Electronic Supplementary Material (ESI) for Nanoscale.

Electronic Supplementary Information (ESI)

^{99m}Tc Radiolabelling of Fe_3O_4-Au core-shell and Au-Fe_3O_4 Dumbbell-like nanoparticles

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1) Materials

All reagents were purchased from commercial sources and used without further purification. Ethyl cyanoacetate (98%), di-*tert*-butyl dicarbonate (97%) and sodium borohydride (>96%) were acquired from ABCR (Germany). Glacial acetic acid (100%), hydrochloric acid (37%), dichloromethane, ethanol, ethyl acetate, hexane, tetrahydrofurane, butanol, toluene, iso-propanol, 1,2-dichloroethane, chloroform, dimethylformamide and methanol (all reagent grade) were purchased from Merck (Switzerland). Sodium nitrite (≥97%), sodium bicarbonate (99%), diethyl ether (≥97%), sodium dithionite (technical grade, 85%), *p*-toluenesulfonic acid monohydrate (≥98.5%), magnesium sulfate (97%), *N,N*-diisopropylethylamine (≥99%), sodium chloride (97%), triethylene glycol (99%), sodium hydride (60% dispersion in mineral oil), benzyl bromide (98%), tetrabromomethane (99%), triphenylphosphine (≥98.5%), sodium (cubes), nickel(II) chloride hexahydrate (≥98%), diethylenetriamine (99%), palladium on carbon (10 wt. % loading), triphenylmethanethiol (97%), triethylsilane (97%), tetraethylene glycol (99%), *p*-toluenesulfonyl chloride (97%), potassium hydroxide (flakes, 90%), sodium azide (≥99%), sodium triacetoxyborohydride (97%), 2-pyridinecarboxaldehyde (99%), DL-α-lipoic acid (≥98%), methanesulfonyl chloride (≥99.7%), triethylamine (≥99%), ethyl glyoxylate (50% solution in toluene), lithium hydroxide (98%), amberlite IR120 H, *N*-hydroxysuccinimide (≥97%), d-biotin (≥99%), *N,N'*-dicyclohexylcarbodiimide (99%), dimethylaminopyridine (≥99%), iodomethane (≥99%), methoxypolyethylene glycol 750, *tert*-butyl bromoacetate (98%), dopamine hydrochloride, iron(III) acetylacetonate (≥97%), oleylamine (tech. grade, 70%), 1,2-hexadecanediol (tech. grade 90%), iron pentacarbonyl, sodium phosphate monobasic dehydrate (≥99%), sodium phosphate dibasic dodecahydrate (≥99%), tris(2-carboxyethyl)phosphine hydrochloride (≥98%), tetramethylammonium hydroxide solution (25 wt. % in water) and HPLC solvents were purchased from Sigma Aldrich (Switzerland). Trifluoroacetic acid (99%), diphenyl ether (99%), oleic acid (tech. grade 90%), 1,2,3,4-tetrahydronaphthalene (97%), 1-octadecene (tech. grade 90%), gold(III) acetate (99.9%) and hydrogen tetrachloroaurate(III) hydrate (99.9%) were obtained from Alfa Aesar (Germany). Deuterated NMR solvents were obtained from Armar Chemicals (Switzerland). Water was doubly distilled before use. PD-10 size exclusion columns (Sephadex G-25 medium) were purchased from GE Healthcare (Switzerland). Isolink™ kits were a gift from Mallinckrodt Medical B.V. (Netherlands). $Na^{99m}TcO_4$ in 0.9% saline was eluted from a $^{99}Mo/^{99m}Tc$ UTK FM generator from Mallinckrodt Medical B.V. (Netherlands).

2) Characterisation

The UV-Vis measurements were collected on a Perkin Elmer Lambda 35 UV-Vis spectrophotometer between 200 and 900 nm. ^{1}H NMR and ^{13}C NMR spectra were recorded on a BrukerDRX 400 MHz or BrukerDRX 500 MHz spectrometer. ^{1}H and ^{13}C chemical shifts were referenced with the residual solvent resonances relative to TMS. Electronspray-Ionisation mass spectrometry (ESI-MS) was performed on a Bruker esquire™/LC spectrometer or on a Bruker esquire™/HCT™ spectrometer. High-resolution mass spectrometry (HR-MS) was performed on a Thermo DFS double-focusing system (ThermoFisher Scientific, Germany). Inductively coupled plasma mass spectrometry (ICP-MS) was measured on an Agilent QQQ8800 Triple Quad, equipped with a standard x-lens setting, nickel cones and a “micro-mist” quartz nebulizer. Tune settings were based on the Agilent General Purpose method and only slightly modified by an autotune procedure. Iron was measured as isotope ^{56}Fe, gold as isotope ^{197}Au and the values are reported as the average of 50 sweeps with five replicates. Dynamic light scattering (DLS) measurements were carried out on a Malvern Zetasizer Nano Series instrument utilizing 90° backscatter at 25 °C. The concentration of stock NPs solutions were 0.5 mg/ml in phosphate buffered saline (PBS, pH 7.4), and all NPs were filtered through a 0.2 µm filter before analysis. Typical count rates were 150-300 kHz. Hydrodynamic diameter (HDD) data are reported as the mean of triplicate measurements. Transmission electron microscopy (TEM) was done on a FEI Tecnai G2 Spirit operated at 120 kV (NP analysis after synthesis). One drop of a dilute sample of NPs in hexane or PBS was placed onto a formvar-coated copper grid, allowing the solvent to evaporate. Size analysis was performed on captured digital images using ImageJ V.1.47m, the size was determined from an average of 50 measurements and expressed as mean value ± standard deviation. Analytical HPLC was performed on a Merck L7000 system, using a Macherey-Nagel Nucleosil C18 column. HPLC solvents were 0.1% TFA (solvent A) and MeOH HPLC grade (solvent B). The HPLC gradient used is as follows: 0-3 minutes: 100% A; 3.1-9 minutes: 75% A, 25% B; 9.1-20 minutes: linear gradient from 66% A (34% B) to 0% A (100% B); 20-28 minutes: 100% B; 28.1-30: 100% A. The flow rate was 0.5 ml/min. Detection was performed at 254 nm. The system was equipped with the UV-detector L-7400 and the γ-detector Berthold FlowStar LB513. Activity measurements were carried out with a VDC-304 dose calibrator (Veenstra Instruments).

3) Analyses of Fe_3O_4-Au core-shell nanoparticles

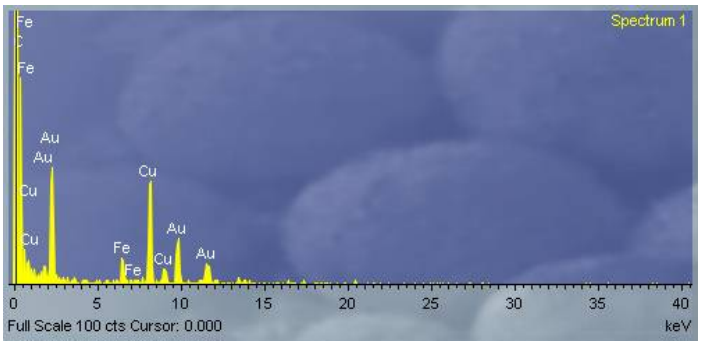


Figure S1. EDX spectrum of hydrophobic Fe_3O_4-Au core-shell nanoparticles (Cu peaks originate from the formvar-coated copper grid).

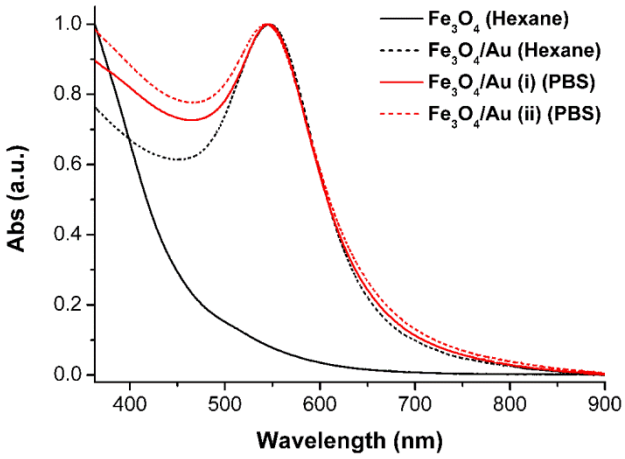


Figure S2a. Normalized UV-Vis spectra of hydrophobic and hydrophilic Fe_3O_4-Au core-shell nanoparticles, coated with (i) ligand **1** and **3** (ratio 3:1); (ii) ligand **1**, **3** and **5** (ratio 3:1:1).

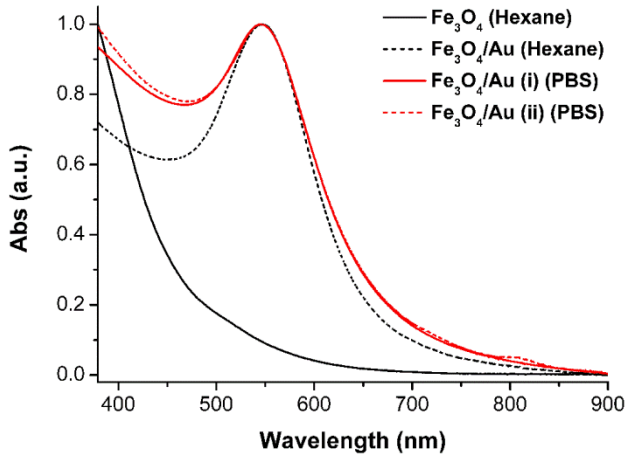


Figure S2b. Normalized UV-Vis spectra of hydrophobic and hydrophilic Fe_3O_4-Au core-shell nanoparticles, coated with (i) ligand **1** and **4** (ratio 3:1); (ii) ligand **1**, **4** and **5** (ratio 3:1:1).

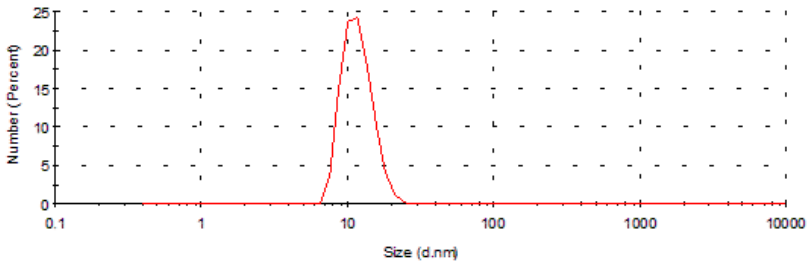


Figure S3. DLS measurement of hydrophilic Fe_3O_4-Au core-shell nanoparticles, coated with ligand **1** and **3** (ratio 3:1).

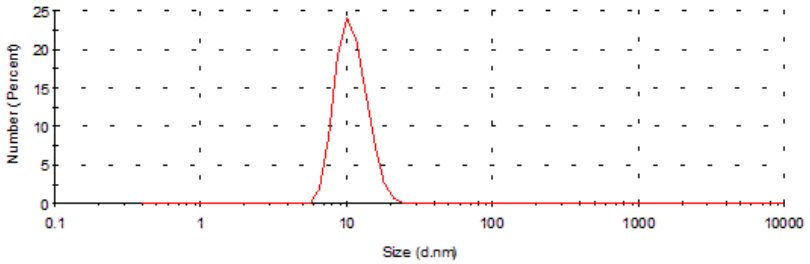


Figure S4. DLS measurement of hydrophilic Fe_3O_4-Au core-shell nanoparticles, coated with ligand **1** and **4** (ratio 3:1).

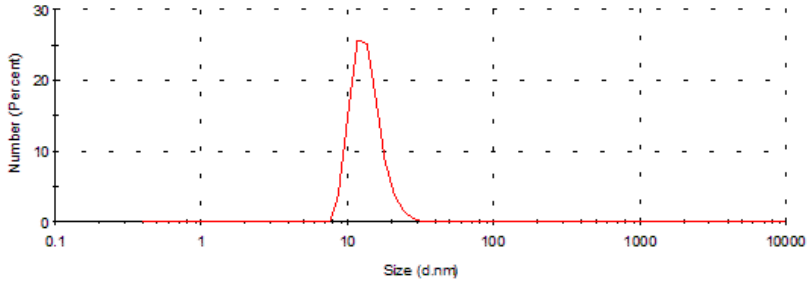


Figure S5. DLS measurement of hydrophilic Fe_3O_4-Au core-shell nanoparticles, coated with ligand **1, 3** and **5** (ratio 3:1:1).

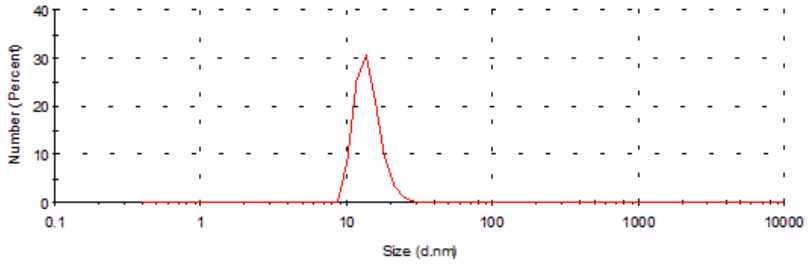


Figure S6. DLS measurement of hydrophilic Fe_3O_4-Au core-shell nanoparticles, coated with ligand **1, 4** and **5** (ratio 3:1:1).

4) Analyses of Au-Fe_3O_4 Dumbbell-like nanoparticles

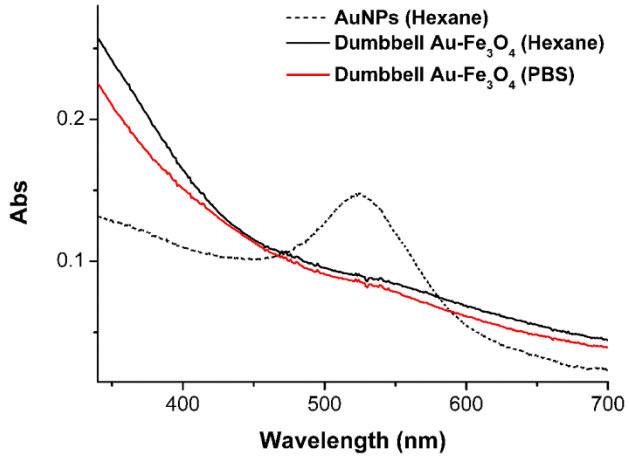


Figure S7. UV-Vis spectra of hydrophobic and hydrophilic Au-Fe_3O_4 Dumbbell-like nanoparticles.

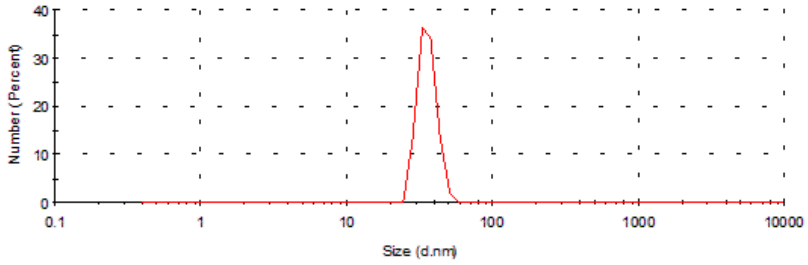


Figure S8. DLS measurement of hydrophilic Au-Fe_3O_4 Dumbbell-like nanoparticles.

