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Supporting Information Available

Bioconjugation of Supramolecular Metallacages to Integrin Ligands for Targeted Delivery of Cisplatin


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1. General remarks

Chemicals. All reagents, solvents and resins were obtained from commercial suppliers and used without further purification, unless otherwise stated.

Chromatography. Semi-preparative reversed phase HPLC was performed on a Waters instrument: Waters 2545 (Binary Gradient Module), Waters SFO (System Fluidics Organizer), Waters 2996 (Photodiode Array Detector), Waters 2767 (Sample Manager) equipped with a C18-column (Reprosil 100 C18, 5 µm, 150 x 30 mm, Dr. Maisch). Suitable linear gradients (40 mL/min) of H2O (0.1%v/v trifluoroacetic acid (TFA), buffer A) and acetonitrile (0.1%v/v TFA, buffer B) were applied for the purification of all compounds. Analytical HPLC-ESI-MS (heated electrospray ionization mass spectrometry) was performed on an UltiMate 3000 UHPLC focused chromatographic system (Dionex) connected to a LCQ Fleet mass spectrometer (Thermo Scientific) equipped with a C18 column (Accucore C18, 80 Å, 2.6 µm, 50 x 2.1 mm, Thermo Scientific). Linear gradients (0.9 mL/min, 5 min) of water (0.1% formic acid) and acetonitrile (0.1% formic acid) were used for analytical purpose. Further, analytical ESI-MS spectra of the metal-ligand L were recorded on a Walter Synapt G2SI QTOF. High resolution mass (HRMS) was measured on a LTQ Orbitrap XL (Thermo Scientific).
NMR. $^1$H-NMR and $^{13}$C-NMR spectra were recorded on a 500 MHz DMX (Bruker), a 500 MHz cryo AV (Bruker), and on a 400 MHz Ultrashield spectrometer (Bruker), respectively, at 298 K. DOSY-NMR was measured on a 400 MHz Ultrashield spectrometer (Bruker) at 298 K. Chemical shifts are given in parts per million (ppm). Abbreviations for NMR multiplicities are: singlet (s), doublet (d), triplet (t), multiplet (m). Coupling constants $J$ are given in Hz. Following solvents were used as internal standards: DMSO-d$_6$: 2.50 ppm ($^1$H-NMR) and 39.52 ppm ($^{13}$C-NMR); CDCl$_3$: 7.26 ppm ($^1$H-NMR) and 77.16 ppm ($^{13}$C-NMR).

2. Synthesis and analysis of ligand L0

Benzyl 3,5-bis(pyridin-3-ylethynyl)benzoate (SI-1)

A mixture of benzyl 3,5-dibromobenzoate (370 mg, 1.00 mmol, 1.00 eq.), 3-ethynylpyridine (309 mg, 3.00 mmol, 3.00 eq.), [Pd(PPh$_3$)$_2$Cl$_2$] (68.1 mg, 0.10 mmol, 0.10 eq.), and Cul (18.5 mg, 0.10 mmol, 0.10 eq.), was suspended in distilled triethylamine (15 mL) and stirred under a nitrogen atmosphere at 90°C. After 24 h, the reaction mixture was diluted with ethylacetate (50 mL) and filtered over glass-fritted funnel (por. 3). The solvent was removed under vacuum and the crude residue further purified by column chromatography on silica gel (Ethylacetate:Methanol = 100:5, $R_f$ = 0.57) to give the product SI-1 as an off white solid (311 mg, 0.75 mmol, 75%).

$^1$H-NMR (400 MHz, DMSO-d$_6$): $\delta$ [ppm] = 8.80 (d, $J$ = 1.4 Hz, 2H, H$_a$), 8.61 (dd, $J$ = 1.6, 5.0 Hz, 2H, H$_b$), 8.12 (d, $J$ = 1.6 Hz, 2H, H$_i$) 8.06 (t, $J$ = 1.6, 1H H$_e$) 8.02 (dt, $J$ = 1.8, 8.0 Hz, 2H, H$_d$) 7.64-7.35 (m, 7H, phenyl, H$_c$), 5.39 (s, 2H, H$_g$).

$^{13}$C{$^1$H}-NMR (101 MHz, DMSO-d$_6$): $\delta$ [ppm] = 164.5 (C$_l$), 152.3 (C$_a$), 149.9 (C$_b$), 139.3 (C$_h$), 138.7 (C$_d$), 136.1 (C$_i$), 132.5 (C$_i$), 131.9 (Cphenyl), 131.4 (C$_n$) 129.2 (Cphenyl), 129.1 (Cphenyl), 128.8 (Cphenyl), 128.7 (Cphenyl), 124.1 (C$_d$), 123.3 (C$_c$), 119.2 (C$_e$), 90.5 (C/C$_g$), 88.6 (C/C$_g$), 67.4 (C$_m$).

