mL of aqua regia (HNO_3 67% mixed with HCl 37% (1/2; v/v) at 80°C. Subsequently, the mixture was diluted to estimated 100, 200 and 400 ppb at precisely 50 mL with HNO_3 5% (v/v). These solutions were filtered through 0.2 µm membrane before being analyzed. Calibrated samples were prepared from 1000 ppm Gd, Tb, Ho and Bi standard solutions by successive dilutions with HNO_3 5% (w/w). The selected wavelengths for measurement were 342.246, 335.048, 336.224 nm for Gd samples; 350.914, 367.636, 387.417 nm for Tb samples; 345.600, 339.895, 341.644 nm for Ho samples and 223.061 nm for Bi samples. The results were the average of the three samples at presumably 100, 200 and 400 ppb at different selected wavelengths.

S5.7. Mass spectrometry

S5.7.1. Parameters for measurements conducted on APTES-DOTAGA

ESI (Electro Spray Ionisation), High resolution and accurate mass measurements (HRMS) were carried out using a Bruker microTOF-Q™ ESI-TOF mass spectrometer (Germany).

S5.7.2. Parameters for experiments conducted on USNP

Sample preparation: Lyophilized powders of NP were dispersed in water at 100 mM in DOTAGA. Then before the experiment, it was diluted in aqueous solution of 0.1% TFA to 0.5 mM. These solutions were injected in electrospray (positive ionization mode) at a flow rate of 300 $\mu L.h^{-1}$.

S5.8. Infrared spectroscopy

Infrared spectra were performed with a IRAffnity-1 Shimadzu. Transmittance mode was used with Happ-Genzel apodization function, 30 scans, 4 cm^{-1} resolution in a range between 400 and 4000 cm^{-1}. pHs of the solutions were adjusted to 2 before being lyophilized. The spectra were recorded on the obtained powders.

S5.9. UV-visible spectroscopy

UV-visible spectra were recorded with Varian Cary 50 spectrophotometer (USA). Solutions of USNPi-5 and USNPi-5@Ho at 5 g/L; USNPi-5, USNPi-5@M (M: Gd, Tb, Ho, Bi) at 0.06 g/L were measured.

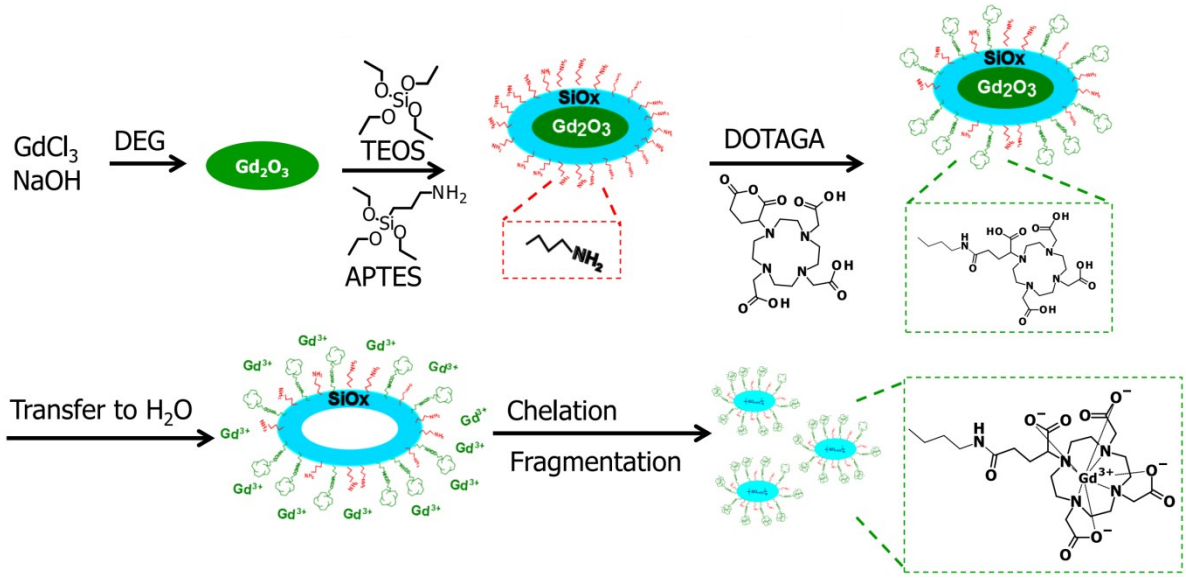

Figure S1. Scheme of top-down synthesis approach for USNP

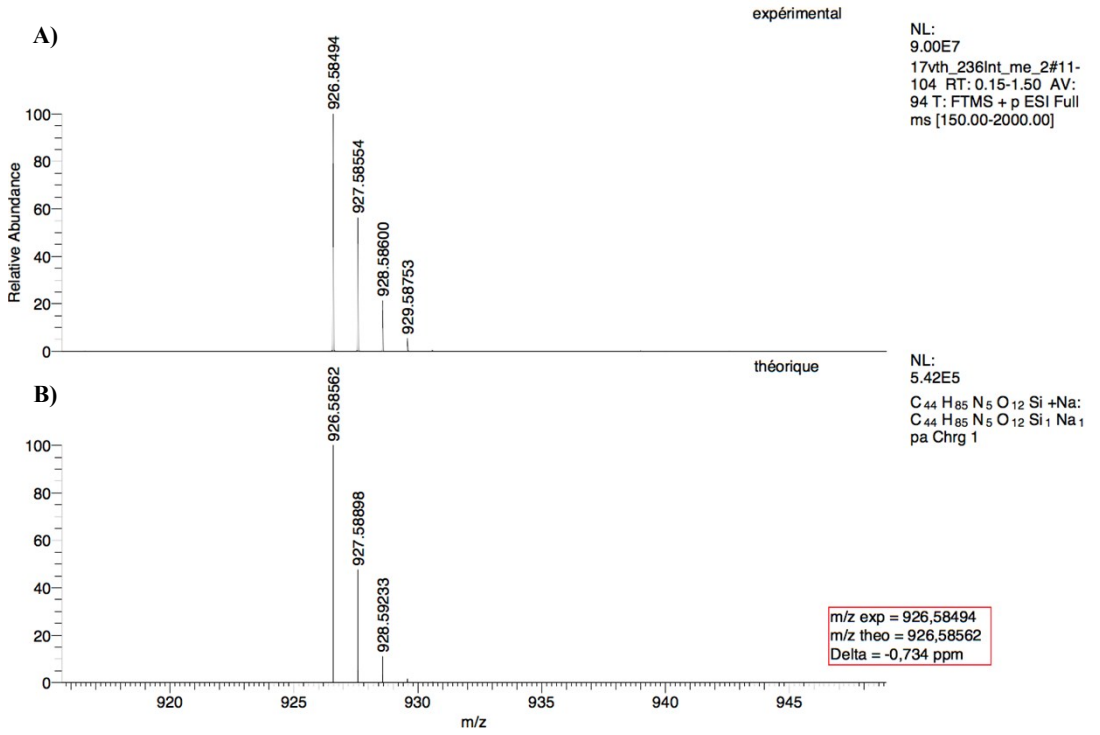

Figure S2. Mass spectra of butyl protected APTES-DOTAGA: A) experimental spectrum, B) simulated spectrum