5) ^{99m}Tc Labelling of Fe_3O_4-Au core-shell nanoparticles

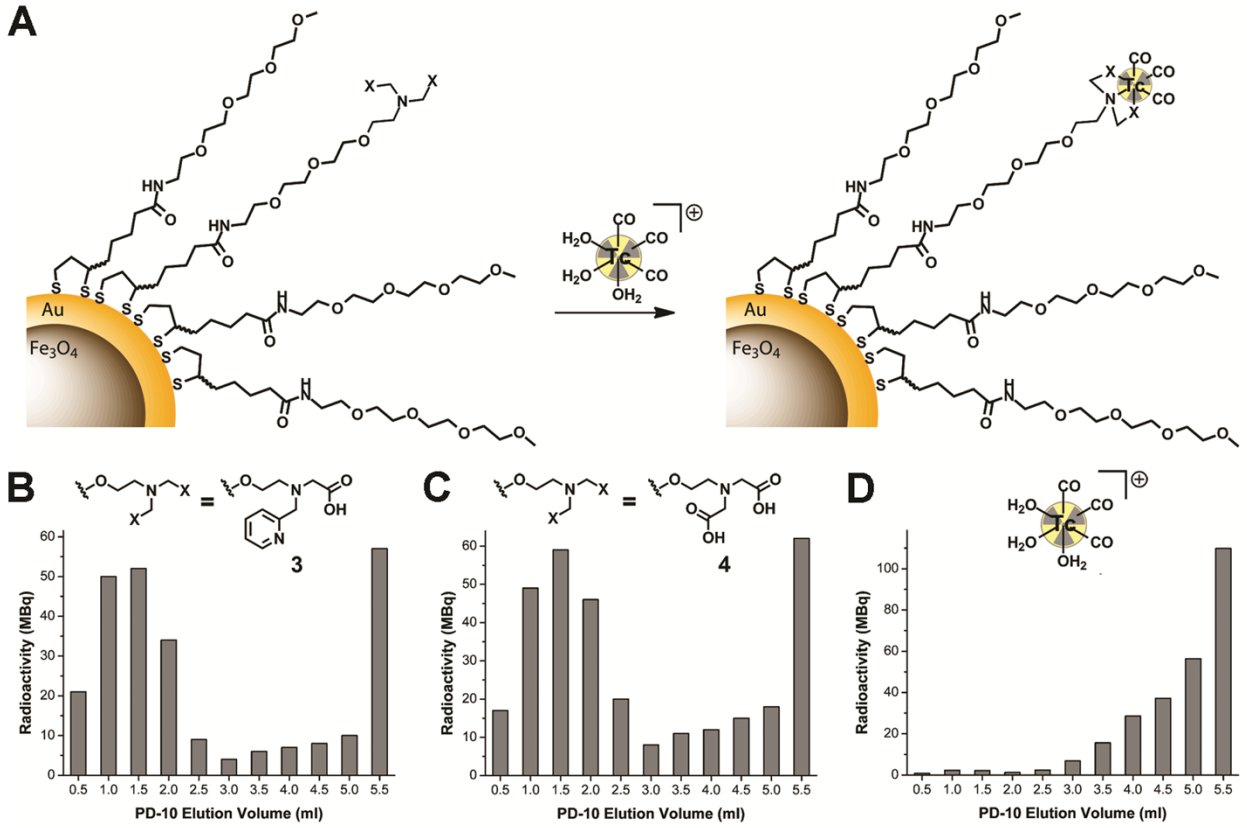


Figure S9. Radiolabelling of Fe_3O_4-Au core-shell NPs with an illustrative scheme of the labelling procedure (A) and the PD-10 size exclusion chromatograms after incubation at 50 °C for 2 h of NPs containing chelator **3** (B), **4** (C) and a control chromatogram with $[^{99m}Tc(OH_2)_3(CO)_3]^+$ (D). Please note that 0.5 ml fractions were collected and the very last fraction was the remainder activity in the PD-10 column (including the activity in the column). The very first 1.0 ml (two 0.5 ml fractions) is not shown in any of the chromatograms since it always was mobile phase only.

6) ^{99m}Tc complexes with ligands 2, 3, 4 and 6

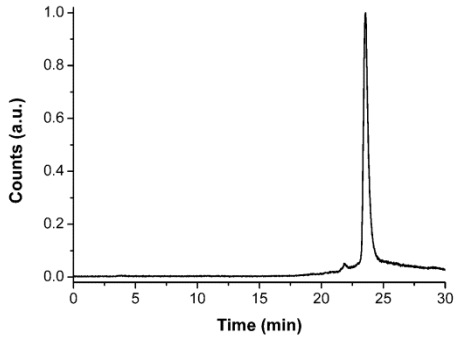


Figure S10. Normalized HPLC analysis of ^{99m}Tc labelled ligand **2** (retention time 23.57 min).

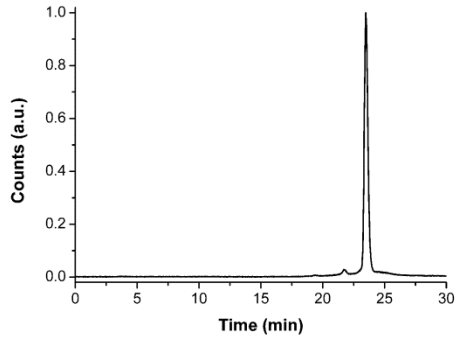


Figure S11. Normalized HPLC analysis of ^{99m}Tc labelled ligand **3** (retention time 23.48 min).

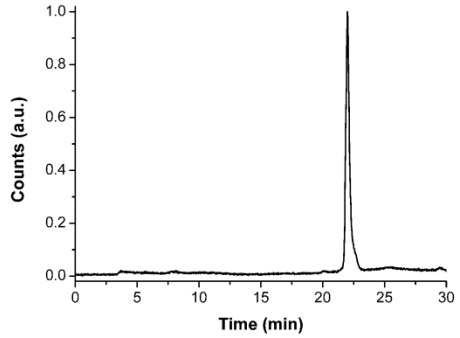


Figure S12. Normalized HPLC analysis of ^{99m}Tc labelled ligand **4** (retention time 22.00 min).

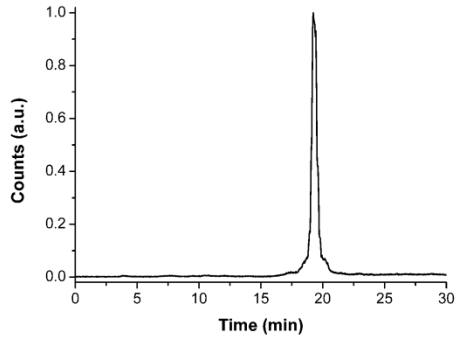


Figure S13. Normalized HPLC analysis of ^{99m}Tc labelled ligand **6** (retention time 19.23 min).

7) ^{99m}Tc labelling of Au-Fe_3O_4 Dumbbell-like nanoparticles

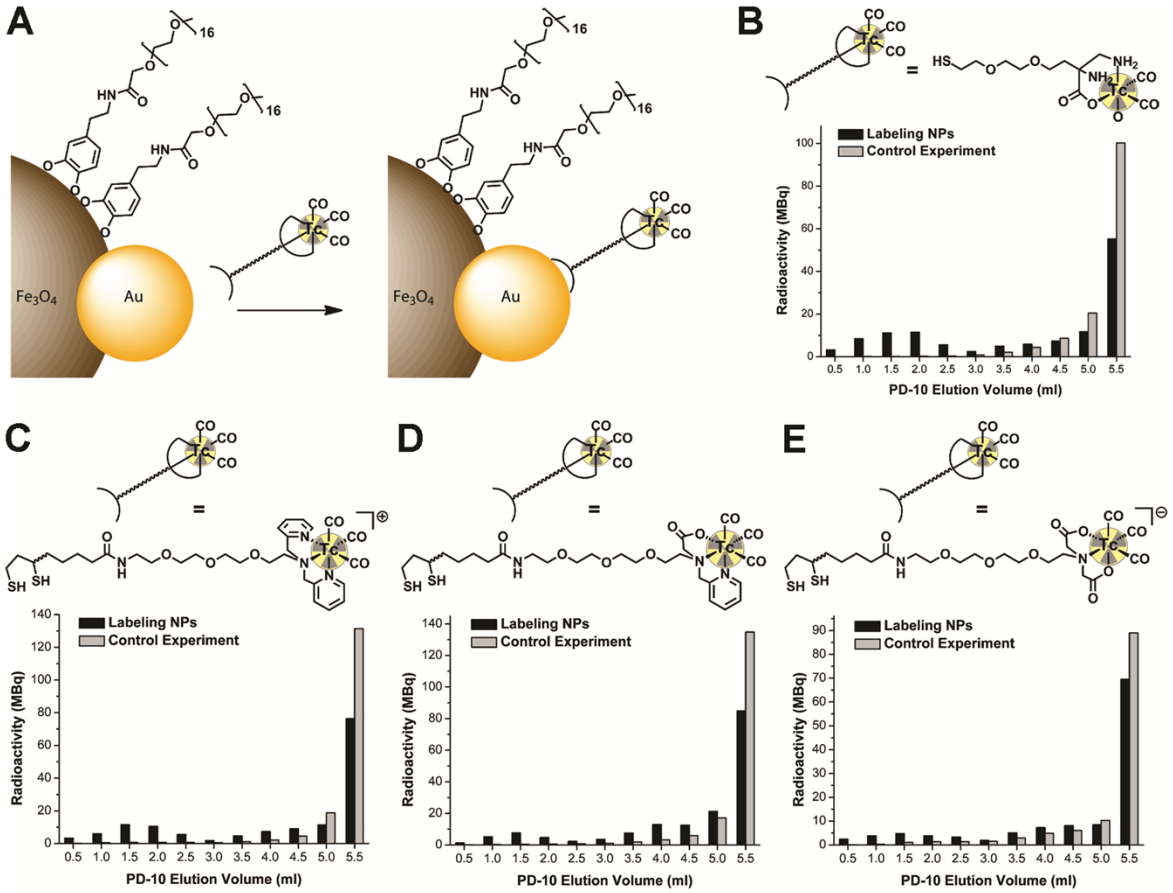


Figure S14. Radiolabelling of Au-Fe_3O_4 Dumbbell-like NPs with an illustrative scheme of the labelling procedure (A) and the PD-10 size exclusion chromatograms after incubation at 50 °C for 60 min of NPs and ^{99m}Tc complexes containing chelator **6** (B), **2** (C), **3** (D), **4** (E) and the corresponding control chromatograms (without reduction with TCEP). Please note that 0.5 ml fractions were collected and the very last fraction was the remainder activity in the PD-10 column (including the activity in the column). The very first 1.0 ml (two 0.5 ml fractions) is not shown in any of the chromatograms since it always was mobile phase only.

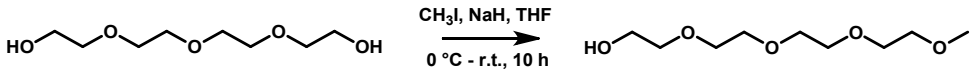
Table S1 Activity measurements of the labelling experiments of Au-Fe_3O_4 Dumbbell-like NPs (without reduction with TCEP).

Coating	*Reaction Vial[1] [MBq]*	*PD-10[2] [MBq]*	*NPs[3] [MBq]*	*RCY[4]*
2, **7**	168	150 (89%)	37	22%
Control[5]	185	163 (88%)	3	1%
3, **7**	172	158 (92%)	21	12%
Control[5]	176	159 (90%)	2	1%
4, **7**	119	109 (91%)	18	15%
Control[5]	117	106 (90%)	4	3%
6, **7**	172	163 (95%)	40	23%
Control[5]	146	137 (94%)	1	1%

[1]Activity after incubation at 50 °C for 2 h; [2]Activity loaded on PD-10 column (in % of the total activity); [3]Combined activity from the fractions 0.5 – 2.5 ml; [4]Radiochemical yield; [5]Control experiments, 1.5 ml ^{99m}Tc complex loaded on PD-10.

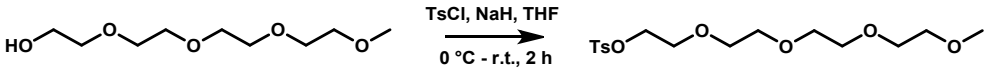
8) Syntheses of lipoic acid based coating ligands

2,5,8,11-tetraoxatridecan-13-ol *(according to Fitch et al.[1])*



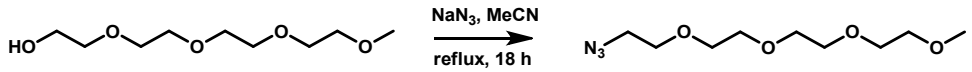
Tetraethylene glycol (10.0 g, 51.4 mmol) was dissolved in dry tetrahydrofurane (35 ml) and sodium hydride (60% dispersion in mineral oil, 2.08 g) was added at 0 °C. The mixture was stirred at 0 °C for 30 min and iodomethane (3.2 ml, 51.4 mmol) was added. After stirring at room temperature for 9 h, the reaction mixture was extracted with dichloromethane (2 x 200 ml). The combined organic phases were washed with water, brine and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (10:1 dichloromethane / methanol) to give a colourless oil. Yield: 2.5 g (23%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.67 (t, 2H, *J*=4.3 Hz), 3.59 – 3.65 (m, 10H), 3.56 (t, 2H, *J*=4.3 Hz), 3.50 (t, 2H, *J*=4.7 Hz), 3.33 (s, 3H), 2.76 (s, 1H). ESI-MS (MeOH): m/z = 231 $[M+Na]^+$. R_f = 0.23 (10:1 dichloromethane / methanol).

2,5,8,11-tetraoxatridecan-13-yl 4-methylbenzenesulfonate *(according to Iverson et al.[2])*



2,5,8,11-tetraoxatridecan-13-ol (1.1 g, 5.4 mmol) was dissolved in dry tetrahydrofurane (5 ml) and cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 0.23 g) was added and the mixture was stirred at 0 °C for 10 min. Afterwards a solution of *p*-toluenesulfonyl chloride (1.1 g, 5.9 mmol) in dry tetrahydrofurane (12 ml) was added dropwise. After stirring for at room temperature 2 h, the reaction mixture was quenched with water (50 ml) and extracted with dichloromethane (3 x 50 ml). The combined organic phases were washed with water, brine and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (2:1 ethyl acetate / hexane) to give a colourless oil. Yield: 1.9 g (99%). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.79 (d, 2H, *J*=8.2 Hz), 7.31 (d, 2H, *J*=8.2 Hz), 4.15 (t, 2H, *J*=4.7 Hz), 3.68 (t, 2H, *J*=4.7 Hz), 3.60 – 3.64 (m, 6H), 3.57 (s, 4H), 3.52 – 3.55 (m, 2H), 3.36 (s, 3H), 2.44 (s, 3H). ESI-MS (MeOH): m/z = 385 $[M+Na]^+$. R_f = 0.20 (2:1 ethyl acetate / hexane).

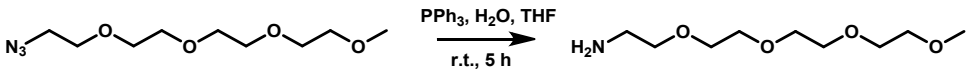
13-azido-2,5,8,11-tetraoxatridecane *(according to Iverson et al.[2])*



2,5,8,11-tetraoxatridecan-13-yl 4-methylbenzenesulfonate (1.9 g, 5.2 mmol) was dissolved in acetonitrile (40 ml) and sodium azide (0.5 g, 7.8 mmol) was added. The suspension was refluxed for 18 h. After cooling to room temperature, water (100 ml) was added and the aqueous phase was extracted with

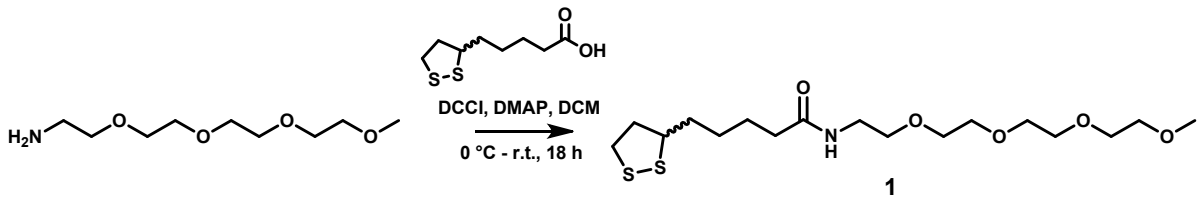
dichloromethane (3 x 50 ml). The combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting yellow oil was dried under vacuum and used directly for the next step without further purification. Yield: 1.2 g (95%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.58 – 3.67 (m, 10H), 3.63 (t, 2H, *J*=5.0 Hz), 3.54 (t, 2H, *J*=5.0 Hz), 3.36 – 3.38 (m, 5H). ESI-MS (MeOH): m/z = 256 $[M+Na]^+$.