HRMS (ESI) calcd. for C$_{28}$H$_{19}$N$_4$O$_2$: [M+H]$^+$: $m/z$ = 415.1447; found: 415.1448; $\delta$ = 0.2 ppm.
Benzyl 3,5-bis(pyridin-3-ylethynyl)benzoate (SI-1) (415 mg, 1.00 mmol, 1.00 eq.) was dissolved in acetonitrile (5 mL). To the yellow solution, deionised water (2 mL) was added and the solution was heated to 70°C before sodium hydroxide (100 mg, 2.50 mmol, 2.50 eq.) was added. The resulting orange solution was stirred at 70°C for 4 h. 1 M HCl was added to acidify the solution (~pH 6). The resulting yellow precipitate was collected by filtration, washed with diethyl ether and re-suspended in methanol. The solvent was removed under vacuum to give the product L0 as a white powder (301 mg, 0.93 mmol, 93%) (Overall yield 66%).

1H-NMR (400 MHz, DMSO-d6): δ = 8.82 (dd, J = 0.89, 2.2 Hz, 2H, H_a), 8.63 (dd, J = 1.7, 4.8 Hz, 2H, H_b), 8.12 (d, J = 1.6, 2H, H_i), 8.08-8.01 (m, 3H, H_e, H_d), 7.50 (ddd, J = 0.90, 4.9, 8.2 Hz, 2H, H_c).

13C{1H}-NMR (101 MHz, DMSO-d6): δ = 166.2 (C_l), 152.3 (C_a), 150.0 (C_b), 139.3 (C_h), 138.1 (C_d/C_k), 132.8 (C_j), 124.2 (C_c), 123.5 (C_i), 119.3 (C_e), 90.7 (C_f/C_g), 88.3 (C_l/C_a).

HRMS (ESI) calcld for C_{21}H_{13}N_{2}O_{2} [M+H]+: m/z = 324.0899; found: 324.0901; δ = 0.6 ppm.

3. Synthesis and Analysis of ligands L1-L4

- cyclo(RGDfK((3,5-bis(pyridin-3-ylethynyl)benzoyl)Ahx)) (L1)

The carboxylic acid L0 (8.37 mg, 25.8 µmol, 1.00 eq.) and the free amine 1 (18.5 mg, 25.8 µmol, 1.00 eq.) were converted according to the above-mentioned procedure. The final bioconjugated metal ligand L1 was isolated after purification via preparative RP-HPLC (20-35% buffer B, 10 min, Waters) and lyophilization as a white solid (9.0 mg, 8.78 µmol, 34%).

1H-NMR (500 MHz, DMSO-d6): δ = 12.25 (bs, 1H), 8.81 (d, J = 2.0 Hz, 2H), 8.71 (t, J = 5.6 Hz, 1H), 8.64 (dd, J = 4.8, 1.7 Hz, 2H), 8.41 (dd, J = 7.5, 4.4 Hz, 1H), 8.15 – 7.98 (m, 7H), 7.96 (t, J = 1.6 Hz, 1H), 7.76 (t, J = 5.6 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.45 (t, J = 5.9 Hz, 1H), 7.29 – 7.21 (m, 2H), 7.20 – 7.14 (m, 1H), 7.17 – 7.11 (m, 2H), 6.43 (td, J = 8.5, 5.9 Hz, 1H), 4.44 (dd, J = 7.5 Hz, 1H), 4.18 – 4.10 (m, 1H), 4.04 (dd, J = 15.0, 7.6 Hz, 1H), 3.95 – 3.86 (m, 1H), 3.32 – 3.21
The carboxylic acid **L0** (2.75 mg, 8.46 µmol, 1.00 eq.) and the free amine **2** (5.50 mg, 8.46 µmol, 1.00 eq.) were converted according to the above-mentioned procedure. The final bioconjugated metal ligand **L2** was isolated after purification via preparative RP-HPLC (20-45% buffer B, 10 min, Waters) and lyophilization as a white solid (6.5 mg, 6.80 µmol, 80%).

