Supporting information for

SUPERIOR PERFORMANCE OF HYBRID BIOHYDROGELS CROSS-LINKED WITH FUNCTIONALIZED GOLD NANOPARTICLES

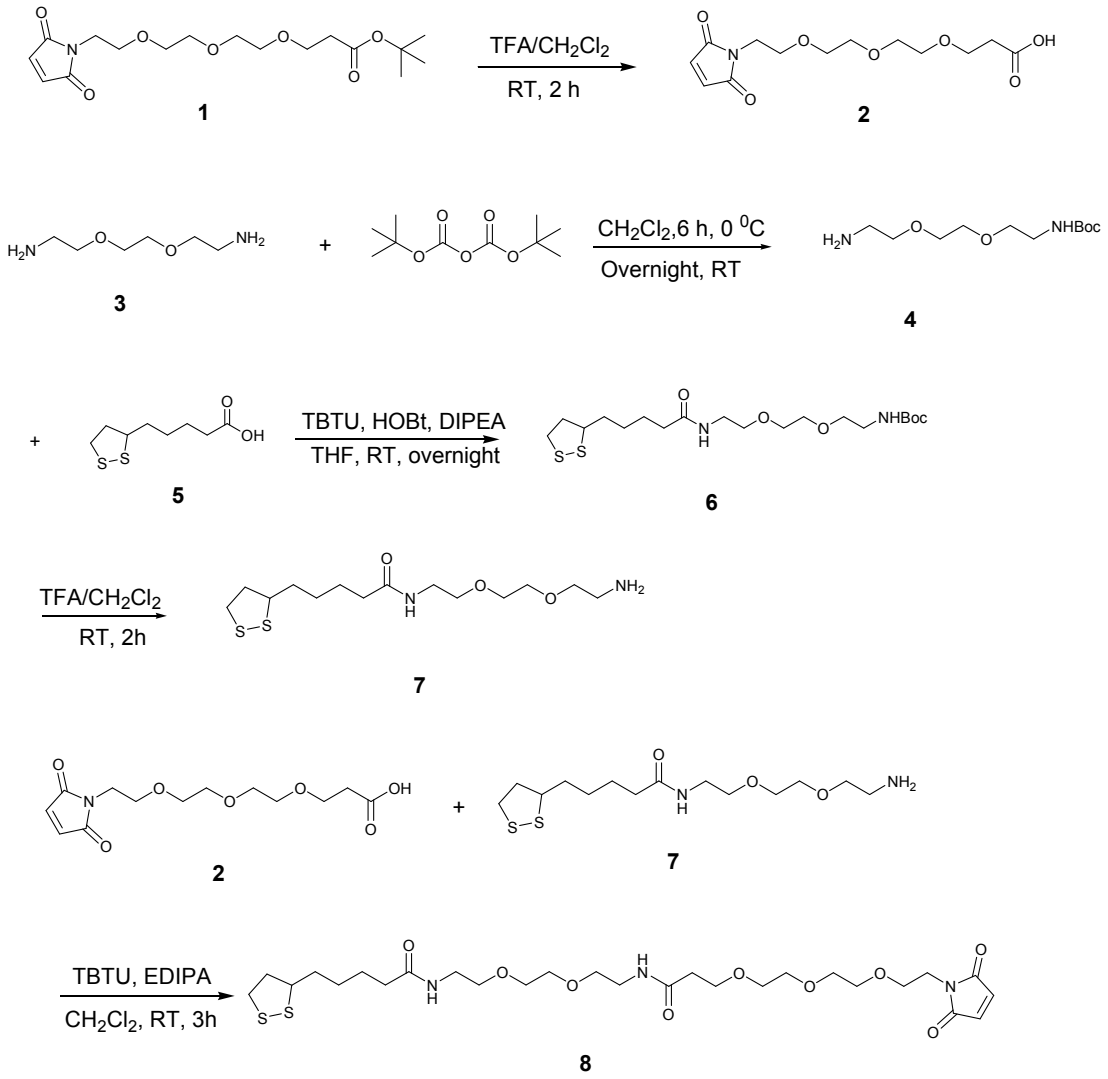
C. García-Astrain[1], I. Ahmed[2], D. Kendziora[2], O. Guaresti[1], A. Eceiza[1], L. Fruk[2], M.A. Corcuera[1], N. Gabilondo[1]

[1] 'Materials + Technologies' Group, Dept. of Chemical and Environmental Engineering, Polytechnic School, University of the Basque Country. Pza. Europa 1. 20018 Donostia-San Sebastián, Spain

[2] DFG-Centre for Functional Nanostrucutres (CFN), Karlsruhe Institute of Technology, Wolfgang-Gaede Str. 1a, 76131 Karlsruhe, Germany

Content

1. Synthesis of LA-TEG-Mal



Scheme S1. Synthesis of LA-TEG-Mal.