2,5,8,11-tetraoxatridecan-13-amine *(according to Iverson et al.[2])*



13-azido-2,5,8,11-tetraoxatridecane (2.3 g, 10.0 mmol) was dissolved in tetrahydrofurane (50 ml) and triphenylphosphine (2.9 g, 11.0 mmol) and water (0.3 ml) was added. The mixture was stirred for at room temperature for 5 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (10:1:0.03 dichloromethane / methanol / 25% ammonia solution) to give a colourless oil. Yield: 1.8 g (88%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.60 – 3.66 (m, 10H), 3.47 – 3.53 (m, 4H), 3.35 (s, 3H), 2.84 (t, 2H, *J*=5.1 Hz), 1.67 (s, 2H). ESI-MS (MeOH): m/z = 208 $[M+H]^+$. R_f = 0.06 (10:1:0.03 dichloromethane / methanol / 25% ammonia solution).

5-(1,2-dithiolan-3-yl)-*N*-(2,5,8,11-tetraoxatridecan-13-yl)pentanamide (2)



2,5,8,11-tetraoxatridecan-13-amine (940 mg, 4.5 mmol) was dissolved in dry dichloromethane (20 ml) and cooled to 0 °C. DL-α-Lipoic acid (932 mg, 4.5 mmol), *N,N'*-dicyclohexylcarbodiimide (1.0 g, 5.0 mmol) and dimethylaminopyridine (50 mg, 0.5 mmol) were added and the suspension was stirred at 0 °C for 15 min and at room temperature for 18 h. The white precipitate was separated from the reaction solution *via* decantation. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate) to give a yellow oil. Yield: 1.5 g (84%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.16 (s, 1H), 3.57 – 3.64 (m, 10H), 3.51 – 3.55 (m, 5H), 3.42 (q, 2H, *J*=5.3 Hz), 3.34 (s, 3H), 3.05 – 3.17 (m, 2H), 2.39 – 2.46 (m, 1H), 2.16 (t, 2H, *J*=7.2 Hz), 1.83 – 1.92 (m, 1H), 1.60 – 1.70 (m, 4H), 1.38 – 1.48 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 172.93, 72.00, 70.67, 70.62, 70.57, 70.30, 70.01, 59.08, 56.52, 40.33, 39.28, 38.55, 36.39, 34.75, 29.01, 25.48. ESI-MS (MeOH): m/z = 418 $[M+Na]^+$. HR-ESI-MS (MeOH + NaI) for $C_{17}H_{34}NO_5S_2$ $[M+H]^+$: calculated, 396.1873; found, 396.1870. R_f = 0.28 (ethyl acetate).

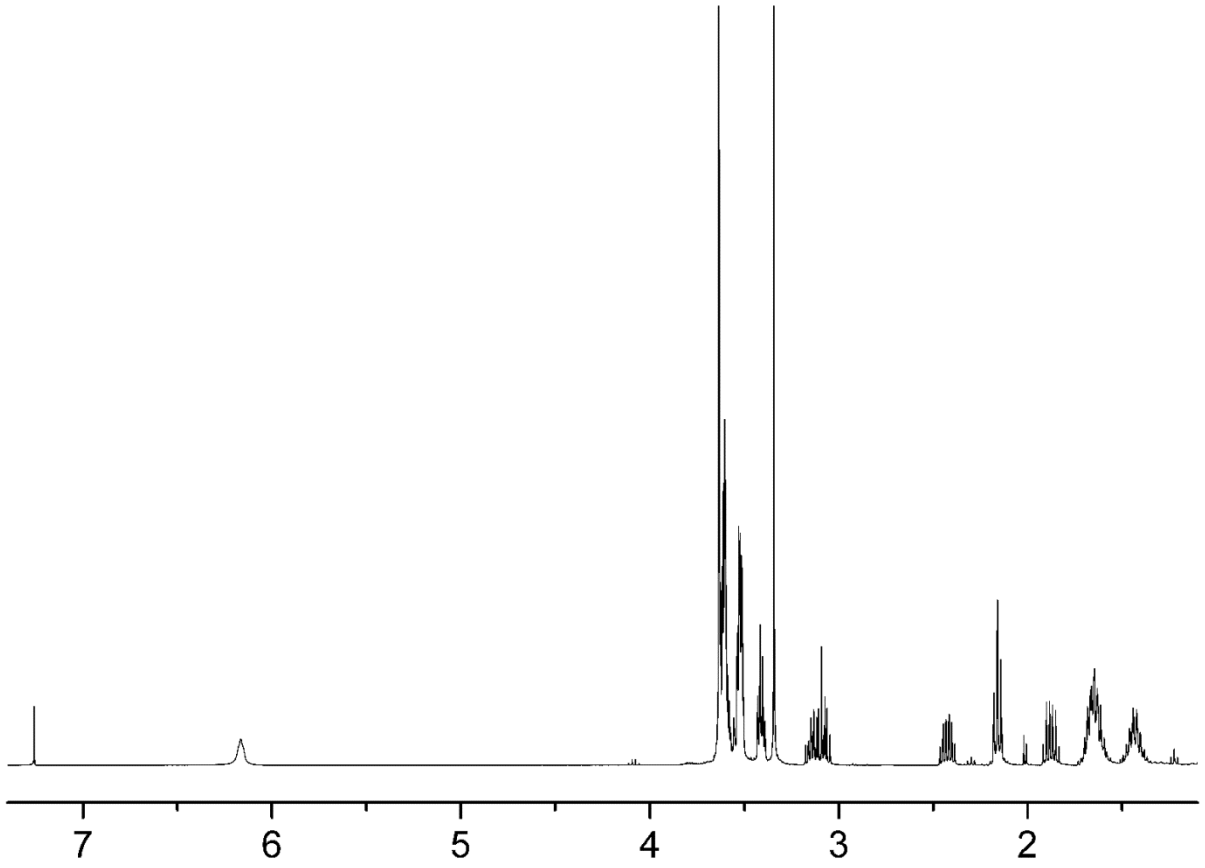
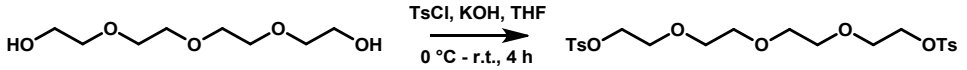


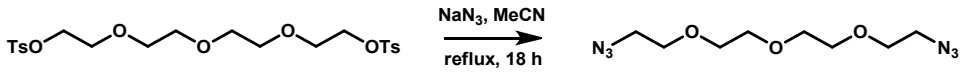
Figure 15. ^{1}H NMR (400 MHz) of compound **1**, measured in $CDCl_3$ (chemical shifts in ppm).

oxybis(ethane-2,1-diyloxyethane-2,1-diyl) bis(4-methylbenzenesulfonate) *(according to König et al.[3])*



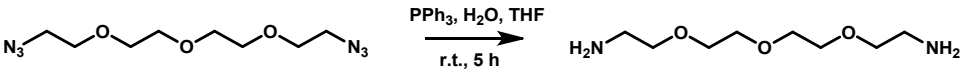
Tetraethylene glycol (5.0 g, 25.7 mmol) and *p*-toluenesulfonyl chloride (14.7 g, 77.2 mmol) were dissolved in tetrahydrofurane (100 ml) and cooled to 0 °C. Potassium hydroxide (10.1 g, 180.2 mmol) in water (25 ml) was added dropwise over a period of 60 min. The mixture was stirred at room temperature for additional 3 h and afterwards poured in a 2:1 diethyl ether / water mixture (150 ml). The water phase was extracted with diethyl ether (2 x 100 ml). The combined ether phases were washed with brine (100 ml), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (95:5 ethyl acetate / methanol) to give a colourless oil. Yield: 12.9 g (99%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.78 (d, 4H, *J*=8.5 Hz), 7.33 (d, 4H, *J*=8.0 Hz), 4.15 (t, 4H, *J*=4.6 Hz), 3.67 (t, 4H, *J*=5.0 Hz), 3.52 – 3.57 (m, 8H), 2.44 (s, 6H). ESI-MS (MeOH): m/z = 525 $[M+Na]^+$. R_f = 0.46 (95:5 ethyl acetate / methanol).

1-azido-2-{2-[2-(2-azidoethoxy)ethoxy]ethoxy}ethane *(according to Iverson et al.[2])*



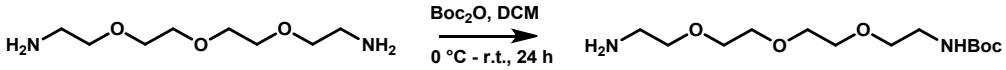
oxybis(ethane-2,1-diyloxyethane-2,1-diyl) bis(4-methylbenzenesulfonate) (12.9 g, 25.7 mmol) was dissolved in acetonitrile (200 ml) and sodium azide (5.0 g, 77.0 mmol) was added. The suspension was refluxed for 18 h. After cooling to room temperature, water (100 ml) was added and the aqueous phase was extracted with dichloromethane (4 x 70 ml). The combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting yellow oil was dried under vacuum and used directly for the next step without further purification. Yield: 6.0 g (95%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.64 – 3.68 (m, 12H), 3.37 (t, 4H, *J*=5.0 Hz). ESI-MS (MeOH): m/z = 267 $[M+Na]^+$.

2,2'-[oxybis(ethane-2,1-diyloxy)]diethanamine *(according to Iverson et al.[2])*



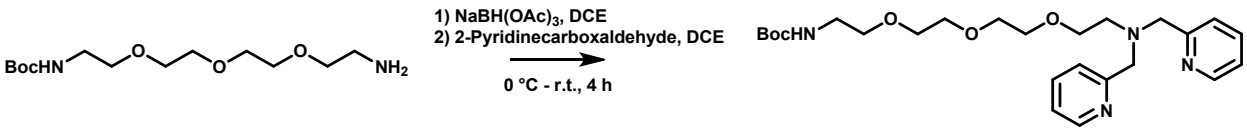
1-azido-2-{2-[2-(2-azidoethoxy)ethoxy]ethoxy}ethane (6.0 g, 24.4 mmol) was dissolved in tetrahydrofurane (100 ml) and triphenylphosphine (14.1 g, 53.6 mmol) and water (1.32 ml) was added. The mixture was stirred at room temperature for 5 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (10:1:0.03 dichloromethane / methanol / 25% ammonia solution) to give a yellow oil. Yield: 4.0 g (85%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.73 (s, 4H), 3.59 – 3.66 (m, 8H), 3.50 (t, 4H, *J*=5.0 Hz), 2.85 (t, 4H, *J*=5.3 Hz). ESI-MS (MeOH): m/z = 193 $[M+H]^+$. R_f = 0.09 (10:1:0.03 dichloromethane / methanol / 25% ammonia solution).

***tert*-butyl (2-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}ethyl)carbamate** *(according to Marchand-Brynaert et al.[4])*



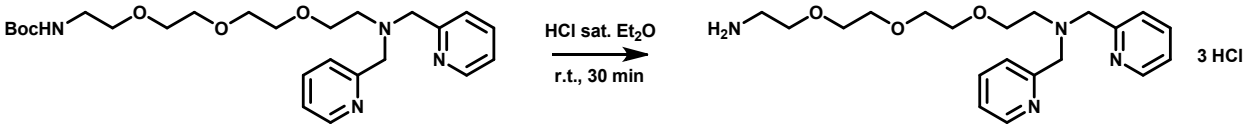
2,2'-[oxybis(ethane-2,1-diyloxy)]diethanamine (2.4 g, 12.6 mmol) was dissolved in dry dichloromethane (80 ml) and cooled to 0 °C. Di-*tert*-butyl dicarbonate (0.4 g, 1.9 mmol), dissolved in dichloromethane (10 ml), was slowly added to the diamine and the mixture was stirred at 0 °C for 5 h and at room temperature for 18 h. The organic phase was washed with water (3 x 150 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was used without further purification. Yield: 0.6 g (99%, calculated for di-*tert*-butyl dicarbonate). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.24 (s, 1H), 3.59 – 3.67 (m, 8H), 3.50 – 3.55 (m, 4H), 3.29 – 3.32 (m, 2H), 2.86 (t, 2H, *J*=5.3 Hz), 1.51 (s, 2H), 1.44 (s, 9H). ESI-MS (MeOH): m/z = 293 $[M+Na]^+$.

***tert*-butyl [1-(pyridin-2-yl)-2-(pyridin-2-ylmethyl)-5,8,11-trioxa-2-azatridecan-13-yl]carbamate** *(according to Zubieta et al.[5])*



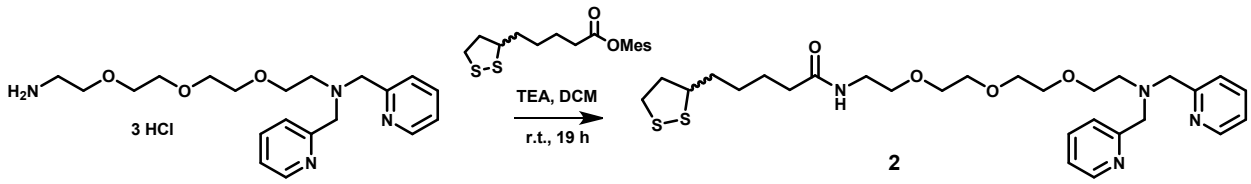
tert-butyl (2-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}ethyl)carbamate (415 mg, 1.4 mmol) was dissolved in dry 1,2-dichloroethane (8 ml) and sodium triacetoxyborohydride (752 mg, 3.6 mmol) was added at 0 °C. 2-Pyridinecarboxaldehyde (280 µl, 3 mmol) was dissolved in 1,2-dichloroethane (3 ml) and added to the suspension. The mixture was stirred at room temperature for 4 h and afterwards quenched with water (10 ml). The mixture was extracted with chloroform (3 x 50 ml) and the combined organic phases were washed with water, brine and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (10:1 dichloromethane / methanol) to give a yellow oil. Yield: 545 mg (81%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.51 (d, 2H, *J*=4.8 Hz), 7.63 (t, 2H, *J*=7.5 Hz), 7.55 (d, 2H, *J*=7.8 Hz), 7.13 (t, 2H, *J*=6.0 Hz), 5.07 (s, 1H), 3.90 (s, 4H), 3.53 – 3.64 (m, 10H), 3.50 (t, 2H, *J*=5.0 Hz), 3.26 – 3.30 (m, 2H), 2.83 (t, 2H, *J*=5.8 Hz), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 159.93, 156.15, 149.08, 136.54, 123.07, 122.05, 70.77, 70.69, 70.50, 70.41, 70.36, 69.77, 61.00, 53.72, 50.87, 40.51, 28.56. ESI-MS (MeOH): m/z = 475 $[M+H]^+$. HR-ESI-MS (MeOH + NaI) for $C_{25}H_{38}N_4NaO_5$ $[M+Na]^+$: calculated, 497.2734; found, 497.2729. R_f = 0.17 (10:1 dichloromethane / methanol).