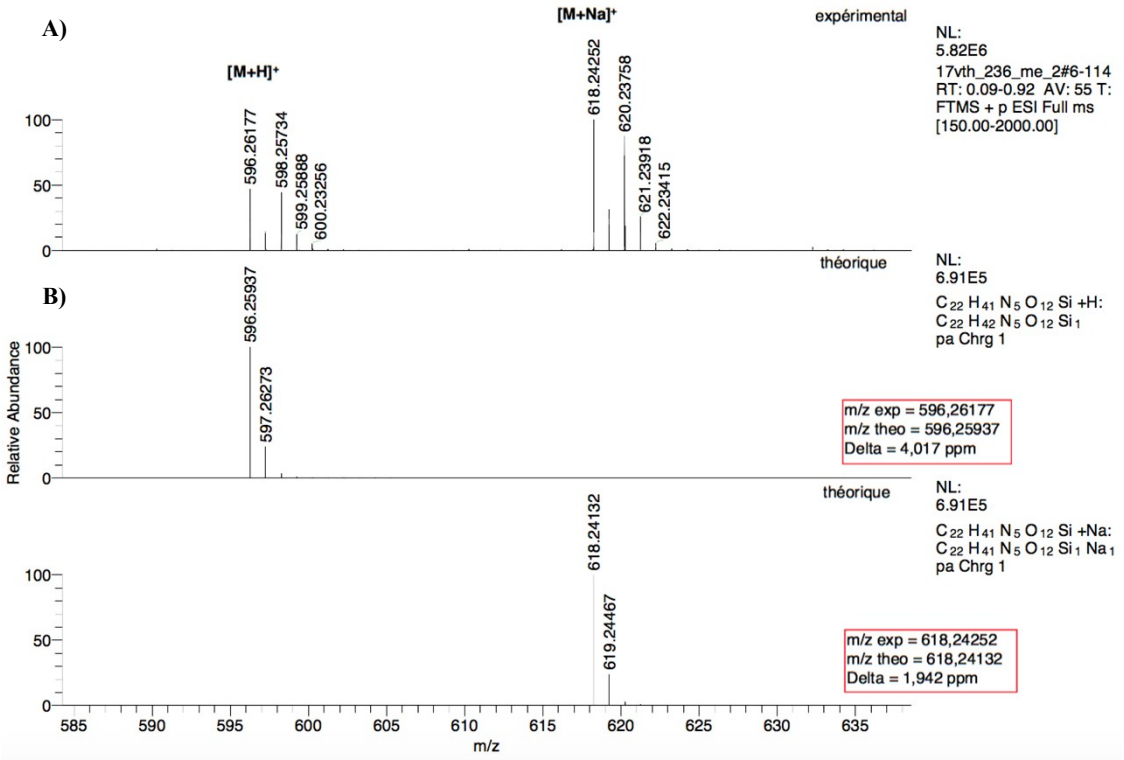

Figure S3. Mass spectra of deprotected APTES-DOTAGA: A) experimental spectrum, B) simulated spectrum

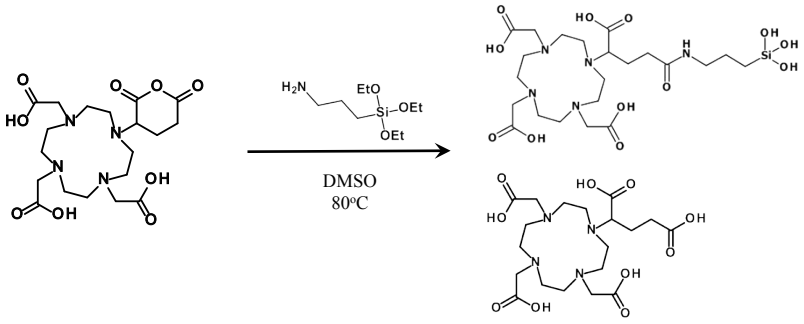

Figure S4. The reaction scheme of the synthesis of APTES-DOTAGA from DOTAGA anhydride

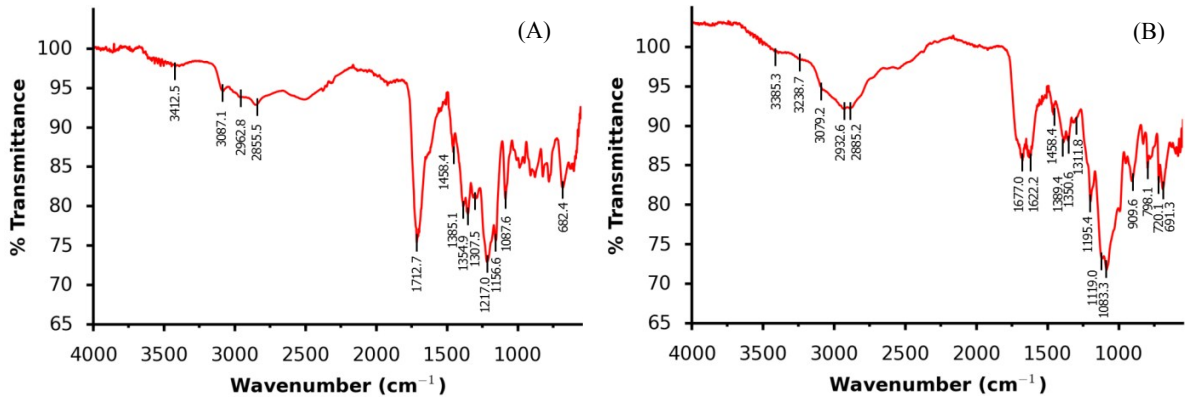

Figure S5. Infrared spectra of DOTAGA powder (A) and APTES-DOTAGA synthesis mixture (B)

Table S1. Assignment of the main peaks in infra-red spectra of DOTAGA and APTES-DOTAGA

Wave number (cm^{-1})	Assignment
3385.3	Si-OH stretching or primary amine N-H stretching
3238.7	Si-OH stretching or secondary amide N-H stretching or carboxylic O-H stretching
3079.2	Secondary amide II overtone or carboxylic O-H stretching
2932.6	Methylene asymmetric C-H stretching
2885.2	Methylene symmetric C-H stretching
1712.7	Carboxylic acid C=O stretching
1677.0	Secondary amide C=O stretching
1622.2	Amine NH_2 scissoring, N-H bending
1385.1	Carboxylic acid C-O-H in-plane bending
1221.3	Carboxylic acid C-O stretching or Aliphatic C-N stretching
1122.1	Si-O-Si asymmetric stretching or Aliphatic C-N stretching
1087.6	Si-O-C stretching

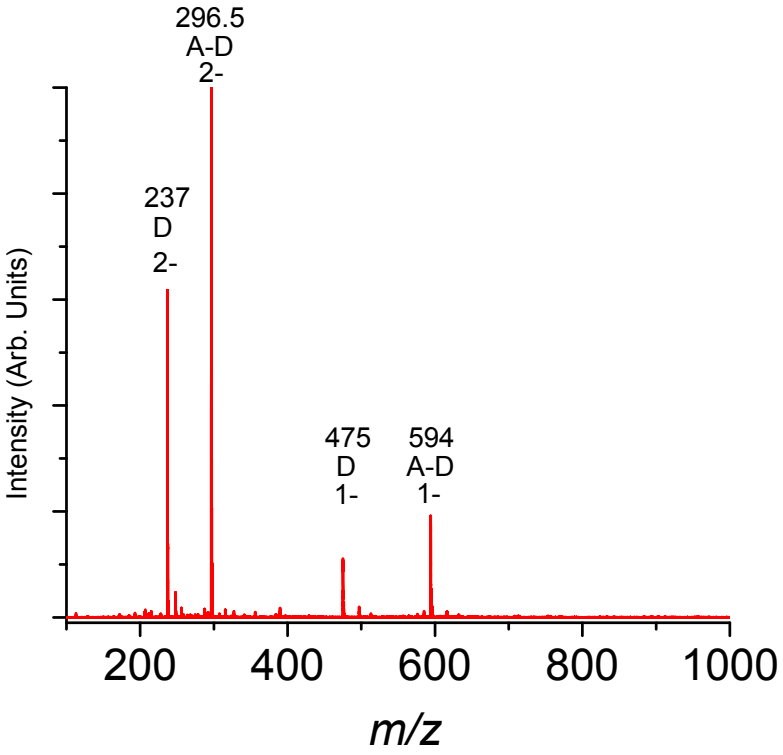

Figure S6. ESI-Mass spectrum of APTES-DOTAGA synthesis mixture in negative mode. D : DOTAGA, A-D : APTES-DOGA, 2- : $(M-2H)^{2-}$, 1- : $(M-H)^{-}$.