**1H-NMR** (500 MHz, DMSO-d6): δ = 12.65 (s, 1H), 8.81 (d, J = 2.1 Hz, 2H), 8.70 (t, J = 5.5 Hz, 1H), 8.63 (dd, J = 4.8, 1.7 Hz, 2H), 8.15 (d, J = 8.3 Hz, 1H), 8.10 (d, J = 1.6 Hz, 2H), 8.02 (dt, J = 8.0, 1.9 Hz, 2H), 7.95 (t, J = 1.6 Hz, 1H), 7.86 (t, J = 5.6 Hz, 1H), 7.79 (d, J = 7.2 Hz, 1H), 7.73 (d, J = 8.7 Hz, 2H), 7.50 (dd, J = 7.9, 4.9 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 6.50 (dd, J = 7.3, 2.5 Hz, 1H), 6.35 (d, J = 2.5 Hz, 1H), 4.41 (q, J = 7.3 Hz, 1H), 4.00 (td, J = 6.0, 3.1 Hz, 4H), 3.87 (q, J = 6.5 Hz, 2H), 3.44 (q, J = 6.7 Hz, 2H), 3.18 (q, J = 6.5 Hz, 2H), 2.79 (dd, J = 13.6, 8.0 Hz, 1H), 2.72 (dd, J = 13.6, 5.9 Hz, 1H), 2.49 (s, J = 15.4, 6.2 Hz, 1H), 2.07 (t, J = 7.4 Hz, 2H), 2.00 (p, J = 6.4 Hz, 2H), 1.83 (p, J = 6.6 Hz, 2H), 1.53 (pd, J = 7.3, 3.1 Hz, 4H), 1.29 (tt, J = 9.8, 6.0 Hz, 2H).

**13C{1H}-NMR** (126 MHz, DMSO-d6): δ = 172.6, 172.1, 165.1, 164.1, 160.8, 156.8, 154.5, 151.7, 149.4, 138.9, 135.8, 131.0, 130.5, 129.0, 126.8, 123.8, 122.7, 118.9, 114.9, 113.8, 104.0 (HSQC), 90.6, 87.5, 65.4, 64.5, 56.6, 48.4, 39.5 (HSQC), 39.1 (HSQC), 28.9 (HSCQ), 38.8, 35.4, 35.4, 28.9, 28.7, 27.8, 26.2, 25.1.

**RP-HPLC** (5-95%, 5 min): tR = 3.38 min.

**MS** (HESI): m/z = 479.04 [M+2H]2+, 956.27 [M+H]+.

**HRMS** (ESI) calcd. for C56H58N7O8+: m/z = 956.43469; found: 956.43355; δ = 1.2 ppm.
The carboxylic acid \( L_0 \) (8.45 mg, 26.0 \( \mu \)mol, 1.00 eq.) and the free amine \( 3 \) (20.0 mg, 26.0 \( \mu \)mol, 1.00 eq.) were converted according to the above-mentioned procedure. The final bioconjugated metal ligand \( L_3 \) was isolated after purification via preparative RP-HPLC (20-35% buffer B, 10 min, Waters) and lyophilization as a white solid (8.0 mg, 7.45 \( \mu \)mol, 59%).

\[ ^{1}H\text{-NMR} \ (500 \text{ MHz}, \text{DMSO-}d_6): \delta = 8.88 – 8.78 \ (m, 3H), 8.70 \ (t, J = 5.6 \text{ Hz}, 1H), 8.67 – 8.59 \ (m, 3H), 8.09 \ (d, J = 1.5 \text{ Hz}, 2H), 8.04 \ (dt, J = 8.0, 1.9 \text{ Hz}, 2H), 7.96 \ (t, J = 1.6 \text{ Hz}, 1H), 7.77 \ (d, J = 8.5 \text{ Hz}, 1H), 7.74 \ (t, J = 5.6 \text{ Hz}, 1H), 7.55-7.48 \ (m, J = 7.9, 4.9, 0.9 \text{ Hz}, 2H), 7.46 \ (t, J = 5.9 \text{ Hz}, 1H), 6.81 \ (d, J = 7.9 \text{ Hz}, 1H), 4.76 – 4.65 \ (m, 2H), 4.58 \ (q, J = 7.6, 6.1 \text{ Hz}, 1H), 4.47 \ (q, J = 7.1 \text{ Hz}, 1H), 4.35 \ (t, J = 7.0 \text{ Hz}, 1H), 3.75 \ (dd, J = 15.0, 5.3 \text{ Hz}, 1H), 3.40 \ (dd, J = 15.0, 6.0 \text{ Hz}, 1H), 3.27 \ (q, J = 6.7 \text{ Hz}, 2H), 3.16 – 3.04 \ (m, 2H), 3.03 – 2.98 \ (m, 1H), 3.01 \ (s, 3H), 2.88 – 2.79 \ (m, 1H), 2.77 \ (s, 3H), 2.18 – 2.08 \ (m, 1H), 2.05 \ (t, J = 7.4 \text{ Hz}, 2H), 1.80 – 1.58 \ (m, 3H), 1.58 – 1.45 \ (m, 5H), 1.45 – 1.34 \ (m, 4H), 1.34 – 1.22 \ (m, 5H), 1.19 \ (d, J = 6.7 \text{ Hz}, 3H), 0.91 \ (d, J = 6.4 \text{ Hz}, 3H), 0.70 \ (d, J = 6.7 \text{ Hz}, 3H).