1-(pyridin-2-yl)-2-(pyridin-2-ylmethyl)-5,8,11-trioxa-2-azatridecan-13-amine



tert-butyl [1-(pyridin-2-yl)-2-(pyridin-2-ylmethyl)-5,8,11-trioxa-2-azatridecan-13-yl]carbamate (545 mg, 1.2 mmol) was dissolved in dichloromethane (5 ml) and added dropwise to a diethyl ether solution, saturated with hydrochloric acid (15 ml). An immediate precipitation was observed and the mixture was stirred at room temperature for additional 30 min. The solvent was removed under reduced pressure and the product as a colourless solid was dried under high vacuum. Yield: 555 mg (99%, product · 3 HCl). ^{1}H NMR (500 MHz, MeOD, ppm) δ 8.91 (d, 2H, *J*=5.7 Hz), 8.62 (t, 2H, *J*=7.9 Hz), 8.19 (d, 2H, *J*=7.9 Hz), 8.05 (t, 2H, *J*=6.6 Hz), 4.50 (s, 4H), 3.72 (t, 2H, *J*=5.0 Hz), 3.66 – 3.68 (m, 6H), 3.62 (t, 2H, *J*=4.7 Hz), 3.52 (t, 2H, *J*=4.7 Hz), 3.12 (t, 2H, *J*=4.7 Hz), 2.93 (t, 2H, *J*=4.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 153.56, 146.93, 141.31, 127.03, 126.04, 69.99, 69.94, 69.82, 68.29, 66.46, 56.25, 53.83, 39.22. ESI-MS (MeOH): m/z = 375 $[M+H]^+$.

5-(1,2-dithiolan-3-yl)-*N*-[1-(pyridin-2-yl)-2-(pyridin-2-ylmethyl)-5,8,11-trioxa-2-azatridecan-13-yl]pentanamide (2) *(according to Mattoussi et al.[6])*



DL-α-Lipoic acid (297 mg, 1.4 mmol) was dissolved in dry dichloromethane (5 ml) and triethylamine (200 µl, 1.4 mmol) was added. The mixture was cooled to 0 °C and stirred for 30 min. Methanesulfonyl chloride (111 µl, 1.4 mmol) was added dropwise. After addition, the mixture was warmed up to room temperature and stirred for 5 h. In the meantime, 1-(pyridin-2-yl)-2-(pyridin-2-ylmethyl)-5,8,11-trioxa-2-azatridecan-13-amine (· 3 HCl; 555 mg, 1.2 mmol) was dissolved in dry dichloromethane (10 ml) and triethylamine (478 µl, 3.5 mmol). The amine solution was added dropwise to the mixture with the activated lipoic acid, followed by stirring at room temperature for 19 h. The reaction mixture was washed with water (2 x 15 ml) and saturated sodium carbonate solution (2 x 15 ml). The organic phase was dried over magnesium sulfate. The solvent was reduced under reduced pressure and the residue was purified by silica gel column chromatography (10:1 dichloromethane / methanol) to give a yellow oil. Yield: 291 mg (45%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.51 (d, 2H, *J*=4.8 Hz), 7.64 (t, 2H, *J*=7.8 Hz), 7.54 (d, 2H, *J*=7.8 Hz), 7.13 (t, 2H, *J*=7.3 Hz), 6.22 (s, 1H), 3.90 (s, 4H), 3.51 – 3.63 (m, 13H), 3.42 (q, 2H, *J*=5.3 Hz), 3.06 – 3.19 (m, 2H), 2.83 (t, 2H, *J*=6.0 Hz), 2.39 – 2.47 (m, 1H), 2.15 (t, 2H, *J*=7.3 Hz), 1.84 – 1.92 (m, 1H), 1.59 – 1.70 (m, 4H), 1.38 – 1.49 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.89, 159.92, 149.09, 136.55, 123.06, 122.08, 70.72, 70.68, 70.48, 70.38, 70.05, 69.76, 60.98, 56.55, 53.67, 40.35, 39.28, 38.58, 36.46, 34.78, 29.04, 25.49. ESI-MS (MeOH): m/z = 563 $[M+H]^+$. HR-ESI-MS (MeOH + NaI) for $C_{28}H_{43}N_4O_4S_2$ $[M+H]^+$: calculated, 563.2720; found, 563.2716. R_f = 0.12 (10:1 dichloromethane / methanol).

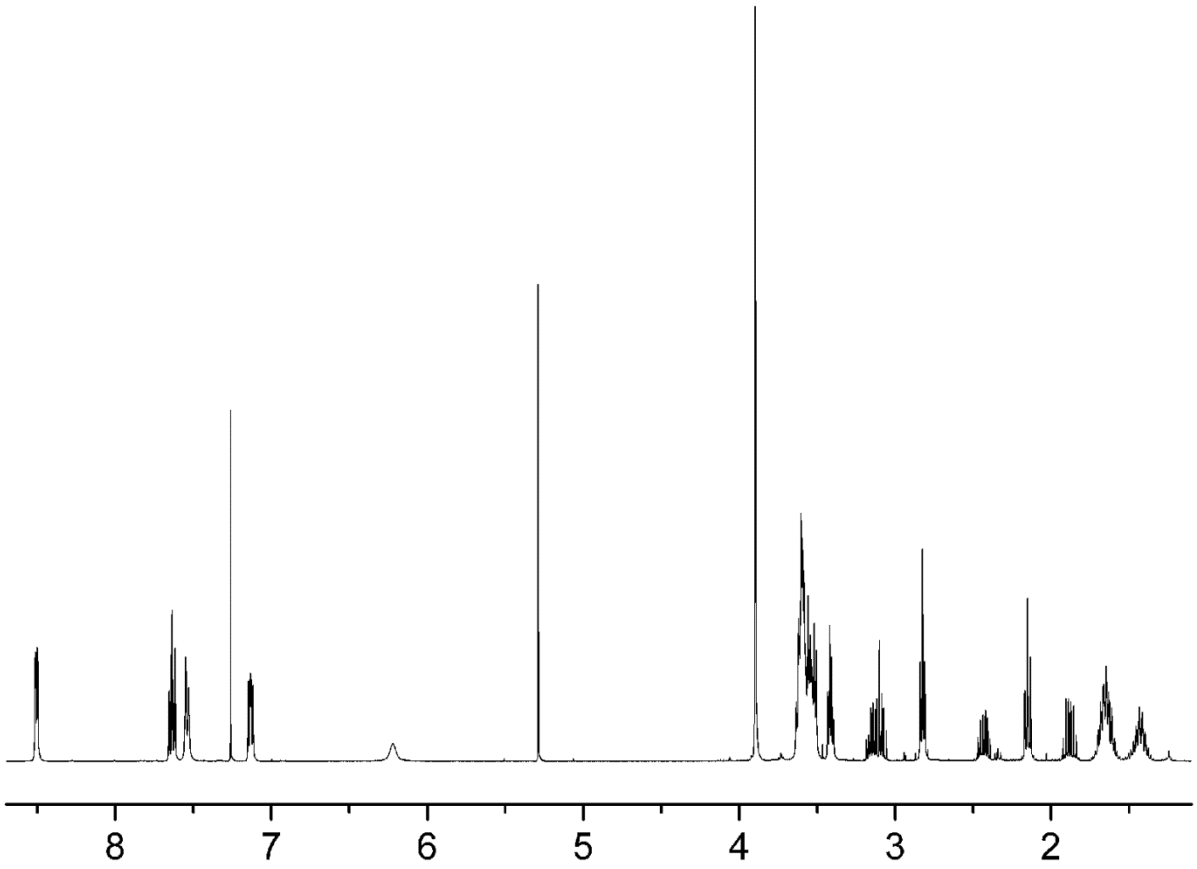
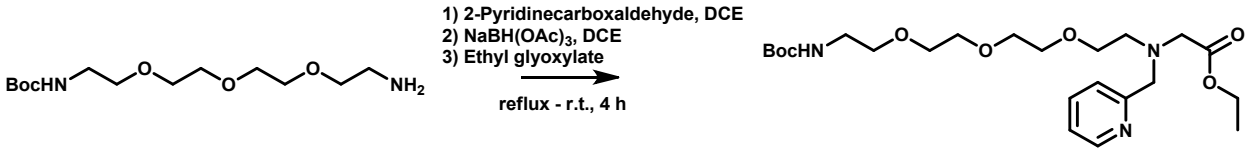


Figure 17. ^{1}H NMR (400 MHz) of compound **2**, measured in $CDCl_3$ (chemical shifts in ppm).

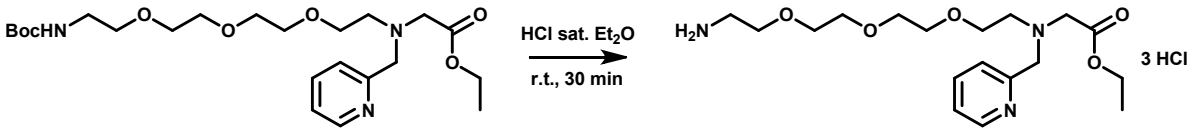
ethyl *N*-(2,2-dimethyl-4-oxo-3,8,11,14-tetraoxa-5-azahexadecan-16-yl)-*N*-(pyridin-2-ylmethyl)glycinate *(according to Zubieta et al.[5])*



A solution of *tert*-butyl (2-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}ethyl)carbamate (558 mg, 1.9 mmol) and 2-pyridinecarboxaldehyde (182 µl, 1.9 mmol) was refluxed in dry 1,2-dichloroethane (10 ml) for 10 min. After cooling to 0 °C, sodium triacetoxyborohydride (1.0 g, 4.8 mmol) and ethyl glyoxylate (50% solution in toluene, 0.39 ml, 1.9 mmol) were sequentially added. The mixture was stirred at room temperature for 3.5 h and afterwards quenched with water (25 ml). The mixture was extracted with chloroform (4 x 50 ml). The combined organic phases were washed with water, brine and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (10:1 dichloromethane / methanol) to give a yellow oil. Yield: 625 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.52 (d, 1H, *J*=4.8 Hz), 7.65 (t, 1H, *J*=7.5 Hz), 7.53 (d, 1H, *J*=7.8 Hz), 7.14 (t,

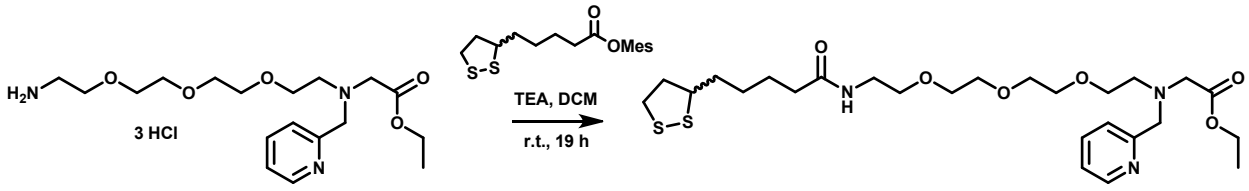
1H, *J*=6.0 Hz), 5.05 (s, 1H), 4.15 (q, 2H, *J*=7.0 Hz), 4.00 (s, 2H), 3.51 – 3.60 (m, 14H), 3.27 – 3.31 (m, 2H), 2.94 (t, 2H, *J*=5.8 Hz), 1.43 (s, 9H), 1.25 (t, 3H, *J*=7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.70, 159.76, 156.14, 149.14, 136.65, 123.19, 122.14, 70.72, 70.69, 70.47, 70.42, 70.38, 70.19, 60.85, 60.45, 55.86, 53.62, 40.52, 28.56, 14.43. ESI-MS (MeOH): m/z = 470 $[M+H]^+$. HR-ESI-MS (MeOH + NaI) for $C_{23}H_{39}N_3NaO_7$ $[M+Na]^+$: calculated, 492.2680; found, 492.2678. R_f = 0.47 (10:1 dichloromethane / methanol).

ethyl *N*-(2-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}ethyl)-*N*-(pyridin-2-ylmethyl)glycinate



ethyl *N*-(2,2-dimethyl-4-oxo-3,8,11,14-tetraoxa-5-azahexadecan-16-yl)-*N*-(pyridin-2-ylmethyl)glycinate (530 mg, 1.1 mmol) was dissolved in dichloromethane (5 ml) and added dropwise to a diethyl ether solution, saturated with hydrochloric acid (15 ml). An immediate precipitation was observed and the mixture was stirred at room temperature for additional 30 min. The solvent was removed under reduced pressure and the product was dried under high vacuum to give a yellow oil. Yield: 538 mg (99%, product · 3 HCl). ^{1}H NMR (500 MHz, MeOD, ppm) δ 8.76 (d, 1H, *J*=4.7 Hz), 8.31 (t, 1H, *J*=7.6 Hz), 7.84 (d, 1H, *J*=7.9 Hz), 7.78 (t, 1H, *J*=6.6 Hz), 4.59 (s, 2H), 4.24 (q, 2H, *J*=7.0 Hz), 4.04 (s, 2H), 3.74 (t, 2H, *J*=4.7 Hz), 3.71 (t, 2H, *J*=5.0 Hz), 3.68 (s, 6H), 3.63 – 3.65 (m, 2H), 3.58 – 3.60 (m, 2H), 3.12 (t, 2H, *J*=5.0 Hz), 1.29 (t, 3H, *J*=7.0 Hz). ^{13}C NMR (125 MHz, MeOD, ppm) δ 170.53, 154.35, 145.59, 144.21, 126.63, 126.42, 71.41, 71.34, 71.30, 71.20, 68.40, 67.87, 62.88, 58.16, 56.35, 55.99, 40.64, 14.43. ESI-MS (MeOH): m/z = 370 $[M+H]^+$.

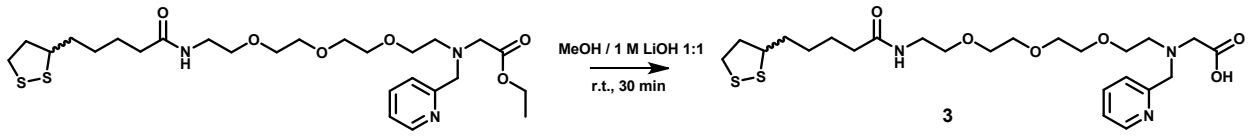
ethyl *N*-[17-(1,2-dithiolan-3-yl)-13-oxo-3,6,9-trioxa-12-azaheptadec-1-yl]-*N*-(pyridin-2-ylmethyl)glycinate *(according to Mattoussi et al.[6])*



DL-α-Lipoic acid (291 mg, 1.4 mmol) was dissolved in dry dichloromethane (5 ml) and triethylamine (196 µl, 1.4 mmol) was added. The mixture was cooled to 0 °C and stirred for 30 min. Methanesulfonyl chloride (1095 µl, 1.4 mmol) was added dropwise, then the mixture was warmed up to room temperature and stirred for 5 h. In the meantime ethyl *N*-(2-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}ethyl)-*N*-(pyridin-2-ylmethyl)glycinate (· 3 HCl; 538 mg, 1.1 mmol) was dissolved in dry dichloromethane (10 ml) and triethylamine (548 µl, 4.0 mmol). Afterwards the amine solution was added dropwise to the mixture with activated lipoic acid, followed by stirring at room temperature for 17 h. The reaction mixture was washed

with water (2 x 20 ml) and saturated sodium carbonate solution (2 x 20 ml). The organic phase was dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (10:1 dichloromethane / methanol) to give a yellow oil. Yield: 464 mg (74%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.53 (d, 1H, *J*=4.8 Hz), 7.65 (t, 1H, *J*=7.8 Hz), 7.52 (d, 1H, *J*=7.8 Hz), 7.15 (t, 1H, *J*=4.8 Hz), 6.16 (s, 1H), 4.15 (q, 2H, *J*=7.0 Hz), 4.00 (s, 2H), 3.51 – 3.63 (m, 15H), 3.44 (t, 2H, *J*=5.0 Hz), 3.07 – 3.20 (m, 2H), 2.94 (t, 2H, *J*=6.0 Hz), 2.41 – 2.48 (m, 1H), 2.17 (t, 2H, *J*=7.8 Hz), 1.85 – 1.94 (m, 1H), 1.61 – 1.72 (m, 4H), 1.40 – 1.51 (m, 2H), 1.26 (t, 3H, *J*=7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.90, 171.71, 159.73, 149.18, 136.66, 123.17, 122.19, 70.69, 70.49, 70.46, 70.41, 70.21, 70.08, 60.85, 60.50, 56.57, 55.90, 53.62, 40.37, 39.31, 38.60, 36.49, 34.81, 29.06, 25.52, 14.44. ESI-MS (MeOH): m/z = 558 $[M+H]^+$. HR-ESI-MS (MeOH + NaI) for $C_{26}H_{44}N_3O_6S_2$ $[M+H]^+$: calculated, 558.2666; found, 558.2662. R_f = 0.44 (10:1 dichloromethane / methanol).