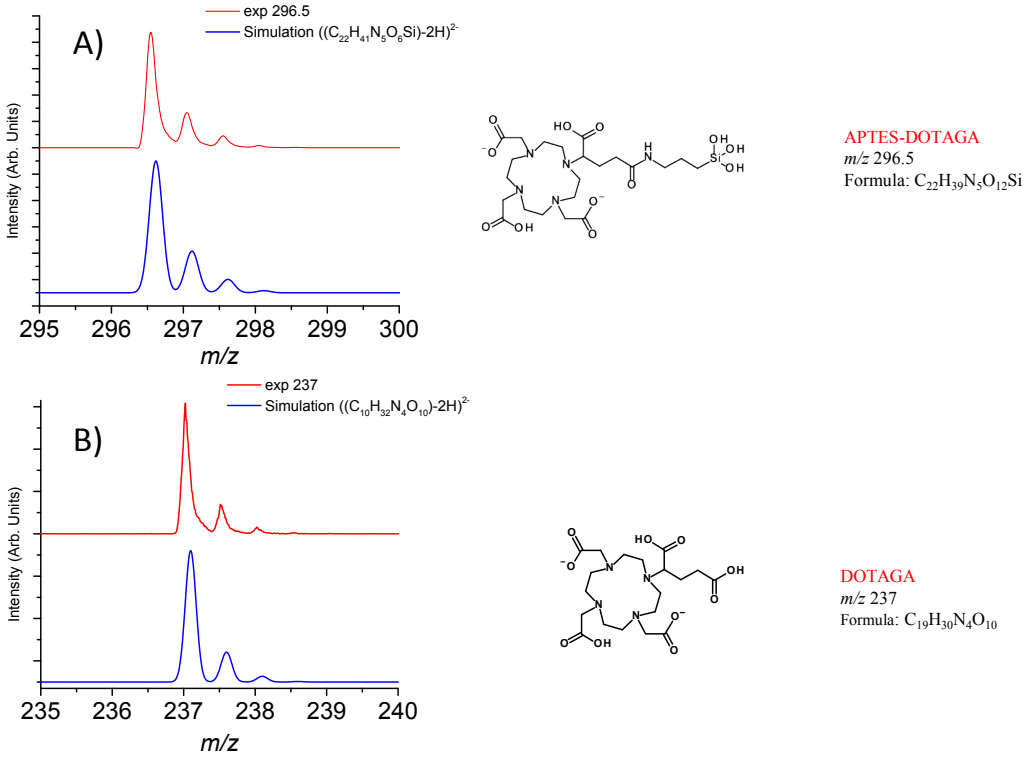

Figure S7. Magnified region of peak at A) 296.5 m/z and B) 237 m/z with simulated spectra and proposed molecular formulas.

EBT at pH 10 EBT(Ca^{2+}) at pH 10

Figure S8. Titrating samples before and after the equivalent point.

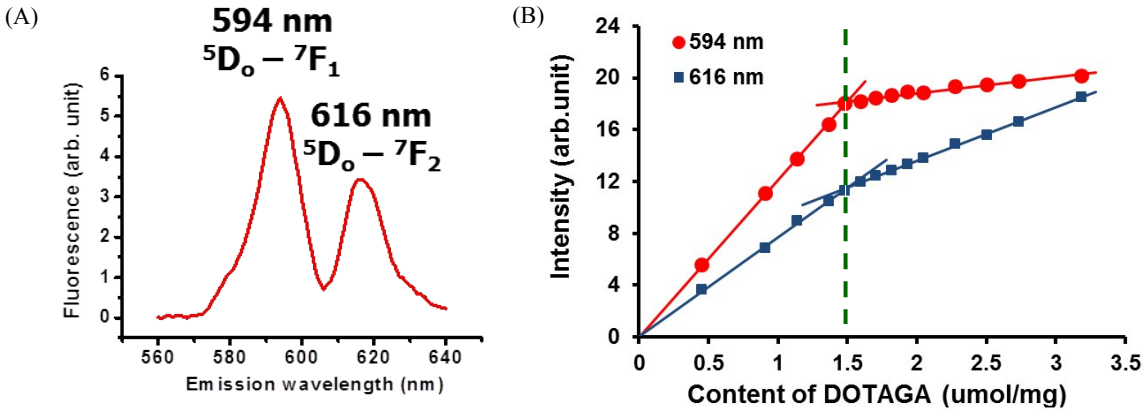

Figure S9. (A) Emission spectrum of a mixture of 40 µM $EuCl_3$ and 100 µM DOTAGA excited at 395 nm, (B) Titration curve of APTES-DOTAGA synthesis mixture at 594 nm (red) and 616 nm (blue)

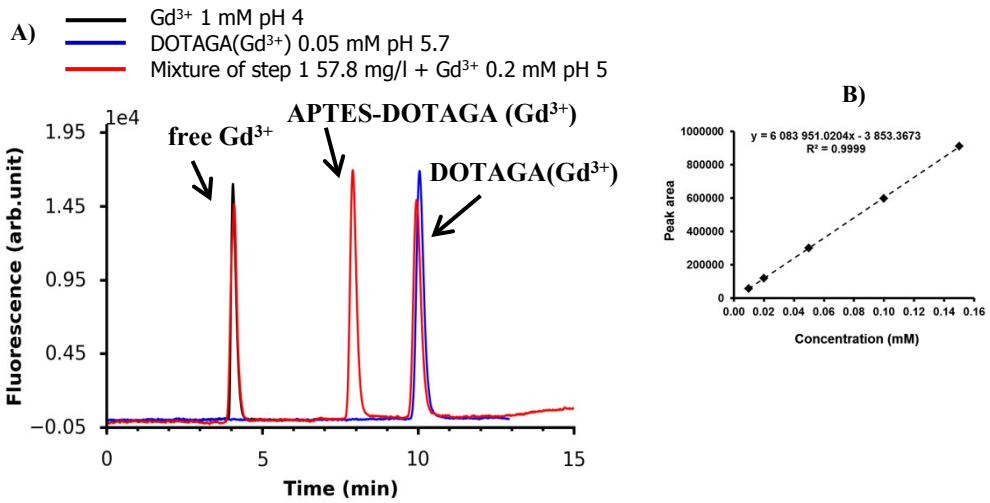

Figure S10. A) Chromatograms of the $GdCl_3$ 1mM solution (black), DOTAGA(Gd) 0.05 mM solution (blue) and products after the reaction betwen DOTAGA anhydride and APTES (red)
B) Calibration curve of DOTAGA(Gd^{3+})

Table S2. Characterizations of APTES-DOTAGA precursor synthesized from DOTAGA anhydride

Features	Method(s)	Result
Amide bond formation	IR	Appearance of C=O amide peak at 1677 cm^{-1}
Molecular weight	Mass spectrometry	Peaks at 594 and 296.5 m/z of APTES-DOTAGA
Content of total DOTAGA	Colorimetry with NET Titration with Eu^{3+}	~ 1.70 µmol/mg 1.47 ± 0.11 µmol/mg
Content of unreacted DOTAGA	HPLC (C18 column, Gd^{3+})	0.74 µmol/mg
Yield APTES-DOTAGA		74.15 %

Table S3. Summary of starting concentrations, starting ratio of components and type of solvent used in different formulas

Formula code	A-D (mM)	A (mM)	T (mM)	M (mM)	A-D : A : T : M	Total Si (mM)	Solvent
USNPr	10	10	20	-	1: 1 : 2 : 0	40	H_2O
USNPr@Gd	100	-	-	90	1: 1 : 2 : 0.9	-	H_2O
USNPr@Gd*	10	10	20	9	1: 1 : 2 : 0.9	40	H_2O
USNPi-1	14	6	-	-	7 : 3 : 0 : 0	20	DMSO/H_2O
USNPi-2	9.3	4	6.7	-	7 : 3 : 5 : 0	20	DMSO/H_2O
USNPi-3	7	3	10	-	7 : 3 : 10 : 0	20	DMSO/H_2O
USNPi-4	5.6	2.4	12	-	7 : 3 : 15 : 0	20	DMSO/H_2O
USNPi-5	12.3	14.1	35.3	-	7 : 8 : 20 : 0	61.6	DEG/H_2O
USNPi-5@Gd	100	-	-	95	7 : 8 : 20 : 6.6	-	H_2O
USNPi-5@Tb	100	-	-	95	7 : 8 : 20 : 6.6	-	H_2O
USNPi-5@Ho	100	-	-	95	7 : 8 : 20 : 6.6	-	H_2O
USNPi-5@Bi	100	-	-	90	7 : 8 : 20 : 6.3	-	H_2O