\[ ^{13}C\text{-NMR} \ (126 \text{ MHz}, \text{DMSO-}d_6): \delta = 172.1, 172.0, 171.9, 171.8, 171.6, 169.7, 169.3, 168.8, 164.1, 156.5, 151.7, 149.4, 138.9, 136.2, 135.8, 130.5, 123.8, 122.6, 118.9, 117.4, 115.0, 90.6, 87.5, 60.7, 57.4, 51.0, 49.1, 45.9, 43.1, 40.3, 38.1, 35.4, 34.6, 32.9, 30.0, 29.1, 28.7, 26.2, 25.7, 25.1, 24.9, 23.7, 20.3, 18.4, 16.5.

\[ \text{RP-HPLC} \ (5-95\%, 5 \text{ min}): t_R = 2.68 \text{ min}.

\[ \text{MS (HESI)}: \ m/z = 538.14 \ [M+2\text{H}]^{2+}, 1074.39 \ [M+\text{H}]^{+}.

\[ \text{HRMS (ESI) calcd. for } C_{366}H_{52}N_{13}O_{10}^{+} \ [M+\text{H}]^{+}: \ m/z = 1074.55196; \text{ found: } 1074.55619; \delta = -3.9 \text{ ppm}.

- \text{cyclo(RGDA*L*v)((3,5-bis(pyridin-3-ylethynyl)benzoyl)Ahx)) (L3)}
• (S)-2-(4-(3-(6-(3,5-bis(pyridin-3-ylethynyl)benzamido)hexanamido)propoxy)-2,6-dimethylbenzamido)-3-(2-(3-guanidinobenzamido)acetamido)propanoic acid (L4)

The carboxylic acid L0 (7.59 mg, 23.4 µmol, 1.00 eq.) and the free amine 4 (15.0 mg, 23.4 µmol, 1.00 eq.) were converted according to the above mentioned procedure. The final bioconjugated metal ligand L4 was isolated after purification via preparative RP-HPLC (20-35% buffer B, 10 min, Waters) and lyophilization as a white solid (8.04 mg, 8.49 µmol, 54%).

$^1$H-NMR (500 MHz, DMSO-d$_6$): $\delta = 12.74$ (s, 1H), 9.80 (s, 1H), 8.84 – 8.79 (m, 2H), 8.78 (t, $J = 6.0$ Hz, 1H), 8.70 (t, $J = 5.6$ Hz, 1H), 8.64 (d, $J = 4.0$ Hz, 2H), 8.35 (d, $J = 7.7$ Hz, 1H), 8.10 (d, $J = 1.6$ Hz, 2H), 8.04 (t, $J = 1.9$ Hz, 1H), 8.04 – 7.99 (m, 2H), 7.96 (t, $J = 1.6$ Hz, 1H), 7.85 (t, $J = 5.7$ Hz, 1H), 7.77 (d, $J = 7.9$ Hz, 1H), 7.72 (t, $J = 1.9$ Hz, 1H), 7.56 – 7.47 (m, 6H), 7.42 – 7.36 (m, 1H), 6.57 (s, 2H), 4.51 (td, $J = 7.8$, 5.2 Hz, 1H), 3.96 – 3.87 (m, 3H), 3.82 (dd, $J = 16.3$, 5.8 Hz, 1H), 3.61 – 3.52 (m, 1H), 3.45 – 3.31 (m, 1H), 3.31 – 3.23 (m, 2H), 3.16 (q, $J = 6.6$ Hz, 2H), 2.20 (s, 6H), 2.08 (t, $J = 7.4$ Hz, 2H), 1.79 (p, $J = 6.7$ Hz, 2H), 1.59 – 1.48 (m, 4H), 1.35 – 1.26 (m, 2H).

$^{13}$C($^1$H)-NMR (126 MHz, DMSO-d$_6$): $\delta = 172.1$, 171.8, 169.3, 169.2, 165.6, 164.1, 158.2, 158.1, 158.0, 155.7, 151.7, 149.4, 138.8, 136.2, 135.8, 135.6, 135.4, 130.7, 130.5, 129.8, 127.4, 125.2, 123.8, 123.5, 122.7, 118.9, 112.9, 90.6, 87.5, 65.1, 52.0, 42.5, 35.5, 35.4, 29.0, 28.7, 26.2, 25.1, 19.2.