N-[17-(1,2-dithiolan-3-yl)-13-oxo-3,6,9-trioxa-12-azaheptadec-1-yl]-*N*-(pyridin-2-ylmethyl)glycine (3)



ethyl *N*-[17-(1,2-dithiolan-3-yl)-13-oxo-3,6,9-trioxa-12-azaheptadec-1-yl]-*N*-(pyridin-2-ylmethyl)glycinate (386 mg, 0.7 mmol) was dissolved in methanol (1.5 ml) and 1 M aqueous lithium hydroxide solution (1.5 ml) was added. The mixture was stirred at room temperature for 1.5 h and neutralized with Amberlite IR120 H to reach pH 7. The suspension was filtered and the solvent was removed under reduced pressure to give a yellow oil. Yield: 337 mg (92%). ^{1}H NMR (500 MHz, MeOD, ppm) δ 8.64 (d, 1H, *J*=5.0 Hz), 7.89 (t, 1H, *J*=7.6 Hz), 7.52 (d, 1H, *J*=7.6 Hz), 7.43 (t, 1H, *J*=5.0 Hz), 4.57 (s, 2H), 3.85 (t, 2H, *J*=4.7 Hz), 3.78 (s, 2H), 3.60 – 3.67 (m, 9H), 3.53 (t, 2H, *J*=5.7 Hz), 3.45 (t, 2H, *J*=5.0 Hz), 3.34 (t, 2H, *J*=5.7 Hz), 3.15 – 3.18 (m, 1H), 3.07 – 3.12 (m, 1H), 2.42 – 2.49 (m, 1H), 2.20 (t, 2H, *J*=7.6 Hz), 1.85 – 1.92 (m, 1H), 1.59 – 1.74 (m, 4H), 1.42 – 1.49 (m, 2H). ^{13}C NMR (125 MHz, MeOD, ppm) δ 175.93, 170.54, 152.83, 150.34, 138.91, 125.12, 125.01, 71.46, 71.39, 71.32, 71.15, 70.44, 66.73, 59.50, 57.77, 57.44, 55.17, 41.16, 40.17, 39.17, 36.64, 35.57, 29.68, 26.53. ESI-MS (MeOH): m/z = 530 $[M+H]^+$. HR-ESI-MS (MeOH + NaI) for $C_{24}H_{38}N_3O_6S_2$ $[M-H]^-$: calculated, 528.2208; found, 528.2214.

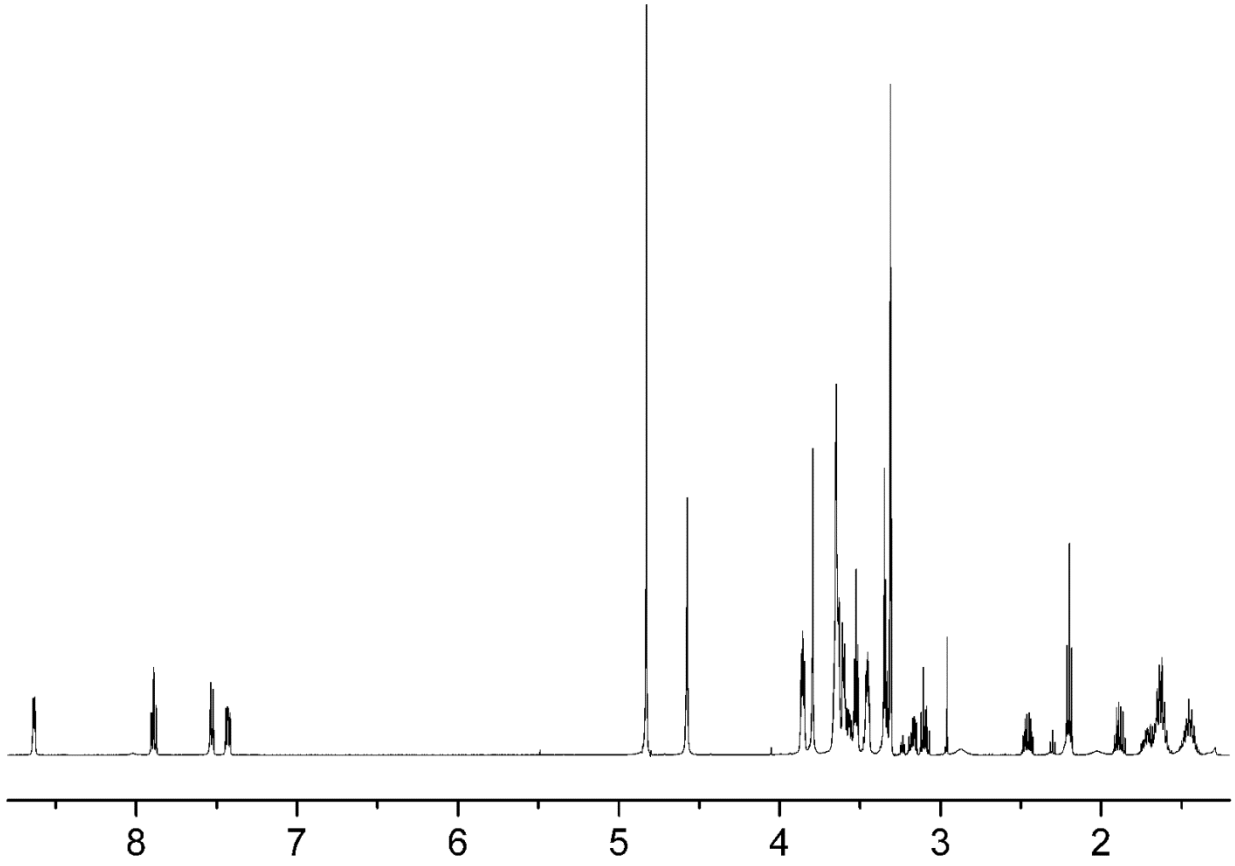
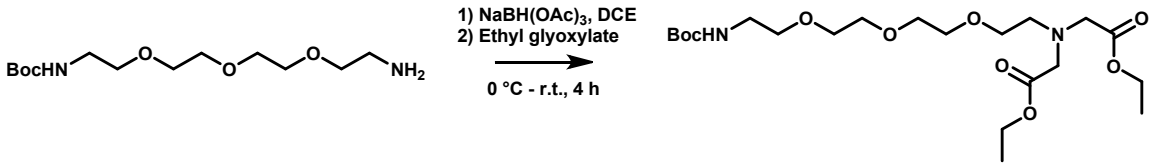


Figure 18. ^{1}H NMR (500 MHz) of compound **3**, measured in MeOD (chemical shifts in ppm).

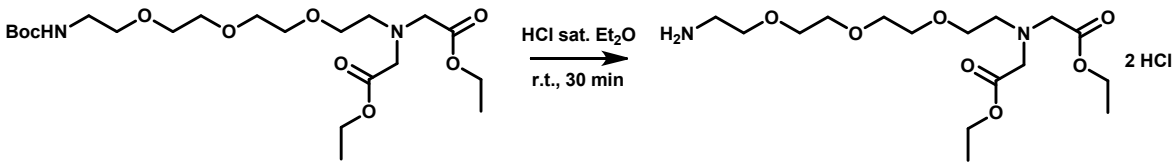
ethyl 17-(2-ethoxy-2-oxoethyl)-2,2-dimethyl-4-oxo-3,8,11,14-tetraoxa-5,17-diazanonadecan-19-oate *(according to Zubieta et al.[5])*



tert-butyl (2-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}ethyl)carbamate (400 mg, 1.4 mmol) was dissolved in dry 1,2-dichloroethane (10 ml) and sodium triacetoxyborohydride (726 g, 3.4 mmol) was added at 0 °C. Ethyl glyoxylate (50% solution in toluene, 0.59 ml, 2.9 mmol) was added to the suspension. The mixture was stirred at room temperature for 4 h and afterwards quenched with water (15 ml). The mixture was extracted with chloroform (3 x 50 ml). The combined organic phases were washed with water, brine and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (10:1 dichloromethane / methanol) to give the product as a colourless oil. Yield: 515 mg (81%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.05 (s, 1H), 4.15 (q, 4H, *J*=7.0

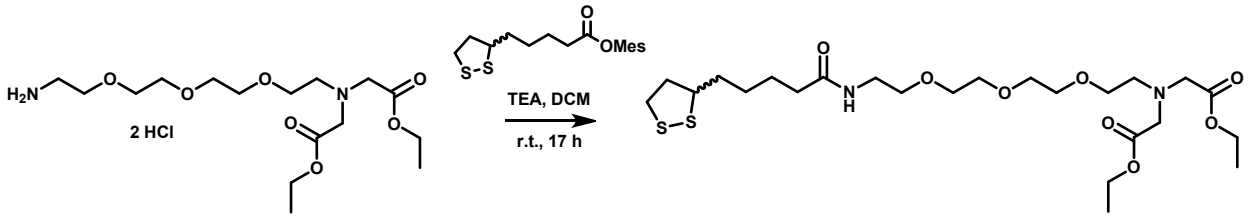
Hz), 3.58 – 3.65 (m, 14H), 3.52 (t, 2H, *J*=5.3 Hz), 3.28 – 3.32 (m, 2H), 2.96 (t, 2H, *J*=5.5 Hz), 1.43 (s, 9H), 1.25 (t, 6H, *J*=7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.55, 156.15, 70.69, 70.65, 70.53, 70.47, 70.42, 70.39, 60.74, 60.56, 56.02, 53.78, 28.56, 14.39. ESI-MS (MeOH): m/z = 487 $[M+H]^+$. HR-ESI-MS (MeOH + NaI) for $C_{21}H_{40}N_2NaO_9$ $[M+Na]^+$: calculated, 487.2626; found, 487.2627. R_f = 0.52 (10:1 dichloromethane / methanol).

ethyl 1-amino-12-(2-ethoxy-2-oxoethyl)-3,6,9-trioxa-12-azatetradecan-14-oate



ethyl 17-(2-ethoxy-2-oxoethyl)-2,2-dimethyl-4-oxo-3,8,11,14-tetraoxa-5,17-diazanonadecan-19-oate (515 mg, 1.1 mmol) was dissolved in dichloromethane (5 ml) and added dropwise to a diethyl ether solution, saturated with hydrochloric acid (15 ml). An immediate precipitation was observed and the mixture was stirred at room temperature for additional 30 min. The solvent was removed under reduced pressure and the product was dried under high vacuum to give a colourless oil. Yield: 460 mg (99%, product · 2 HCl). ^{1}H NMR (400 MHz, MeOD, ppm) δ 4.40 (s, 4H), 4.33 (q, 4H, *J*=7.0 Hz), 3.90 (t, 2H, *J*=4.8 Hz), 3.65 – 3.77 (m, 12H), 3.15 (t, 2H, *J*=4.8 Hz), 1.33 (t, 6H, *J*=7.0 Hz). ^{13}C NMR (125 MHz, MeOD, ppm) δ 167.21, 71.49, 71.46, 71.34, 71.25, 67.90, 66.40, 63.95, 57.12, 56.12, 40.69, 14.33. ESI-MS (MeOH): m/z = 365 $[M+H]^+$.

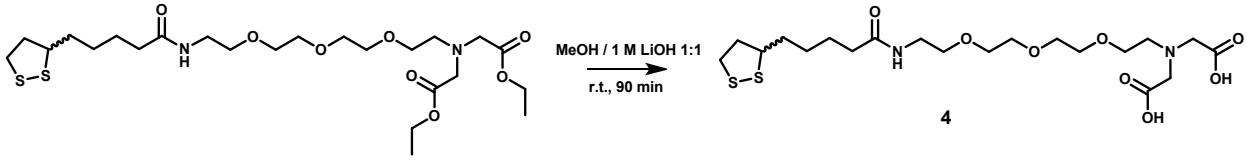
ethyl 20-(1,2-dithiolan-3-yl)-3-(2-ethoxy-2-oxoethyl)-16-oxo-6,9,12-trioxa-3,15-diazaicosan-1-oate *(according to Mattoussi et al.[6])*



DL-α-Lipoic acid (279 mg, 1.4 mmol) was dissolved in dry dichloromethane (5 ml) and triethylamine (187 µl, 1.35 mmol) was added. The mixture was cooled to 0 °C and stirred for 30 min. Methanesulfonyl chloride (105 µl, 1.4 mmol) was added dropwise, then the mixture was warmed up to room temperature and stirred for 5 h. In the meantime ethyl 1-amino-12-(2-ethoxy-2-oxoethyl)-3,6,9-trioxa-12-azatetradecan-14-oate (· 2 HCl; 460 mg, 1.1 mmol) was dissolved in dry dichloromethane (10 ml) and triethylamine (374 µl, 2.7 mmol). Afterwards the amine solution was added dropwise to the mixture with activated lipoic acid, followed by stirring at room temperature for 17 h. The reaction mixture was washed with water (2 x 15 ml) and saturated sodium carbonate solution (2 x 15 ml). The organic phase was dried over magnesium sulfate. The solvent was reduced under reduced pressure and the residue was purified

by silica gel column chromatography (10:1 dichloromethane / methanol) to give a yellow oil. Yield: 443 mg (74%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.20 (s, 1H), 4.15 (q, 4H, *J*=7.0 Hz), 3.58 – 3.64 (m, 16H), 3.55 (t, 2H, *J*=5.3 Hz), 3.07 – 3.20 (m, 2H), 2.96 (t, 2H, *J*=5.8 Hz), 2.41 – 2.49 (m, 1H), 2.19 (t, 2H, *J*=7.5 Hz), 1.86 – 1.94 (m, 1H), 1.62 – 1.72 (m, 4H), 1.41 – 1.52 (m, 2H), 1.26 (t, 6H, *J*=7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 176.29, 173.00, 171.54, 70.66, 70.62, 70.45, 70.39, 70.33, 70.11, 60.63, 56.58, 56.01, 53.79, 40.36, 39.31, 38.61, 36.47, 34.78, 33.63, 29.05, 25.40, 14.28. ESI-MS (MeOH): m/z = 553 $[M+H]^+$. HR-ESI-MS (MeOH + NaI) for $C_{24}H_{44}N_2NaO_8S_2$ $[M+Na]^+$: calculated, 575.2431; found, 575.2429. R_f = 0.48 (10:1 dichloromethane / methanol).