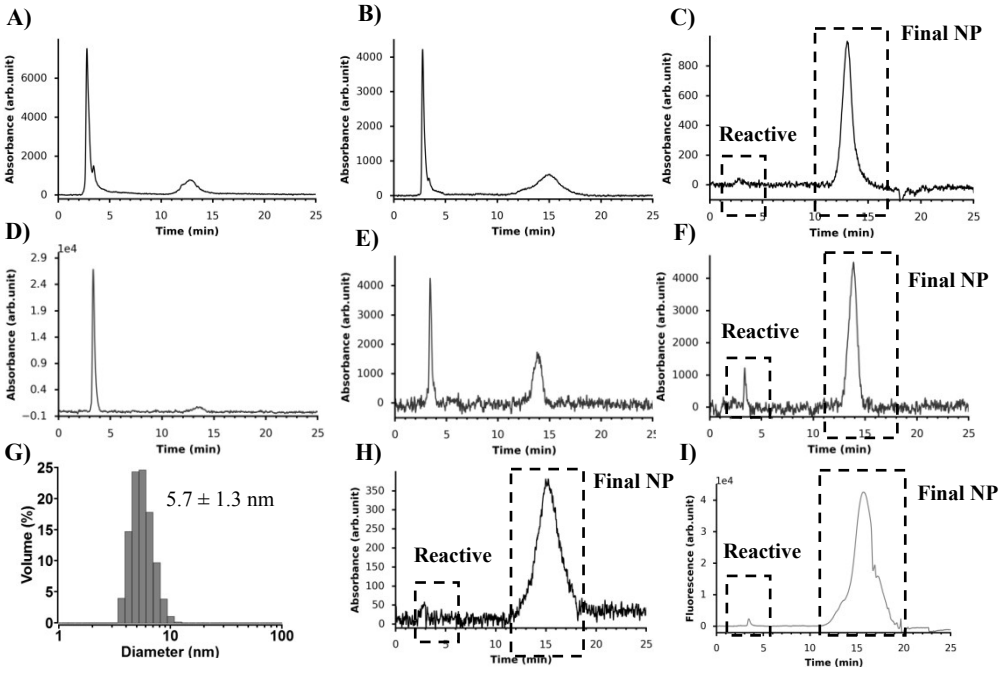

Figure S11. Characterizations during the synthesis of USNPr@Gd:
Chromatogram at 295 nm A) before concentration; B) after concentration and C) after purification;
Chromatogram at 700 nm after complexation with Cu^{2+} D) before concentration; E) after concentration and F) after purification;

G) DLS diagram of USNPr@Gd;
H) Chromatogram at 295 nm after complexation with Gd^{3+}; I) Chromatogram detected by fluorescence (λex = 274 nm, λem = 312 nm) after complexation with Gd^{3+}.

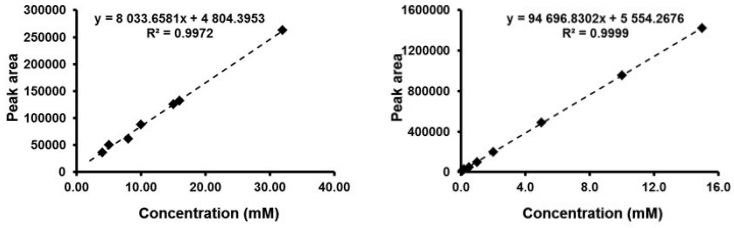

Figure S12. Calibration curves of $CuSO_4$ (left) and DOTAGA(Cu^{2+}) (right) in HPLC with C4 column at 700 nm

Table S4. Summarized table of peak areas in the chromatogram of USNPr complexed with Cu^{2+}

Peak	Area	Concentration (mM)	%
Cu^{2+}	44342	4.92	
Silane-DOTAGA(Cu^{2+})	53630	0.51	9.94
NP-DOTAGA(Cu^{2+})	441283	4.60	90.06
	Total	10.03	

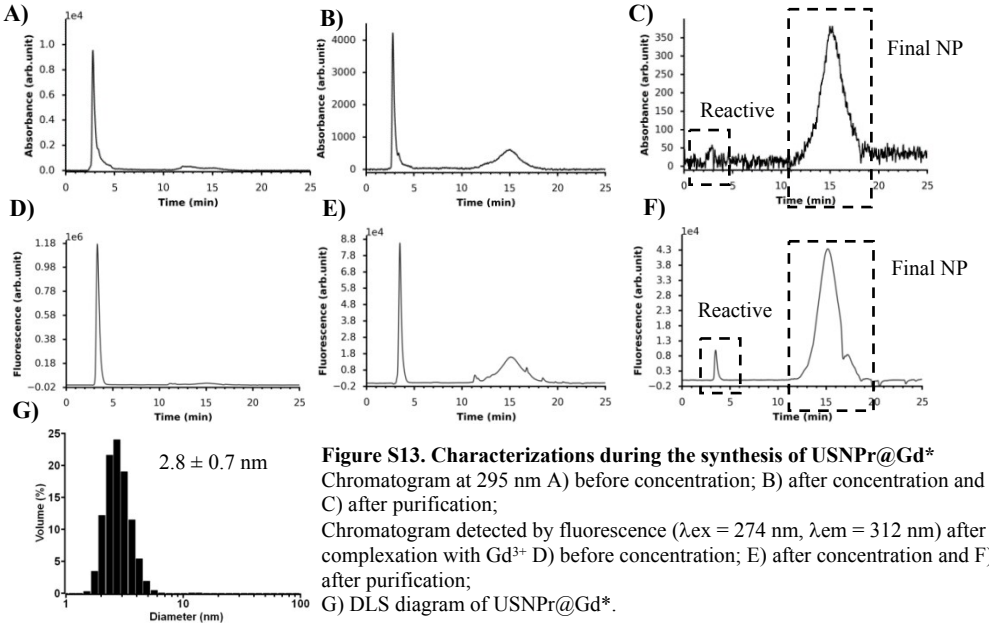

Figure S13. Characterizations during the synthesis of USNPr@Gd*
Chromatogram at 295 nm A) before concentration; B) after concentration and C) after purification;
Chromatogram detected by fluorescence (λex = 274 nm, λem = 312 nm) after complexation with Gd^{3+} D) before concentration; E) after concentration and F) after purification;
G) DLS diagram of USNPr@Gd*.