3-(2-(2-(2-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy)ethoxy)ethoxy)propanoic acid (**2**)

Tert-butyl-3-(2-(2-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) ethoxy) ethoxy) ethoxy) propanoate (**1**) was firstly synthesized according to the literature methods.[1,2] Then 5 mL trifluoroacetic acid (TFA) was added to 10 mL dry CH_2Cl_2 solution containing 1.40 mmol *tert*-butyl 3-(2-(2-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) ethoxy) ethoxy) ethoxy) propanoate. The reaction mixture was stirred at room temperature for 2 h. 15 mL CH_2Cl_2 was then added and the solvent was removed under reduced pressure. The procedure was repeated three times to remove traces of TFA to afford compound **2** as yellow thick oil (Yield: 88%).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.65 (t, J = 6.4 Hz, 2H), 3.58-3.65 (m, 10H), 3.70-3.77 (m, 4H), 6.72 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 34.6, 37.0, 66.2, 67.8, 69.9, 70.2, 70.3, 70.4, 134.1, 176.1; HRMS (FAB) for $C_{13}H_{20}NO_7$ $[M+H]^+$: 302.1236.

N-Boc-2,2'-(ethylene-l,2-dioxy)bisethylamine (**4**)

Compound **4** was firstly synthesized according to a reported method with slight modification.[3,4] A solution of di-*tert*-butyl dicarbonate (16.8 mmol) in 50 mL CH_2Cl_2 was added to a solution of 2,2′-(ethylene-l,2-dioxy)bis(ethylamine) (**3**) (33.7 mmol) in 100 mL dry CH_2Cl_2 at 0 °C under nitrogen atmosphere over a period of 4 h. The reaction mixture was stirred at 0 °C for 6 h and then at room temperature overnight. After removal of the solvent in *vacuo*, the residue was dissolved in 50 mL of chloroform and washed twice with aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give compound **4** (yield: 62%).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.41 (s, 9H). 2.61 (t, J = 5.3 Hz, 2H), 3.02 (m, 2H), 3.24-3.36 (m, 4H), 3.38-3.44 (m, 4H), 5.41 (br, 1H); HRMS (FAB) for $C_{11}H_{24}N_2O_4$ $[M+H]^+$: 249.1.

tert-butyl (2-(2-(2-(5-(1,2-dithiolan-3-yl)pentanamido)ethoxy)ethoxy)ethyl)carbamate **(6)**

To a solution of lipoic acid (**5**) (1.0 mmol) in dry CH_2Cl_2 (40 mL), N,N,N′,N′-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate (TBTU) (1.19 mmol) and N,N-diisopropylethylamine (DIPEA) (3.0 mmol) were added. The reaction mixture was cooled to 0 °C, and then *N-Boc-2,2'-(ethylene-l,2-dioxy)bisethylamine* (**4**) dissolved in 10 mL CH_2Cl_2 was added to the reaction mixture dropwise in 30 min. The as-obtained slurry was purged with argon and stirred at room temperature overnight. The volatiles were then removed under reduced pressure and the remaining semi-solid was partitioned between CH_2Cl_2 (100 mL) and H_2O (3×30 mL). The combined organic phase was dried over anhydrous sodium sulfate and the volatiles were removed under reduced pressure to obtain an oily mass which was further purified by silica gel chromatography (EtOAc/cyclohexane 3:1) to afford compound **6** as yellow thick oil (Yield: 73%).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.30-1.45 (m, 13H), 1.51-1.65 (m, 4H), 1.76-1.87 (m, 1H), 2.11 (t, *J* = 7.3 Hz, 2H), 2.31-2.42 (m, 1H), 2.93-3.11 (m, 2H), 3.21-3.23 (m, 2H), 3.33-3.38 (m, 2H),3.45-3.48 (m, 4H), 3.50-3,53 (m, 4H), 5.07 (br, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 25.2, 28.2, 28.6, 34.4, 35.9, 38.2, 38.4, 38.9, 40.0, 40.1, 56.2, 69.6, 69.9, 70.0, 78.8, 155.8, 172.8; FT-IR (ATR) υ_{max}: 3321, 2926, 2862, 1694, 1647, 1520, 1452, 1389, 1363, 1247cm^{-1}; HRMS (FAB) for $C_{19}H_{37}O_5N_2S_2$ $[M+H]^+$: 437.2138.

***N-(2-(2-(2-aminoethoxy)ethoxy)ethyl)-5-(1,2-dithiolan-3-yl)pentanamide* (7)**

To a stirred solution of tert-butyl (2-(2-(2-(5-(1,2-dithiolan-3-yl)pentanamido)ethoxy)ethoxy)ethyl)carbamate (**6**) (0.42 mmol) in dry CH_2Cl_2 (15 mL) was added trifluoroacetic acid (5 mL). The reaction mixture was stirred for 2 h at room temperature. Dichloromethane (15 mL) was then added and the solvent was removed under reduced pressure. The procedure was repeated three times to remove the traces of trifluoroacetic acid to afford N-(2-(2-(2-aminoethoxy)ethoxy)ethyl)-5-(1,2-dithiolan-3-yl)pentanamide (**7**) as yellow thick oil (93%). The amine **7** was used without further purification.