3-(carboxymethyl)-20-(1,2-dithiolan-3-yl)-16-oxo-6,9,12-trioxa-3,15-diazaicosan-1-oic acid (4)



ethyl 20-(1,2-dithiolan-3-yl)-3-(2-ethoxy-2-oxoethyl)-16-oxo-6,9,12-trioxa-3,15-diazaicosan-1-oate (158 mg, 0.3 mmol) was dissolved in methanol (1.5 ml) and 1 M aqueous lithium hydroxide solution (1.5 ml) was added. The mixture was stirred at room temperature for 1.5 h and neutralized with Amberlite IR120 H to reach pH 7. The suspension was filtered and the solvent was removed under reduced pressure to give a yellow oil. Yield: 119 mg (86%). ^{1}H NMR (500 MHz, MeOD, ppm) δ 3.92 (s, 2H), 3.83 (t, 1H, *J*=5.0 Hz), 3.56 – 3.67 (m, 12H), 3.55 (t, 2H, *J*=5.4 Hz), 3.45 (t, 1H, *J*=4.3 Hz), 3.36 (t, 2H, *J*=5.4 Hz), 3.15 – 3.20 (m, 1H), 3.08 – 3.13 (m, 1H), 2.43 – 2.50 (m, 1H), 2.22 (t, 2H, *J*=7.3 Hz), 1.86 – 1.93 (m, 1H), 1.71 – 1.76 (m, 1H), 1.61 – 1.67 (m, 4H), 1.42 – 1.51 (m, 2H). ^{13}C NMR (125 MHz, MeOD, ppm) δ 176.05, 170.28, 71.49, 71.45, 71.42, 71.30, 71.15, 70.49, 57.57, 57.43, 55.74, 41.16, 40.17, 39.17, 36.63, 35.57, 29.68, 26.54. ESI-MS (MeOH): m/z = 495 $[M-H]^-$. HR-ESI-MS (MeOH + NaI) for $C_{20}H_{35}N_2O_8S_2$ $[M-H]^-$: calculated, 495.1840; found, 495.1848.

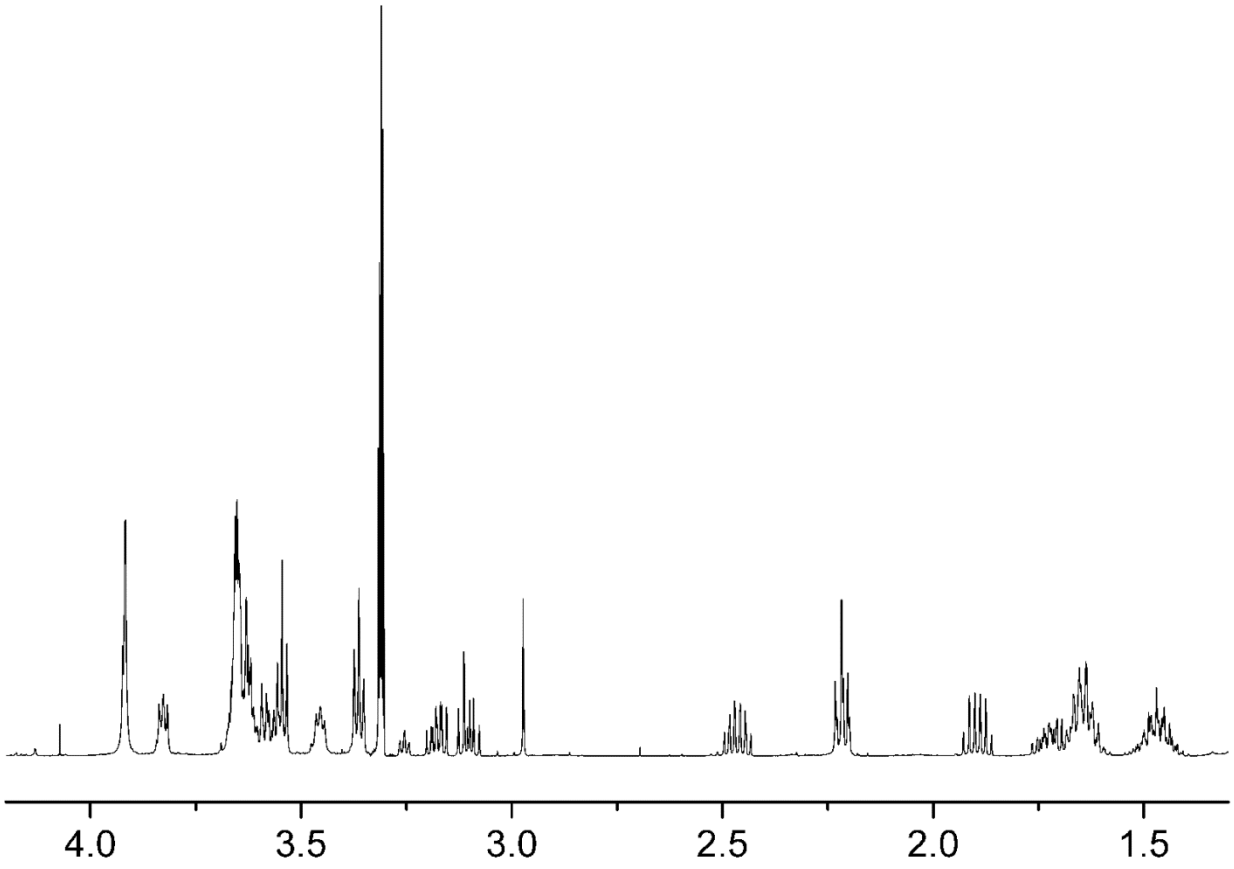
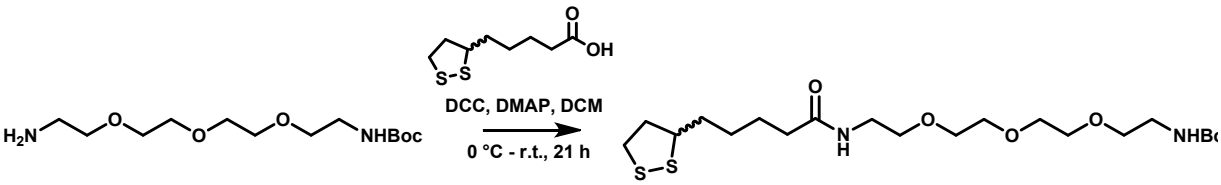


Figure 19. ^{1}H NMR (500 MHz) of compound **4**, measured in MeOD (chemical shifts in ppm).

tert-butyl [17-(1,2-dithiolan-3-yl)-13-oxo-3,6,9-trioxa-12-azaheptadec-1-yl]carbamate
(according to Marchand-Brynaert et al.[4])



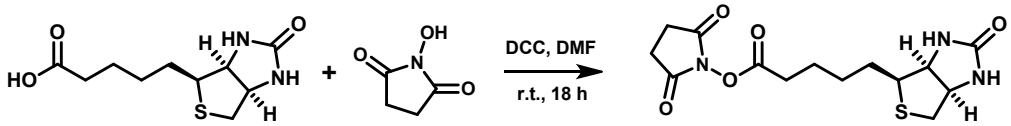
tert-butyl (2-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}ethyl)carbamate (847 mg, 2.9 mmol) was dissolved in dry dichloromethane (80 ml) and cooled to 0 °C. DL-α-Lipoic acid (598 mg, 2.9 mmol), *N,N'*-dicyclohexylcarbodiimide (643 mg, 3.1 mmol) and dimethylaminopyridine (35 mg, 0.3 mmol) were added and the suspension was stirred at 0 °C for 15 min and at room temperature for 21 h. The white precipitate was separated from the reaction solution *via* decantation. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate) to give a yellow oil. Yield: 1.1 g (79%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.07 (s, 1H), 5.04 (s, 1H), 3.60 – 3.66 (m, 8H), 3.53 – 3.58 (m, 5H), 3.45 (q, 2H, *J*=5.3 Hz), 3.29 – 3.33 (m, 2H), 3.07 – 3.20 (m, 2H), 2.41 – 2.49

(m, 1H), 2.19 (t, 2H, *J*=7.3 Hz), 1.86 – 1.94 (m, 1H), 1.62 – 1.73 (m, 4H), 1.41 – 1.50 (m, 11H). ESI-MS (MeOH): m/z = 503 $[M+Na]^+$. HR-ESI-MS (MeOH + NaI) for $C_{21}H_{40}N_2NaO_6S_2$ $[M+Na]^+$: calculated, 503.2220; found, 503.2220. R_f = 0.29 (ethyl acetate).

***N*-(2-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}ethyl)-5-(1,2-dithiolan-3-yl)pentanamide**
(according to Marchand-Brynaert et al.[4])

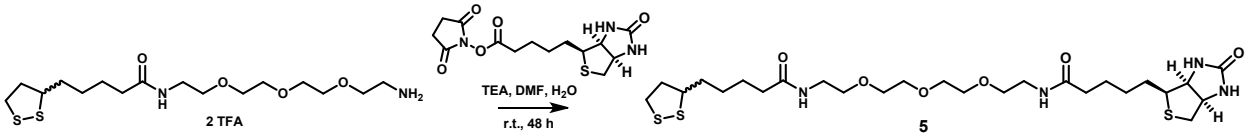
tert-butyl [17-(1,2-dithiolan-3-yl)-13-oxo-3,6,9-trioxa-12-azaheptadec-1-yl]carbamate (615 mg, 1.3 mmol) was dissolved in dichloromethane (2 ml) and trifluoroacetic acid (2 ml) was added. The mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was used without further purification. Yield: 779 mg (99%, product · 2 TFA). ^{1}H NMR (400 MHz, MeOD, ppm) δ 3.64 – 3.77 (m, 10H), 3.56 (t, 2H, *J*=5.5 Hz), 3.39 (t, 2H, *J*=5.8 Hz), 3.12 – 3.18 (m, 2H), 2.84 – 2.94 (m, 2H), 2.43 – 2.51 (m, 1H), 2.25 (t, 2H, *J*=7.3 Hz), 2.00 – 2.06 (m, 1H), 1.86 – 1.94 (m, 1H), 1.61 – 1.72 (m, 4H), 1.44 – 1.53 (m, 2H). ESI-MS (MeOH): m/z = 381 $[M+H]^+$.

Biotinyl-*N*-hydroxysuccinimide *(according to Mattoussi et al.[7])*



d-Biotin (1.0 g, 4.1 mmol) was dissolved in 60 °C warm dimethylformamide (30 ml). *N*-hydroxysuccinimide (0.5 g, 4.1 mmol) and *N,N'*-dicyclohexylcarbodiimide (1.1 g, 5.3 mmol) were added and the mixture was stirred at room temperature for 18 h. The formed precipitate was filtered and washed with ethanol to afford the product as a white solid. Yield: 1.4 g (98%). ^{1}H NMR (400 MHz, DMSO, ppm) δ 6.40 (s, 1H), 6.34 (s, 1H), 4.31 (t, 1H, *J*=5.7 Hz), 4.15 (t, 1H, *J*=5.3 Hz), 3.33 – 3.36 (m, 1H), 3.08 – 3.13 (m, 1H), 2.81 (s, 4H), 2.67 (t, 2H, *J*=7.5 Hz), 2.57 – 2.60 (m, 1H), 1.60 – 1.73 (m, 4H), 1.43 – 1.53 (m, 2H). ESI-MS (MeOH): m/z = 364 $[M+Na]^+$.

5-(1,2-dithiolan-3-yl)-*N*-{13-oxo-17-[d-biotin]-3,6,9-trioxa-12-azaheptadec-1-yl}pentanamide (5)



N-(2-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}ethyl)-5-(1,2-dithiolan-3-yl)pentanamide (· 2 TFA, 780 mg, 1.3 mmol) was dissolved in dimethylformamide (4 ml) and water (1 ml). Triethylamine (887 µl, 6.4 mmol) and Biotinyl-*N*-hydroxysuccinimide (437 mg, 1.3 mmol) were added and the mixture was stirred at room

temperature for 48 h. The formed precipitate was filtered and washed with ethanol. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (10:1 dichloromethane / methanol) to give the product as a yellow oil. Yield: 224 mg (30%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.65 (s, 1H), 6.53 (s, 1H), 4.52 (t, 1H, *J*=5.8 Hz), 4.34 (t, 1H, *J*=5.8 Hz), 3.53 – 3.64 (m, 12H), 3.40 – 3.48 (m, 4H), 3.08 – 3.21 (m, 4H), 2.88 – 2.92 (m, 1H), 2.71 – 2.77 (m, 1H), 2.42 – 2.50 (m, 1H), 2.17 – 2.24 (m, 4H), 1.86 – 1.95 (m, 1H), 1.58 – 1.76 (m, 8H), 1.41 – 1.51 (m, 4H), 1.37 (t, 2H, *J*=*7.3* Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 173.72, 173.53, 164.32, 70.48, 70.22, 64.25, 62.19, 60.65, 56.65, 55.63, 50.95, 45.85, 0.52, 40.41, 39.29, 38.62, 36.40, 35.89, 34.77, 29.84, 29.69, 29.06, 25.51, 8.70. ESI-MS (MeOH): m/z = 629 $[M+Na]^+$. HR-ESI-MS (MeOH + NaI) for $C_{26}H_{46}N_4NaO_6S_3$ $[M+Na]^+$: calculated, 629.2472; found, 629.2465. R_f = 0.10 (10:1 dichloromethane / methanol).

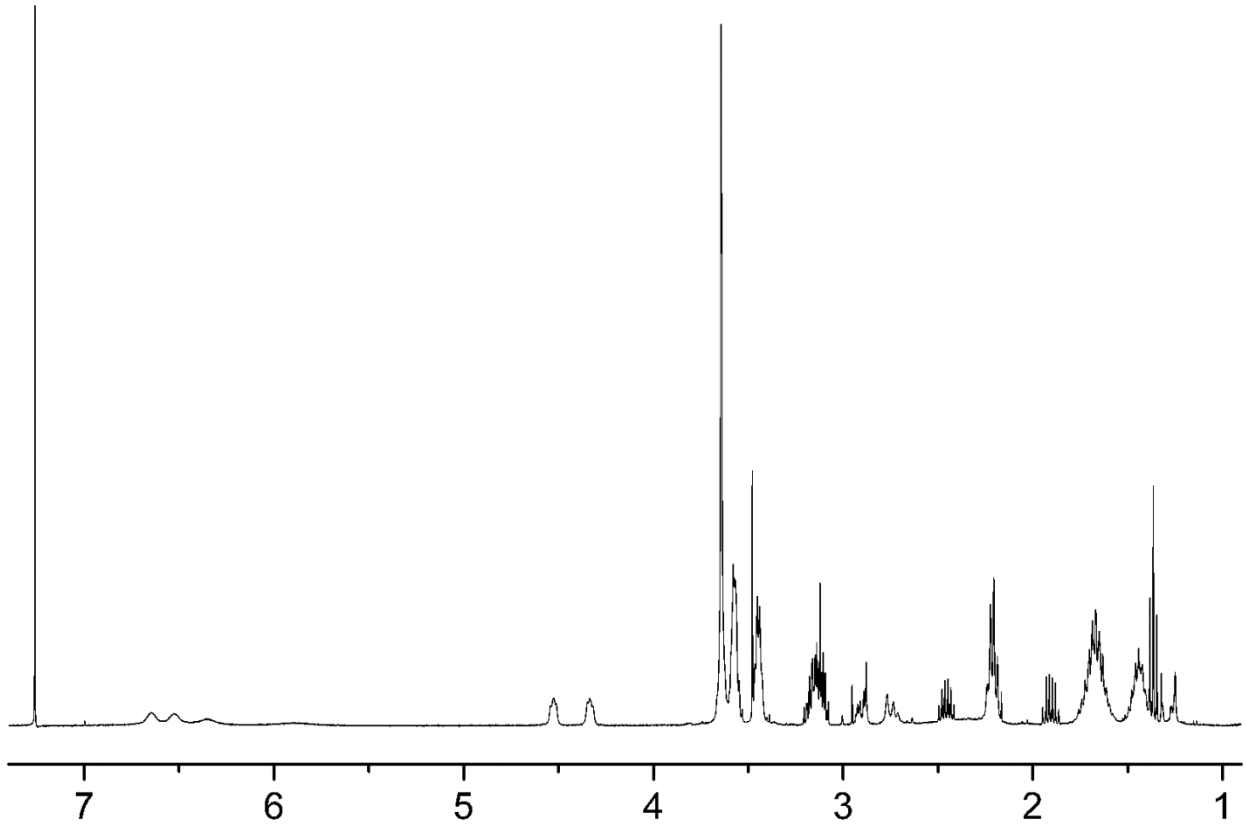
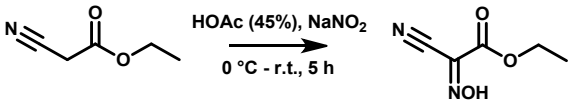


Figure 20. ^{1}H NMR (400 MHz) of compound **5**, measured in $CDCl_3$ (chemical shifts in ppm).