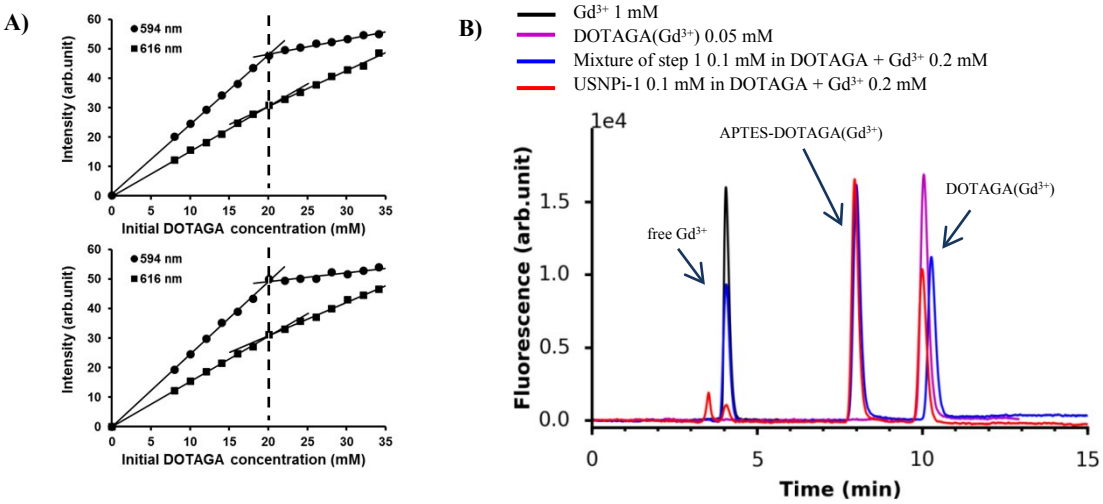

Figure S14. Quantification of produced APTES-DOTAGA in one-pot synthesis (USNPi-1, 2, 3, 4):
A) Quantification of total DOTAGA by Eu titration: titration curve at 594 nm (circles) and 616 nm (squares) of mixture after the reaction between APTES and DOTAGA anhydride (upper) and the same mixture exposed at pH 9 overnight (lower).
B) Quantification of unreacted DOTAGA by HPLC probed by Gd^{3+}: chromatograms of Gd^{3+} 1 mM solution (black), DOTAGA(Gd^{3+}) solution (violet) and reacted mixture at around 0.1 mM in DOTAGA complexed with 0.2 mM Gd^{3+}(blue) and the same mixture exposed at pH 9 overnight (red).

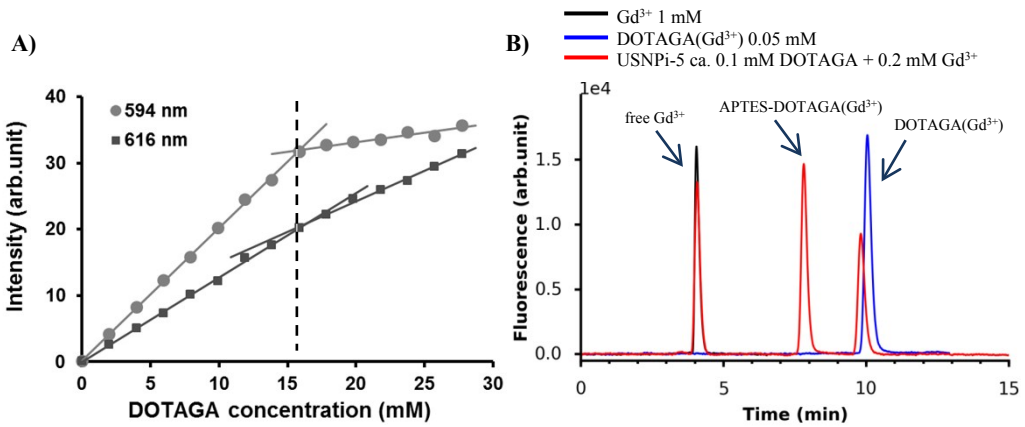

Figure S15. Quantification of produced APTES-DOTAGA in scaled up batch USNPi-5:
A) Quantification of total DOTAGA by Eu titration: titration curve at 594 nm (circles) and 616 nm (squares)
B) Quantification of unreacted DOTAGA by HPLC probed by Gd^{3+}: chromatograms of Gd^{3+} 1 mM solution (black), DOTAGA(Gd^{3+}) solution (blue) and reacted mixture at around 0.1 mM in DOTAGA complexed with 0.2 mM Gd^{3+}(red)

Table S5. Total DOTAGA and unreacted DOTAGA concentrations of USNPi-1 and 5 after the step of coupling reaction between DOTAGA anhydride and APTES

Samples	Measured time	[DOTAGA$_{total}$] (mM)	[DOTAGA$_{unreacted}$] (mM)	% DOTAGA$_{unreacted}$
USNPi-1	After the reaction	20	6.21	30.9
	In pH 9 overnight	20	5.91	29.4
USNPi-5	After the reaction	16	4.68	29.5

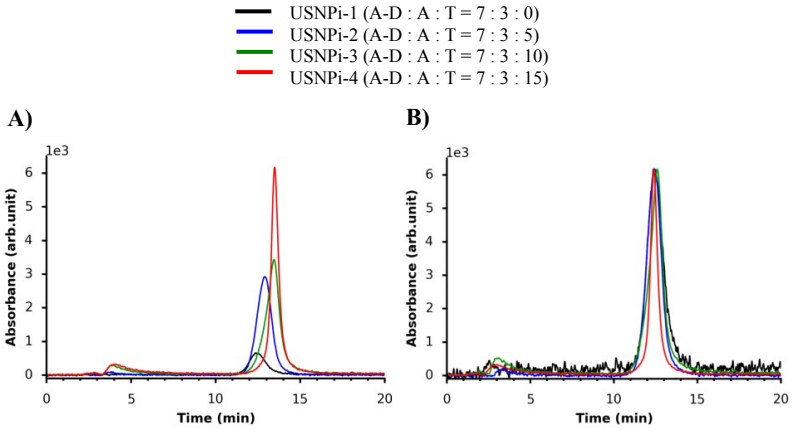

Figure S16. Chromatograms of USNPi with different ratio of starting silanes:
A) as originally acquired, B) normalized to the same height and shifted to the same t_R of NPs (A-D : A : T = APTES-DOTAGA : APTES : TEOS)

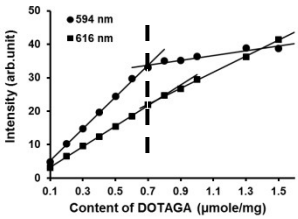

Figure S17. Eu titration curves of USNPi-4

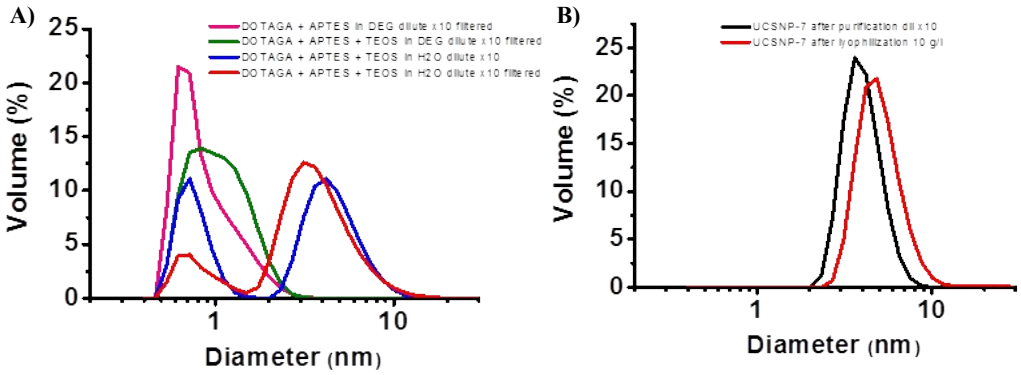

Figure S18. DLS diagrams of USNPi-5: A) at different step during the synthesis: APTES + DOTAGA anhydride in DEG (pink), APTES + DOTAGA anhydride + TEOS in DEG (green), APTES + DOTAGA + TEOS in H_2O (blue), APTES + DOTAGA + TEOS in H_2O filtered through 0.2 µm membrane (red); B) After purification (black)

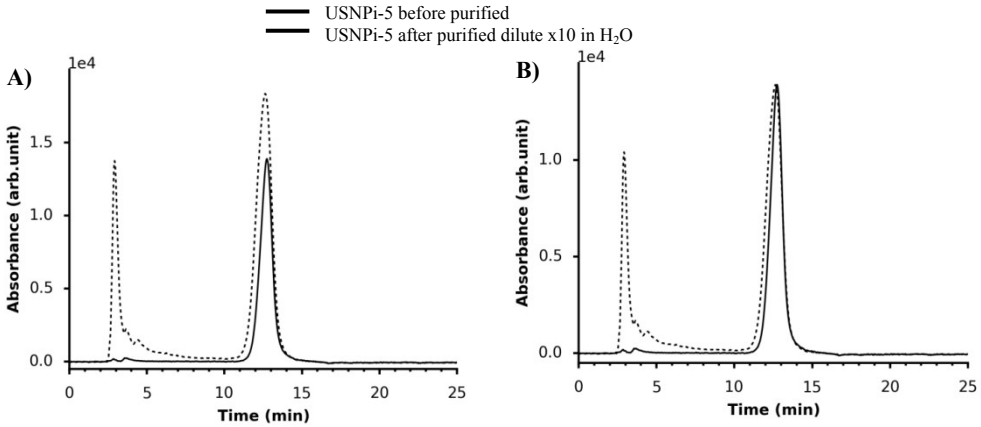

Figure S19. Chromatograms of USNPi-5 at 295 nm: as A) originally acquired or B) normalized to the same height (dashed line: before purified, solide line: after purified)