HRMS (FAB) for $C_{14}H_{29}O_3N_2S_2$ $[M+H]^+$: 337.1614

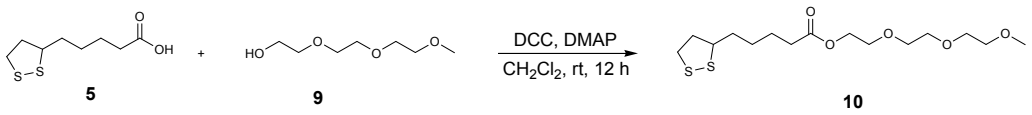
***N-(21-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-10-oxo-3,6,13,16,19-pentaoxa-9-azahenicosyl)-5-(1,2-dithiolan-3-yl)pentanamide* (8)**

N,N,N′,N′-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate (TBTU) (1.19 mmol) and N,N-diisopropylethylamine (DIPEA) (2.0 mmol) were added to a solution of compound **2** (0.99 mmol) in dry CH_2Cl_2 (40 mL). The reaction mixture was cooled to 0 ^oC, and N-(2-(2-(2-aminoethoxy)ethoxy)ethyl)-5-(1,2-dithiolan-3-yl)pentanamide (**7**) (1.19 mmol) dissolved in 10 mL CH_2Cl_2 was added to the above solution dropwise in 30 min. The slurry obtained was purged with argon and stirred at room temperature for 3 h. The volatiles were then removed under reduced pressure to get yellow semi-solid which was further purified by silica gel chromatography (EtOAc/cyclohexane 3:1) to afford compound **8** as yellow thick oil (Yield: 71%).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.18-1.25 (m, 2H), 1.29-1.44 (m, 2H), 1.53-1.69 (m, 4H), 1.75-1.88 (m, 1H), 2.11 (t, *J* = 7.3 Hz, 2H), 2.34-2.42 (m, 2H), 2.48 (m, 1H), 2.94-3.11 (m, 2H), 3.35-3.40 (m, 4H),3.47-3.59

(m, 18H), 3.64-3.68 (m, 4H), 56.28(br, 1H), 6.65 (s, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 25.3, 28.8, 34.6, 36.2, 36.9, 37.0, 38.4, 39.0, 40.2, 56.4, 67.1, 67.7, 69.8, 70.0, 70.1, 70.2, 70.3, 70.4, 134.1, 170.6, 171.5, 172.8; FT-IR (ATR) υ_{max}: 3306, 3079, 2863, 1705, 1646, 1540, 1433cm^{-1}; HRMS (FAB) for $C_{27}H_{46}O_9N_3S_2$ $[M+H]^+$: 620.2668.

2. Synthesis of LA-TEG-IL



5 9 10

Scheme S2. Synthesis of LA-TEG-IL.

2-(2-(2-methoxyethoxy)ethoxy)ethyl 5-(1,2-dithiolan-3-yl)pentanoate (10)

The Steglich esterification was done according to literature involving *N,N*-dicyclohexylcabodiimide (DCC) activation and *N,N*-dimethylaminopyridine (DMAP) as catalyst.[5] To a solution of lipoic acid (**5**) (0.48 mmol) and 2-(2-(2-methoxyethoxy)ethoxy)ethan-1-ol (**9**) (0.48 mmol) in 20 mL CH_2Cl_2 was added 0.026 mmol DMAP . After stirring the reaction mixture for 10 min the solution of DCC (0.69 mmol) dissolved in 10 mL CH_2Cl_2 was added dropwise over a 45 min period at room temperature. The reaction mixture was stirred at room temperature for 12 h. The solvent was then evaporated under reduced pressure and urea was removed by repeated precipitation with EtOAc/cyclohexane (1:9). The filtrate was concentrated under reduced pressure and the product was purified by silica gel flash chromatography starting with cyclohexane to cyclohexane/EtOAc (10:3), affording compound **10** as colorless oil (Yield: 89%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.08-1.22 (m, 2H), 1.31-1.45 (m, 5H), 1.55-1.65 (m, 1H), 2.05 (t, J = 7.3 Hz, 2H), 2.10-2.21 (m, 1H), 2.74-2.91 (m, 2H), 3.06 (s, 3H), 3.22-3.26 (m, 2H), 3.29-3.34 (m, 6H), 3.39 (t, J = 4.6 Hz, 2H), 3.91 (t, J = 4.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 24.3, 28.4, 33.6, 34.3, 38.2, 39.3, 56.0, 58.6, 63.1, 68.8, 70.2, 70.3, 71.6, 172.8; FT-IR (ATR) υ_{max}: 2922, 2857, 1730, 1656, 1517, 1450, 1105cm^{-1}; HRMS (FAB) for $C_{15}H_{28}O_5S_2$ $[M + H]^+$: 352.1375.

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