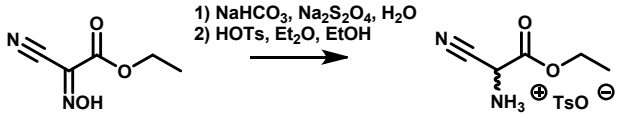
9) Synthesis of 2,3-diaminopropionic acid based chelator

ethyl 2-cyano(hydroxyimino)ethanoate *(Hu et al.[8])*



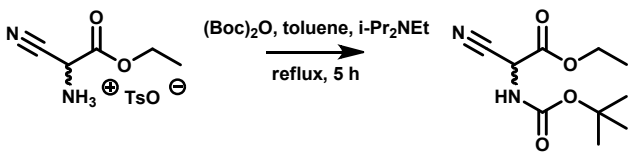
A mixture of ethyl cyanoacetate (10.6 ml, 0.1 mol) and aqueous acetic acid (45%, 45 ml) was stirred at 0 °C. Sodium nitrite (21.0 g, 0.3 mol) was added portionwise during a period of 90 min. After the addition the reaction mixture was stirred at room temperature for another 4 h. The crude product was extracted with diethyl ether (2 x 200 ml). The solvent was removed under reduced pressure and the yellow solid dried in vacuum. Yield: 13.9 g (97%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 4.38 (q, 2H, *J*=7.2 Hz), 1.40 (t, 3H, *J*=7.2 Hz).

1-cyano-2-ethoxy-2-oxoethanaminium 4-methylbenzenesulfonate *(Middelhoven et al.[9])*



Water (60 ml) was added to ethyl 2-cyano(hydroxyimino)ethanoate (10.0 g, 70.0 mmol) and the suspension was carefully treated with a saturated sodium hydrogen carbonate solution (30 ml). To the yellow solution sodium dithionite (34.0 g, 0.2 mol) was added in portions over a period of about an hour. The temperature was kept below 20 °C during the addition. After stirring for another 30 min, extraction with dichloromethane (4 x 60 ml) was carried out. The combined organic phases were dried with magnesium sulfate and the solvent was removed under reduced pressure. The resulting yellow oil was dried under vacuum. Yield: 6.1 g (67%). This oil was immediately diluted with diethyl ether (50 ml) and a solution of *p*-toluenesulfonic acid monohydrate (10.1 g, 53.1 mmol) in ethanol (30 ml) was added. After stirring at room temperature for 15 min, the mixture was diluted with diethyl ether (100 ml) to induce crystallization. The flask was kept overnight at -20 °C and the precipitated white crystals were collected via filtration. Yield: 7.8 g (37%).

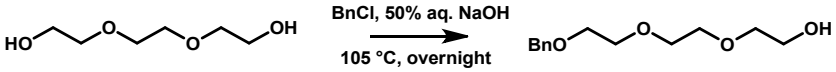
ethyl *N*-(*tert*-butoxycarbonyl)-3-nitriloalaninate *(Jacobsen et al.[10])*



To a solution of di-*tert*-butyl dicarbonate (8.0 g, 36.6 mmol) in toluene (25 ml) was added 1-cyano-2-ethoxy-2-oxoethanaminium 4-methylbenzenesulfonate (6.4 g, 20.9 mmol) and *N,N*-diisopropylethylamine

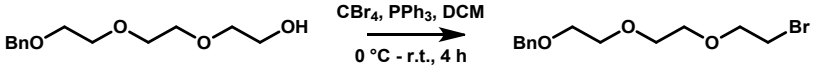
(3.6 ml, 20.9 mmol). The reaction mixture was refluxed at 100 °C for 6 h. After cooling to room temperature, water (25 ml) was added, and the resulting suspension was poured into ethyl acetate (300 ml). The organic layer was extracted with 1:1 water / saturated aqueous sodium hydrogen carbonate (200 ml), water (200 ml) and brine (200 ml). The organic phase was dried over sodium sulfate, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (4:1 hexane / ethyl acetate) to give the product as a white solid. Yield: 3.2 g (70%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.37 (s, 1H), 5.26 (d, 1H, *J*=7.8 Hz), 4.36 (q, 2H, *J*=7.2 Hz), 1.48 (s, 9H), 1.36 (t, 3H, *J*=7.2 Hz). R_f = 0.35 (4:1 hexane / ethyl acetate).

2-{2-[2-(benzyloxy)ethoxy]ethoxy}ethanol *(Ambudkar et al.[11])*



Triethylene glycol (5.5 ml, 41.3 mmol) was dissolved in 50% aqueous sodium hydroxide solution and stirred at room temperature for 10 min. Benzyl chloride (5.0 ml, 43.4 mmol) was added and the mixture was refluxed at 105 °C for 15 h. After cooling to room temperature, extraction with dichloromethane (3 x 200 ml) was carried out and the organic layer was washed with water (150 ml) and brine (150 ml). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate) to give a colourless oil. Yield: 4.2 g (43%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.28 – 7.38 (m, 5H), 4.61 (s, 2H), 3.62 – 3.75 (m, 12H), 2.67 (s, 1H). ESI-MS (MeOH): m/z = 263 $[M+Na]^+$. R_f = 0.25 (ethyl acetate).

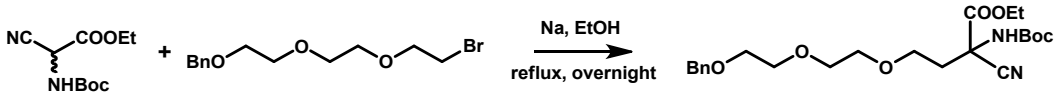
({2-[2-(2-bromoethoxy)ethoxy]ethoxy}methyl)benzene *(according to Wagener et al.[12])*



2-{2-[2-(benzyloxy)ethoxy]ethoxy}ethanol (4.2 g, 17.4 mmol) was dissolved in dry dichloromethane (25 ml) and cooled to 0 °C. Tetrabromomethane (6.4 g, 19.2 mmol) was added and the mixture was stirred for 5 min. Afterwards triphenylphosphine (5.0 g, 19.2 mmol) was added portionwise over the course of 30 min. The mixture was stirred at room temperature for additional 3 h. After concentration to half of its volume, hexane (300 ml) was added and the white precipitate was filtered. The solvent was removed under reduced pressure and the resulting crude was purified by silica gel column chromatography (ethyl acetate) to give a colourless oil. Yield: 4.2 g (80%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.27 – 7.36 (m, 5H), 4.58 (s, 2H), 3.82 (t, 2H, *J*=8.0 Hz), 3.64 – 3.72 (m, 8H), 3.47 (t, 2H, *J*=8.0 Hz). ESI-MS (MeOH): m/z = 325 $[M+Na]^+$. R_f = 0.63 (ethyl acetate).

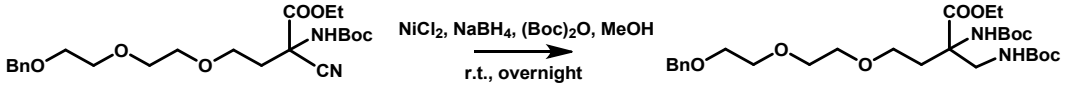
ethyl 4-{2-[2-(benzyloxy)ethoxy]ethoxy}-*N*-(*tert*-butoxycarbonyl)-2'-nitriloisovalinate

(according to Alberto et al.[13])



Sodium (0.22 g, 9.4 mmol) was dissolved in dry ethanol (75 ml) and ethyl *N*-(*tert*-butoxycarbonyl)-3-nitriloalaninate (1.94 g, 8.5 mmol) was added. The mixture was stirred at 60 °C for 30 min and then cooled to room temperature. ({2-[2-(2-bromoethoxy)ethoxy]ethoxy}methyl)benzene (2.51 g, 9.4 mmol) was added to the solution and the reaction mixture was refluxed overnight while it became red. The solvent was removed under reduced pressure and the resulting residue was treated with water (100 ml) and extracted with ethyl acetate (2 x 300 ml). The organic phase was washed with brine, dried over magnesium sulfate and filtered. The solvent was removed under reduced pressure and the resulting crude was purified by silica gel column chromatography (2:1 hexane / ethyl acetate) to give a yellow oil. Yield: 1.92 g (50%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.25 – 7.34 (m, 5H), 6.61 (s, 1H), 4.56 (s, 2H), 4.29 (q, 2H, *J*=7.0 Hz), 3.61 – 3.90 (m, 10H), 2.23 – 2.36 (m, 1H), 1.95 – 2.13 (m, 1H), 1.45 (s, 9H) 1.32 (t, 3H, *J*=7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.81, 154.32, 138.35, 129.83, 128.53, 127.89, 127.79, 81.48, 73.41, 70.77, 70.49, 69.67, 67.26, 66.77, 63.52, 62.62, 32.32, 29.84, 28.44, 28.34, 14.09. ESI-MS (MeOH): m/z = 473 $[M+Na]^+$. HR-ESI-MS (MeCN) for $C_{23}H_{34}N_2NaO_7$ $[M+Na]^+$: calculated, 473.2258; found, 473.2252. R_f = 0.15 (2:1 hexane / ethyl acetate).

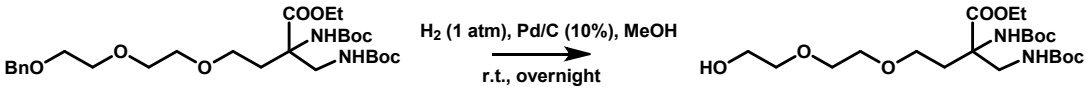
ethyl 4-{2-[2-(benzyloxy)ethoxy]ethoxy}-*N*-(*tert*-butoxycarbonyl)-2'-[(*tert*-butoxycarbonyl)amino]isovalinate *(according to Alberto et al.[13])*



ethyl 4-{2-[2-(benzyloxy)ethoxy]ethoxy}-*N*-(*tert*-butoxycarbonyl)-2'-nitriloisovalinate (1.21 g, 2.7 mmol) was dissolved in dry methanol (40 ml) and cooled to 0 °C. Di-*tert*-butyldicarbonat (1.17 g, 5.4 mmol) and nickel(II) chloride hexahydrate (0.06 g, 0.3 mmol) was added. Afterwards sodium borohydride (0.81 g, 21.4 mmol) was added portionwise during a time period of 1 h. The black mixture was stirred at room temperature for 14 h. Diethylenetriamine (0.32 ml, 3.0 mmol) was added and the mixture was stirred at room temperature for an additional 90 min. The solvent was evaporated and the residue was partitioned between ethyl acetate and saturated sodium hydrogen carbonate. The organic phase was dried over magnesium sulfate and the resulting colourless oil was purified by silica gel column chromatography (1:1 hexane / ethyl acetate). Yield: 1.12 g (78%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.25 – 7.35 (m, 5H), 6.05 (s, 1H), 5.08 (s, 1H), 4.56 (s, 2H), 4.17 (q, 2H, *J*=7.3 Hz), 3.51 – 3.68 (m, 12H), 2.25 – 2.29 (m, 1H), 2.07 – 2.13 (m, 1H), 1.42 (s, 9H), 1.41 (s, 9H), 1.25 (t, 3H, *J*=7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ

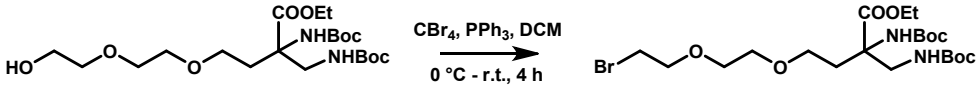
172.91, 156.16, 154.87, 138.41, 129.88, 128.56, 127.93, 127.81, 79.51, 73.44, 70.66, 70.61, 69.64, 69.43, 67.14, 62.49, 61.85, 44.85, 32.95, 29.88, 28.52, 14.23. ESI-MS (MeOH): m/z = 577 $[M+Na]^+$. HR-ESI-MS (MeCN) for $C_{28}H_{46}N_2NaO_9$ $[M+Na]^+$: calculated, 577.3095; found, 577.3092. R_f = 0.28 (2:1 hexane / ethyl acetate).

ethyl *N*-(*tert*-butoxycarbonyl)-2'-[(*tert*-butoxycarbonyl)amino]-4-[2-(2-hydroxyethoxy)ethoxy]isovalinate



ethyl 4-{2-[2-(benzyloxy)ethoxy]ethoxy}-*N*-(*tert*-butoxycarbonyl)-2'-[(*tert*-butoxycarbonyl)amino]isovalinate (1.01 g, 1.8 mmol) was dissolved in dry methanol (20 ml). Palladium on carbon (10%) (50 mg) was added and the benzyl protecting group was cleaved under atmospheric hydrogen pressure overnight at room temperature. The reaction mixture was filtered and the volatile part was removed to give a colourless oil. Yield: 0.74 g (90%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.08 (s, 1H), 5.07 (s, 1H), 4.19 (q, 2H, *J*=7.0 Hz), 3.54 – 3.75 (m, 12H), 2.25 – 2.29 (m, 1H), 2.07 – 2.13 (m, 1H), 1.43 (s, 9H), 1.42 (s, 9H), 1.28 (t, 3H, *J*=7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 173.10, 156.16, 154.87, 79.92, 79.64, 72.73, 70.42, 67.07, 62.52, 62.01, 44.77, 29.91, 28.55, 14.25. ESI-MS (MeOH): m/z = 487 $[M+Na]^+$. HR-ESI-MS (MeCN) for $C_{21}H_{40}N_2NaO_9$ $[M+Na]^+$: calculated, 487.2626; found, 487.2624. R_f = 0.29 (ethyl acetate).