Table S6. Summary of DLS and HPLC results of USNPi-5 in different step during the synthesis

Samples	D_H (nm)	t_R (min)	FWHM (min)	Purity (%)
DOTAGA + APTES in DEG	0.9 ± 0.4	-	-	-
DOTAGA + APTES + TEOS in DEG	1.1 ± 0.4	-	-	-
DOTAGA + APTES + TEOS in H_2O	4.7 ± 1.7 & 0.8 ± 0.2	-	-	-
DOTAGA + APTES + TEOS in H_2O filtered	4.1 ± 1.9 & 0.8 ± 0.2	12.63	1.1333	68.6
USNPi-5 after purified	4.1 ± 1.0	12.76	0.8583	98.3
USNPi-5 redispersed after lyophilized	5.2 ± 2.0			

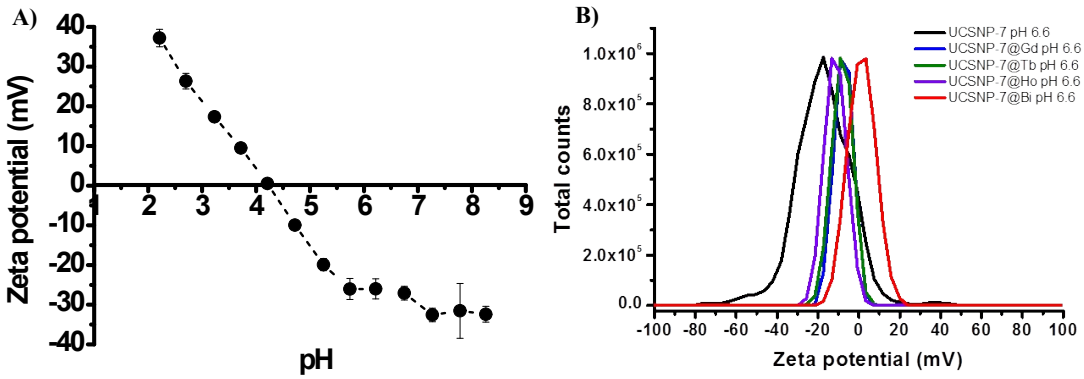

Figure S20. Zeta potentials of USNPi-5:
A) Full curve at different pHs of empty USNPi-5
B) Zeta potential graphs at pH 6.6 of empty USNPi-5 (black) and the same NP after complexed with metals: Gd (blue), Tb (green), Ho (violet), Bi (red)

Table S7. Zeta potential of empty USNPi-5 at different pHs

pH	Zeta potential (mV)
2.21	37.2
3.23	17.3
4.21	0.558
5.25	-19.9
6.22	-26
6.75	-27.1
7.27	-32.6
7.78	-31.5
8.26	-32.4

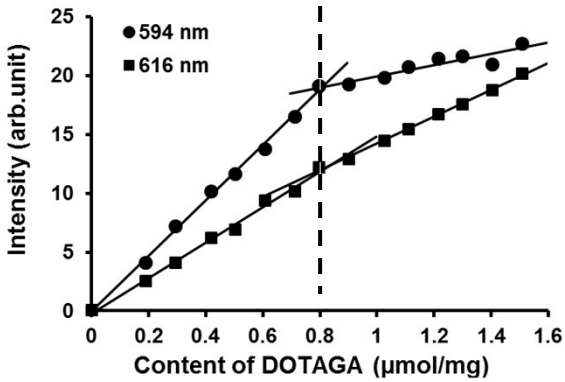

Figure S21. Eu titration curve of USNPi-5

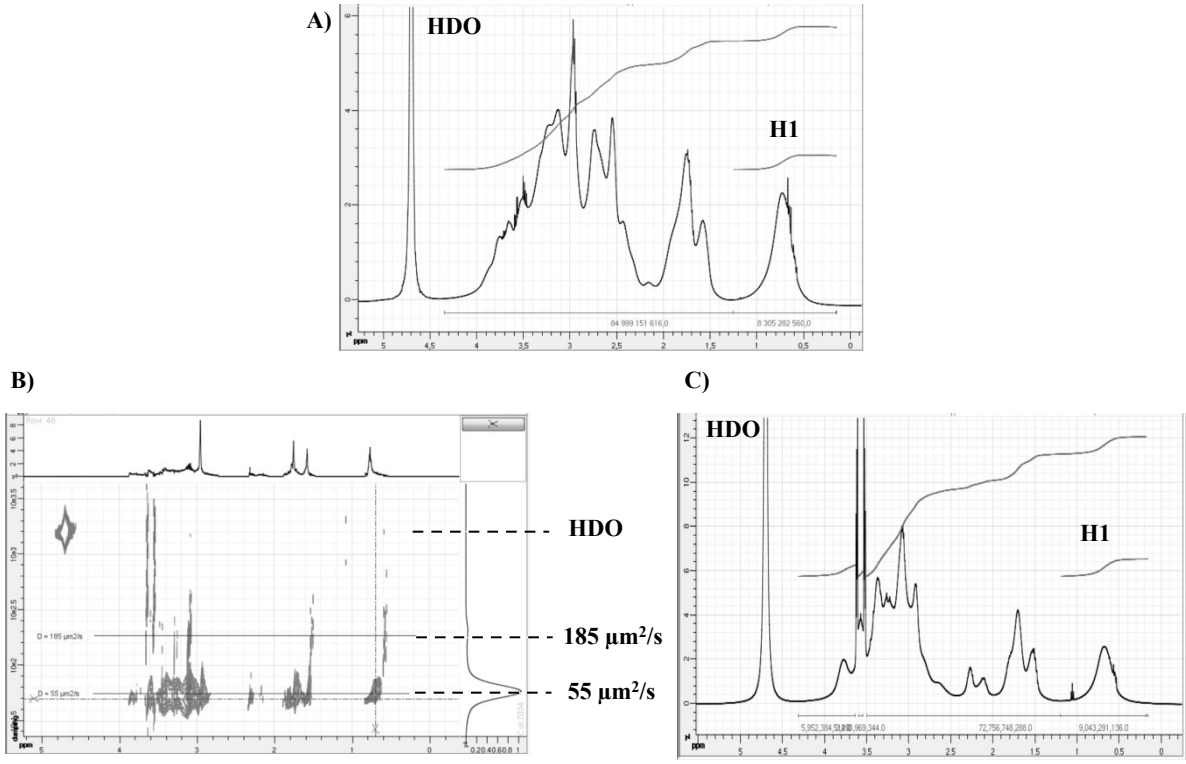

Figure S22. NMR spectra of USNPr@Lu and USNPi-5: A) ^{1}H NMR spectrum of USNPr@Lu at 127 g/l; B) NMR-DOSY spectrum and C) ^{1}H NMR spectrum of USNPi-5 at 100 g/l.

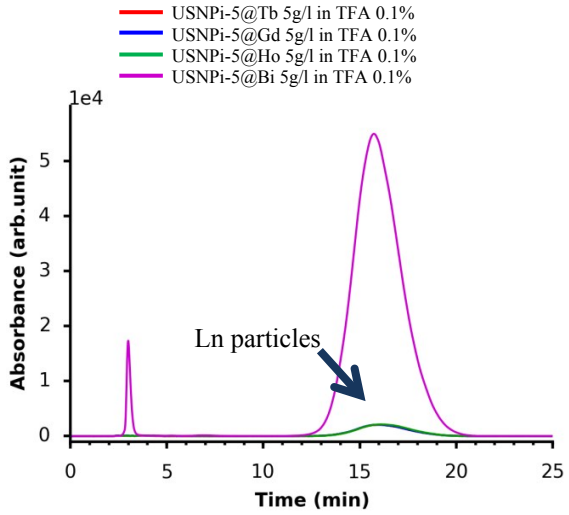

Figure S23. Chromatograms at 295 nm as originally acquired of USNPi-5 complexed with metals: Tb (red), Gd (blue), Ho (green), Bi (violet)

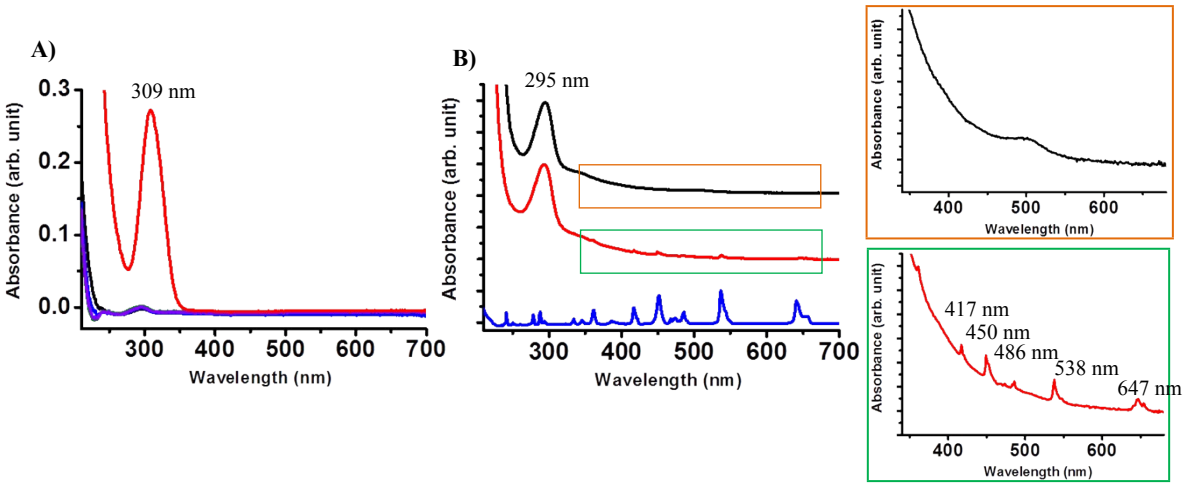

Figure S24. UV-visible absorption spectra of empty and metal complexed USNPi-5:
A) Absorption spectra of empty (black), Gd (green), Tb (blue), Ho (violet), Bi (red) NP at 0.06 g/l
B) Absorption spectra of empty (black) and Ho (red) NP at 5 g/l as well as solution of $HoCl_3$ 50 mM in HCl 0.1 mM (blue).
Insets: zoomed ROI of the spectrum of the empty (orange) and Ho complexed NP (green)

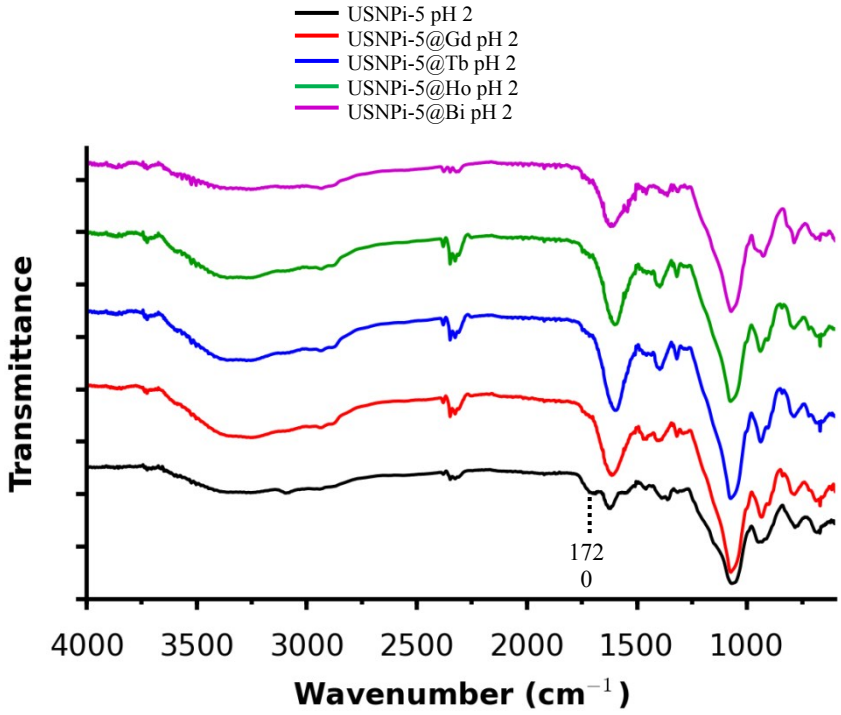

Figure S25. Infrared spectra of empty and metal-complexed USNPi-5

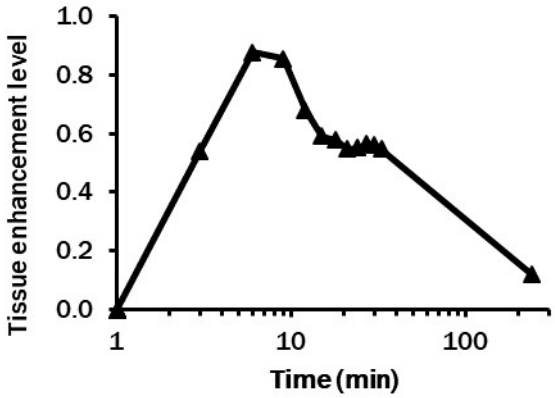

Figure S26. Dynamic MRI signal enhancement in the liver after injection of USNPr@Gd*.

Table S8. Elemental analysis of USNP(r/i)

Batch	USNPr			USNPr@Gd			USNPr@Gd*			USNPi-2			USNPi-3			USNPi-4			USNPi-5		
%mass Gd	0.0000			9.5000			9.9000			0.0000			0.0000			0.0000			0.0000		
relative mol Gd	0.0000			1.0000			1.0000			0.0000			0.0000			0.0000			0.0000		
%mass Si	19.0000			18.0000			17.0000			15.9000			19.9000			23.7000			16.7000		
relative mol Si	1.1845			10.6069			9.6129			0.9554			1.3596			1.8185			1.1256		
%mass C	28.6000			24.1000			25.9000			27.3000			23.8000			22.0000			27.9000		
relative mol C	4.1703			33.2155			34.2541			3.8369			3.8032			3.9482			4.3981		
%mass N	8.0000			6.8000			7.0000			8.3000			7.3000			6.5000			7.4000		
relative mol N	1.0000	Ratio	Content (μmol/mg)	8.0341	Ratio	Content (μmol/mg)	7.9363	Ratio	Content (μmol/mg)	1.0000	Ratio	Content (μmol/mg)	1.0000	Ratio	Content (μmol/mg)	1.0000	Ratio	Content (μmol/mg)	1.0000	Ratio	Content (μmol/mg)
relative mol Gd	0.0000		0.0000	1.0000	0.7681	0.6041	1.0000	0.6702	0.6296	0.0000		0.0000	0.0000		0.0000	0.0000		0.0000	0.0000		0.0000
relative mol A-D*	0.1672	1.0000	0.9547	1.3019	1.0000	0.7865	1.4922	1.0000	0.9394	0.1196	1.0000	0.7083	0.1147	1.0000	0.6798	0.1355	1.0000	0.8025	0.1683	1.0000	0.8889
relative mol A	0.1640	0.9812	0.9367	1.5247	1.1711	0.9211	0.4753	0.3185	0.2992	0.4022	3.3643	2.3829	0.4263	3.7151	2.5255	0.3227	2.3820	1.9117	0.1586	0.9422	0.8375
relative mol T	0.8533	5.1038	4.8725	7.7803	5.9762	4.7003	7.6454	5.1236	4.8133	0.4337	3.6273	2.5692	0.8186	7.1341	4.8496	1.3604	10.0424	8.0594	0.7987	4.7461	4.2188
relative mol DEG																			0.0550	0.3270	0.2907
free chelators						0.1824			0.3099												
% free chelators						23.1883			32.9844												