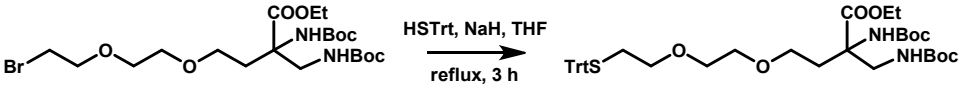
ethyl 4-[2-(2-bromoethoxy)ethoxy]-*N*-(*tert*-butoxycarbonyl)-2'-[(*tert*-butoxycarbonyl)amino]isovalinate *(according to Wagener et al.[12])*



ethyl *N*-(*tert*-butoxycarbonyl)-2'-[(*tert*-butoxycarbonyl)amino]-4-[2-(2-hydroxyethoxy)ethoxy]isovalinate (1.09 g, 2.4 mmol) was dissolved in dry dichloromethane (40 ml) and cooled to 0 °C. Tetrabromomethane (0.94 g, 2.8 mmol) was added and the mixture was stirred for 5 min. Afterwards triphenylphosphine (0.79 g, 2.8 mmol) was added portionwise over the course of 30 min. The mixture was stirred at room temperature for additional 3 h. After concentration to half of its volume, hexane (100 ml) was added and the white precipitate was filtered. The solvent was removed under reduced pressure and the resulting crude was purified by silica gel column chromatography (1:1 hexane / ethyl acetate). Yield: 0.95 g (77%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.04 (s, 1H), 5.07 (s, 1H), 4.18 (q, 2H, *J*=7.1 Hz), 3.79 (t, 2H, *J*=6.3Hz), 3.52 – 3.69 (m, 8H), 3.47 (t, 2H, *J*=6.3Hz), 2.26 – 2.29 (m, 1H), 2.07 – 2.14 (m, 1H), 1.43 (s, 9H), 1.42 (s, 9H), 1.28 (t, 3H, *J*=7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.97, 156.18, 154.86, 79.56, 71.39, 70.53, 70.43, 67.26, 62.52, 61.89, 44.83, 32.97, 30.36, 28.56, 14.28. ESI-MS (MeOH): m/z

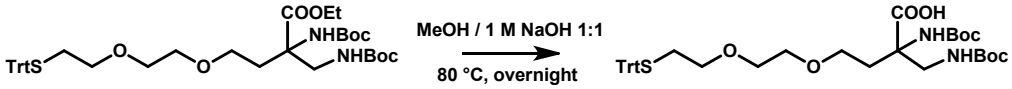
= 549 $[M+Na]^+$. HR-ESI-MS (MeOH+HCOOH) for $C_{21}H_{39}BrN_2NaO_8$ $[M+Na]^+$: calculated, 549.1782; found, 549.1776. R_f = 0.55 (1:1 hexane / ethyl acetate).

ethyl *N*-(*tert*-butoxycarbonyl)-2'-[(*tert*-butoxycarbonyl)amino]-4-{2-[2-(tritylsulfanyl)ethoxy]ethoxy}isovalinate



Triphenylmethanethiol (0.51 g, 1.8 mmol) was dissolved in dry tetrahydrofurane (15 ml) and sodium hydride (60% dispersion in mineral oil, 78 mg) was added. The yellow solution was stirred at room temperature for 20 min. Afterwards ethyl 4-[2-(2-bromoethoxy)ethoxy]-*N*-(*tert*-butoxycarbonyl)-2'-[(*tert*-butoxycarbonyl)amino]isovalinate (0.85 g, 1.6 mmol), dissolved in dry tetrahydrofurane (10 ml), was added and the mixture was refluxed for 3 h. The solvent was removed under reduced pressure and the resulting residue was treated with water (30 ml) and extracted with ethyl acetate (3 x 80 ml). The organic phase was washed with brine, dried over magnesium sulfate and filtered. The solvent was removed under reduced pressure and the resulting crude was purified by silica gel column chromatography (2:1 hexane / ethyl acetate) to give a colourless oil. Yield: 1.04 g (91%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.40 – 7.44 (m, 6H), 7.25 – 7.31 (m, 6H), 7.18 – 7.22 (m, 3H), 6.01 (s, 1H), 5.06 (s, 1H), 4.15 (q, 2H, *J*=7.2 Hz), 3.63 – 3.71 (m, 2H), 3.35 – 3.55 (m, 6H), 3.28 (t, 2H, *J*=7.0 Hz), 2.41 (t, 2H, *J*=7.0 Hz), 2.23 – 2.27 (m, 1H), 2.05 – 2.11 (m, 1H), 1.42 (s, 18H), 1.24 (t, 3H, *J*=7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.87, 156.11, 154.80, 145.00, 130.28, 129.79, 128.05, 126.83, 79.47, 71.21, 70.31, 70.05, 67.09, 62.45, 61.82, 44.81, 32.89, 31.76, 28.51, 14.21. ESI-MS (MeOH): m/z = 745 $[M+Na]^+$. HR-ESI-MS (MeOH+NaOH) for $C_{40}H_{54}N_2NaO_8S$ $[M+Na]^+$: calculated, 745.3493; found, 745.3483. R_f = 0.29 (2:1 hexane / ethyl acetate).

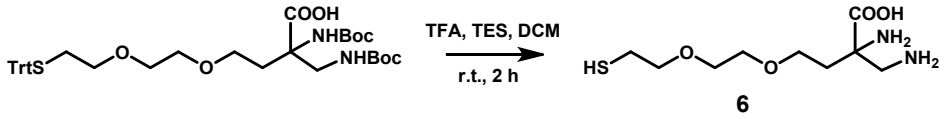
N-(*tert*-butoxycarbonyl)-2'-[(*tert*-butoxycarbonyl)amino]-4-{2-[2-(tritylsulfanyl)ethoxy]ethoxy}isovaline



ethyl *N*-(*tert*-butoxycarbonyl)-2'-[(*tert*-butoxycarbonyl)amino]-4-{2-[2-(tritylsulfanyl)ethoxy]ethoxy}isovalinate (1.04 g, 1.4 mmol) was dissolved in a 1:1 mixture of 1 M NaOH (5 ml) and methanol (5 ml). The solution was stirred at 80 °C for 13 h. Afterwards, the solution was allowed to cool to room temperature and the pH was adjusted to pH ~ 7 with 1 M HCl. The solvent was removed under reduced pressure and the resulting residue was washed with water (4 x 10 ml) to remove the sodium chloride. Yield: 0.981 g (98%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.41 – 7.44 (m, 6H), 7.26 – 7.31 (m, 6H), 7.20 – 7.24 (m, 3H), 6.37 (s, 1H), 5.11 (s, 1H), 3.63 – 3.68 (m, 2H), 3.31 – 3.56 (m, 6H), 3.25 (t, 2H, *J*=7.0 Hz), 2.44 (t, 2H, *J*=7.0 Hz), 2.23 – 2.27 (m, 1H), 1.99 – 2.04 (m, 1H), 1.39 (s, 9H), 1.37 (s, 9H). ^{13}C NMR (100 MHz,

$CDCl_3$, ppm) δ 156.61, 154.89, 144.86, 129.65, 127.89, 126.66, 79.46, 69.81, 69.61, 69.49, 67.55, 66.67, 61.88, 45.87, 31.32, 29.74, 28.54, 28.43. ESI-MS (MeOH): m/z = 693 $[M-H]^-$, m/z = 717 $[M+Na]^+$. HR-ESI-MS (MeOH+NaOH) for $C_{38}H_{50}N_2NaO_8S$ $[M+Na]^+$: calculated, 717.3180; found, 717.3177.

2'-amino-4-[2-(2-sulfanylethoxy)ethoxy]isovaline *(6)*



6

N-(*tert*-butoxycarbonyl)-2'-[(*tert*-butoxycarbonyl)amino]-4-{2-[2-(tritylsulfanyl)ethoxy]ethoxy}isovaline (150 mg, 0.21 mmol) was dissolved in dichloromethane (1.3 ml, 20.2 mmol). Trifluoroacetic acid (0.63 ml, 8.2 mmol) and triethylsilane (0.25 ml, 1.6 mmol) was added and the solution was stirred for 2 h at room temperature. The solvent was removed under reduced pressure and the resulting residue was washed with diethylether (4 x 10 ml). Yield: 52 mg (98%). ^{1}H NMR (400 MHz, D_2O, ppm) δ 3.82 – 3.87 (m, 2H), 3.68 – 3.76 (m, 6H), 2.78 (t, 2H, *J*=6.0 Hz), 2.24 – 2.29 (m, 2H). ^{13}C NMR (100 MHz, D_2O, ppm) δ 171.85, 72.00, 69.65, 68.89, 66.26, 60.31, 42.32, 32.53. ESI-MS (MeOH): m/z = 249 $[M-H]^-$, m/z = 253 $[M+H]^+$. HR-ESI-MS (MeOH+HCOOH) for $C_9H_{21}N_2O_4S$ $[M+H]^+$: calculated, 253.1217; found, 253.1211.

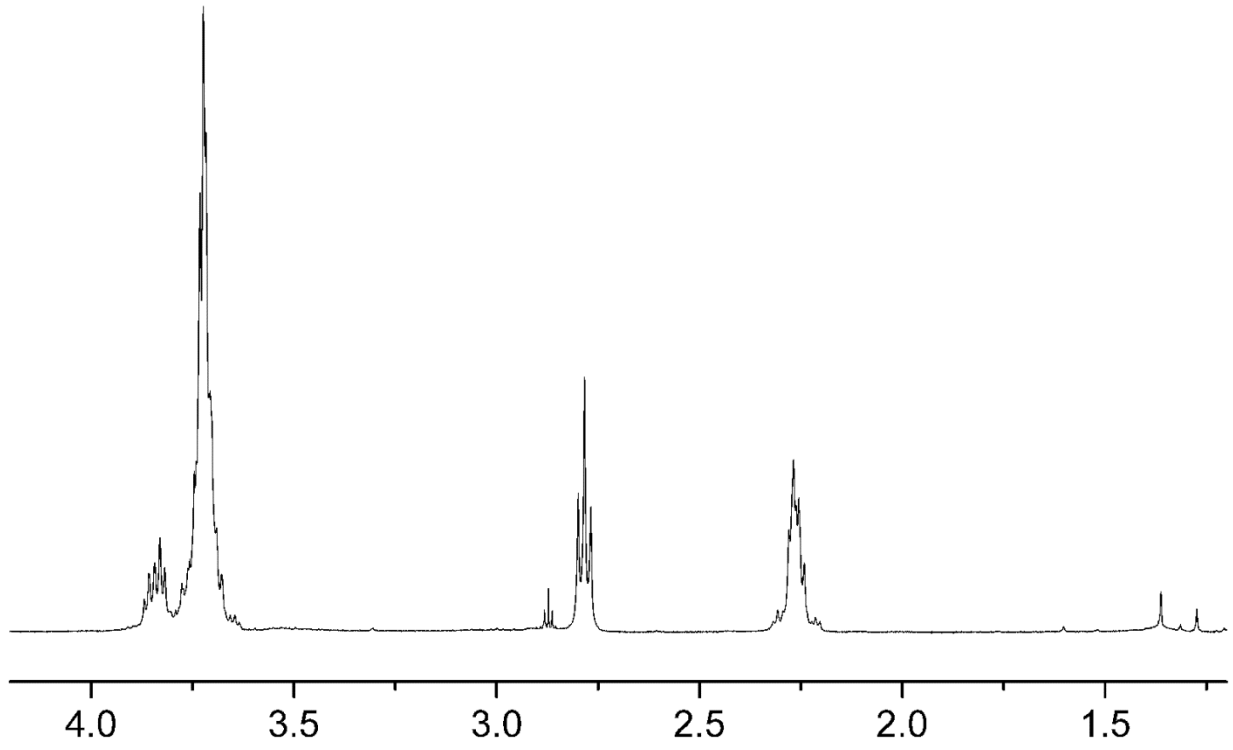
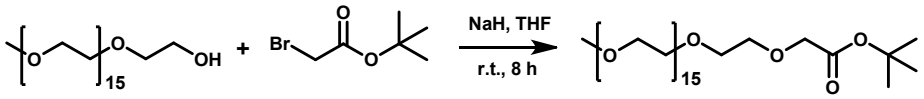


Figure 21. ^{1}H NMR (400 MHz) of compound **6**, measured in D_2O (chemical shifts in ppm).

10) Synthesis of dopamine based coating ligand

tert-butyl 2-methoxypolyethylene glycol(750) acetate *(according to Paduano et al.[14])*

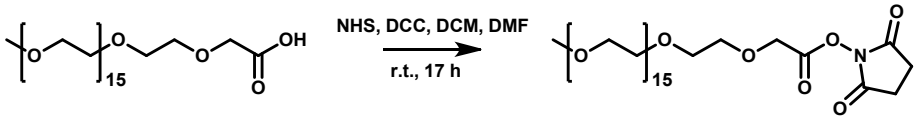


Methoxypolyethylene glycol 750 (6.84 g, 9.1 mmol) was dissolved in tetrahydrofurane (20 ml) and cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 0.73 g) was added portionwise. Afterwards *tert*-butyl bromoacetate (3.4 ml, 22.8 mmol) was added and the reaction mixture was stirred at room temperature for 8 h. Then methanol (1 ml) was added and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (10:1 dichloromethane / methanol). Yield: 7.05 g (91%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.00 (s, 2H), 3.66 – 3.70 (m, 4H), 3.61 – 3.64 (m, 58), 3.51 – 3.54 (m, 2H), 3.36 (s, 3H), 1.45 (s, 9H). ESI-MS (MeOH): m/z = 873 $[M+Na]^+$. R_f = 0.43 (10:1 dichloromethane / methanol).

2-methoxypolyethylene glycol(750) acetic acid

tert-butyl 2-methoxypolyethylene glycol(750) acetate (2.0 g, 2.48 mmol) was dissolved in dichloromethane (10 ml) and trifluoroacetic acid (5 ml). The mixture was stirred at room temperature for 3 h. The solvent was removed under vacuum and the residue was used directly for the next step without further purification. Yield: 1.96 g (99%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.16 (s, 2H), 3.74 – 3.76 (m, 2H), 3.63 – 3.69 (m, 60), 3.55 – 3.57 (m, 2H), 3.38 (s, 3H). ESI-MS (MeOH): m/z = 817 $[M+Na]^+$.

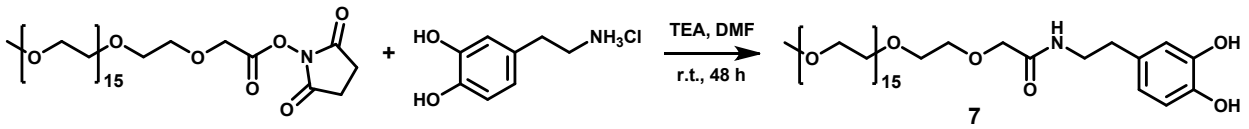
2,5-dioxopyrrolidin-1-yl-2-methoxypolyethylene glycol(750) acetate



2-methoxypolyethylene glycol(750) acetic acid (1.97 g, 2.5 mmol), *N*-hydroxysuccinimide (0.30 g, 2.6 mmol) and *N,N'*-dicyclohexylcarbodiimide (0.61 g, 3.0 mmol) were dissolved in dichloromethane (20 ml) and *N,N*-dimethylformamid (3 ml). The mixture was stirred at room temperature for 19 h, while a white precipitate was formed. The precipitate was separated from the solution with the help of centrifugation. The solvent was removed under reduced pressure the residue was purified by silica gel column chromatography (10:1 dichloromethane / methanol). Yield: 1.36 g (64%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm)

δ 4.14 (s, 2H), 3.67 – 3.69 (m, 2H), 3.52 – 3.56 (m, 60), 3.42 – 3.44 (m, 2H), 3.35 (s, 3H), 2.67 (s, 4H). ESI-MS (MeOH): m/z = 848 $[M+Na]^+$. R_f = 0.46 (10:1 dichloromethane / methanol).

N-(3,4-dihydroxyphenethyl)-2-methoxypolyethylene glycol(750) acetamide (7)



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2,5-dioxopyrrolidin-1-yl-2-methoxypolyethylene glycol(750) acetate (1.15 g, 1.3 mmol), dopamine hydrochloride (0.24 g, 1.3 mmol) and triethylamine (0.36 ml, 2.6 mmol) were dissolved in *N,N*-dimethylformamid (10 ml). The mixture was stirred at room temperature for 48 h. After evaporation of the solvent the resulting residue was purified by silica gel column chromatography (10:1 dichloromethane / methanol). Yield: 496 mg (44%). ^{1}H NMR (500 MHz, MeOD, ppm) δ 6.74 (d, 1H, *J*=7.9 Hz), 6.70 (s, 1H), 6.58 (d, 1H, *J*=7.9 Hz), 3.73 (s, 2H), 3.69 – 3.71 (m, 2H), 3.62 – 3.67 (m, 60), 3.53 – 3.55 (m, 2H), 3.36 (s, 3H), 3.13 (t, 2H, *J*=7.9 Hz), 2.81 (t, 2H, *J*=7.9 Hz). ESI-MS (MeOH): m/z = 885 $[M-H]^-$. R_f = 0.41 (10:1 dichloromethane / methanol).

11) References

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