**A-D: APTES-DOTAGA, A: APTES, T: TEOS*

Table S9. Properties of USNP synthesized from ready-to-use APTES-DOTAGA (USNPr)

Properties	Method(s)	USNPr	USNPr@Gd	USNPr@Gd*
Starting ratio A-D : A : T (: Gd)*	-	1 A-D : 1 A : 2 T	1 A-D : 1 A : 2 T : 0.9 Gd	1 A-D : 1 A : 2 T : 0.9 Gd
Total silane concentration (mM)	-	40	-	40
D_H (nm)	DLS	4.6 ± 1.6	5.7 ± 1.3	2.8 ± 0.7
D_H (nm)	NMR DOSY	7.0 ± 2.5 (empty) 6.8 ± 2.4 (Lu^{3+})	-	-
Zeta potential (mV)	Zeta potentiometry	-21.4 (pH 6.63) -27.1 (pH 7.37)	- 5.8 (pH 6.65) -8.2 (pH 7.34)	-35.6 (pH 7.38)
Retention time (min)	HPLC (295 nm)	13.0	15.7	15.2
Peak shape#	HPLC (295 nm)	S	S	S
FWHM (min)	HPLC (295 nm)	1.0250	2.4083	2.6583
Purity (%)	HPLC (295 nm)	97.6	~ 100	96.8
	HPLC (Cu^{2+})	93.9	-	-
DOTAGA content (µmol/mg)	EBT titration	-	-	-
	Eu^{3+} titration	0.787	-	-
	HPLC (Cu^{2+})	0.715	-	-
r_1 ($mM^{-1}.s^{-1}$) (37°C, 60 MHz)	Relaxometry	-	21.4	18.5
r_2/r_1 (37°C, 60 MHz)	Relaxometry	-	1.59	1.55
A/A-D	1H NMR	1.35 (empty) 0.87 (Lu^{3+})	-	-
Gd content (µmol/mg)	ICP-OES	-	0.604	0.630
(Gd :) Si : N : C (% mass)	Elemental analysis	19.0 Si : 8.0 N : 28.6 C	9.5 Gd : 18 Si : 6.8 N : 24.1 C	9.9 Gd : 17.0 Si : 7.0 N : 25.9 C
A-D : A : T (: Gd) (molar ratio)	Elemental analysis	1.0 A-D : 1.0 A : 5.1 T	1.0 A-D : 1.2 A : 6.0 T : 0.8 Gd	1.0 A-D : 0.3 A : 5.1 T: 0.7 Gd
Free DOTAGA (%)	Eu^{3+} titration	100	10	24
Free DOTAGA (%)	Elemental analysis	100	23.2	33.0
Yield (%) (in DOTAGA)	-	9.2	6.9	10.7
Yield (%) (in Gd)	-	-	64	10.6

**A-D: APTES-DOTAGA, A: APTES, T: TEOS, #S: symmetrical*

Table S10. Properties of USNP synthesized from *in-situ* formed APTES-DOTAGA (USNPi)

Properties	Method(s)	USNPi-1	USNPi-2	USNPi-3	USNPi-4	USNPi-5
Starting ratio A-D : A : T*	-	7 A-D : 3 A : 0 T	7 A-D : 3 A : 5 T	7 A-D : 3 A : 10 T	7 A-D : 3 A : 15 T	7 A-D : 8 A : 20 T
Total [silane] (mM)		20	20	20	20	60
Solvent		DMSO/H_2O	DMSO/H_2O	DMSO/H_2O	DMSO/H_2O	DEG/H_2O
D_H after synthesized (nm)	DLS	too weak signal	5.2 ± 1.2	7.5 ± 2.1	13.6 ± 3.9	4.1 ± 1.0
D_H redispersed pH 7 (nm)	DLS	2.8 ± 0.5	4.3 ± 0.9	7.6 ± 1.9	14.4 ± 7.1	5.2 ± 2.0
D_H (nm)	NMR DOSY	-	-	-	-	7.0 ± 2.5 (empty)
Zeta potential (mV)	Zeta potentiometry	-	-	-	-	Full curve -32.6 (pH 7.27)
Retention time (min)	HPLC (295 nm)	12.4	12.9	13.4	13.5	12.76
Peak shape[#]	HPLC (295 nm)	S	S	S	S	S
FWHM (min)	HPLC (295 nm)	1.1250	0.9917	0.8417	0.4750	0.8583
Purity (%)	HPLC (295 nm)	94.0	97.1	90.1	88.6	98.3
DOTAGA content (µmol/mg)	Eu^{3+} titration	1.1	0.8	0.7	0.7	0.8
r_1 ($mM^{-1}.s^{-1}$) (37°C, 60 MHz)	Relaxometry	-	16.92	19.21	19.79	-
r_2/r_1 (37°C, 60 MHz)	Relaxometry	-	1.53	1.80	2.04	-
A/A-D	1H NMR	-	-	-	-	1.26 (empty)
Si : N : C (molar ratio)	Elemental analysis	-	1.0 : 1.0 : 3.8	1.4 : 1.0 : 3.8	1.8 : 1.0 : 3.9	1.1 : 1.0 : 4.4
A-D : A : T (molar ratio)	Elemental analysis	-	1.0 : 3.4 : 3.6	1.0 : 3.7 : 7.1	1.0 : 2.4 : 10.0	1.0 : 1.0 : 4.7
Yield (%) (in DOTAGA)	-	1.15	7.94	12.20	15.41	24.7

**A-D: APTES-DOTAGA, A: APTES, T: TEOS, [#]S: symmetrical*

Table S11. Properties of metals complexed USNPi

Properties	Method(s)	USNPi-5@Gd	USNPi-5@Tb	USNPi-5@Ho	USNPi-5@Bi
Starting ratio A-D : A : T (: M)*	-	7 A-D : 8 A : 20 T : 6.6 Gd	7 A-D : 8 A : 20 T : 6.6 Tb	7 A-D : 8 A : 20 T : 6.6 Ho	7 A-D : 8 A : 20 T : 6.3 Bi
D_H (nm)	DLS	6.3 ± 1.7	6.1 ± 1.7	5.8 ± 1.6	6.0 ± 1.6
Zeta potential (mV)	Zeta potentiometry	-6.9 (pH 6.65) -21.8 (pH 7.36)	-7.9 (pH 6.64) -19.3 (pH 7.39)	-12.0 (pH 6.65) -19.8 (pH 7.42)	2.3 (pH 6.67) -3.4 (pH 7.35)
Retention time (min)	HPLC (295 nm)	15.96	15.96	16.05	15.74
Peak shape	HPLC (295 nm)	S	S	S	S
FWHM (min)	HPLC (295 nm)	3.0333	3.0333	3.1083	2.7417
Purity (%)	HPLC (295 nm)	96.6	98.3	97.3	97.4
r_1 ($mM^{-1}.s^{-1}$) (37°C, 60 MHz)	Relaxometry	23.23	-	-	-
r_2/r_1 (37°C, 60 MHz)	Relaxometry	1.65	-	-	-
M content (µmol/mg)	ICP-OES	0.654	0.558	0.625	0.442
A-D : A : T : M	Assumption	1.0 A-D : 1.0 A : 4.7 T : 0.7 Gd	1.0 A-D : 1.0 A : 4.7 T : 0.6 Tb	1.0 A-D : 1.0 A : 4.7 T : 0.7 Ho	1.0 A-D : 1.0 A : 4.7 T : 0.5 Bi
Yield (%) (in metal)	-	69.2	62.7	68.2	51.2

**A-D: APTES-DOTAGA, A: APTES, T: TEOS, M: metal (Gd, Tb, Ho or Bi), [#]S: symmetrical*

References

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