RP-HPLC (5-95%, 5 min): $t_R = 2.80$ min.

MS (HESI): $m/z =$ 474.51 [M+2H]$^{2+}$, 947.22 [M+H]$^+$. 

HRMS (ESI) calcd. for C$_{52}$H$_{55}$N$_{10}$O$_8$: $m/z =$ 947.41989; found: 947.41991; $\delta = 0.02$ ppm.
4. Synthesis and Analysis of Ligands 1-4

**Synthesis of 1**

- **cyclo(RGDfK(Ahx))** (1)

The linear peptide was synthesized according GP1 – GP3 on solid support starting with Fmoc-Gly-OH following standard Fmoc-strategy. After cleavage according GP4 and cyclisation according GP5 the Cbz-group of lysine was cleaved according GP6. Coupling of Boc-Ahx-OH according GP7 followed by a general deprotection according GP8. The final compound 1 was isolated after purification via preparative RP-HPLC (05-40% buffer B, 10 min, Waters) and lyophilization as a white solid.

**RP-HPLC** (5-95%, 5 min): $t_R = 1.38$ min.

**MS** (HESI): $m/z = 359.49$ [M+2H]$^{2+}$, $717.43$ [M+H]$^+$. 

**HRMS** (ESI) calc. for C$_{33}$H$_{53}$N$_{10}$O$_8$: $m/z = 717.40478$; found: 717.40424, $\delta = 0.8$ ppm.

The spectral data correspond to those given in the literature.$^3$

**Synthesis of 2**

- **(S)-3-(4-(3-(6-aminohexanamido)propoxy)benzamido)-4-(4-(3-((4-methoxypyridin-2-yl)amino)propoxy)phenyl)butanoic acid** (2)

The unprotected ligand was synthesized on solid support according to the literature.$^4$ The crude product was purified via preparative HPLC (05-60% buffer B, 10 min, Waters) and after lyophilization isolated as a white TFA-salt.

**$^1$H-NMR** (500 MHz, DMSO-$d_6$): $\delta = 12.83$ (bs, 1H), 12.16 (bs, 1H), 8.33 (bs, 1H), 8.17 (d, $J = 8.3$ Hz, 1H), 7.89 (t, $J = 5.6$ Hz, 1H), 7.81 (d, $J = 7.2$ Hz, 1H), 7.75 (d, $J = 8.8$ Hz, 2H), 7.67 (s, 3H), 7.13 (d, $J = 8.6$ Hz, 2H), 6.96 (d, $J = 8.9$ Hz, 2H), 6.83 (d, $J = 8.7$ Hz, 2H), 6.48 (dd, $J = 7.2$, 2.4 Hz, 1H), 6.34 (d, $J = 2.5$ Hz, 1H), 4.46 – 4.35 (m, 1H), 4.02 (virt. q, $J = 6.1$ Hz, 4H), 3.87 (s, 3H), 3.44 (q, $J = 6.5$ Hz, 2H), 3.19 (q, $J = 6.6$ Hz, 2H), 2.85 – 2.68 (m, 4H), 2.53 – 2.51 (m, 1H), 2.40 (dd, $J = 15.4$, 6.1 Hz, 1H),
2.07 (t, J = 7.4 Hz, 2H), 2.00 (p, J = 6.5 Hz, 2H), 1.85 (p, J = 6.6 Hz, 2H), 1.50 (h, J = 8.0 Hz, 4H), 1.32 – 1.20 (m, 2H).

$^{13}$C($^1$H)-NMR (126 MHz, DMSO-d$_6$): δ = 172.6, 171.9, 165.1, 160.8, 156.8, 130.9, 130.1, 129.0, 126.8, 114.2, 113.8, 103.8 (HSQC), 91.4 (HSQC), 65.5, 64.6, 56.5, 48.4, 38.7, 35.5, 35.1, 28.9, 27.9, 26.9, 25.6, 24.8.

RP-HPLC (5-95%, 5 min): $t_R$ = 1.98 min.

MS (HESI): $m/z$ = 325.94 [M+2H]$,^2$+, 650.32 [M+H]$^+$.

HRMS (ESI) calc. for C$_{35}$H$_{48}$N$_{5}$O$_{7}$: $m/z$ = 650.35483; found: 650.35528, $\delta$ = -0.7 ppm.

### Synthesis of 3

- (S)-3-(4-(3-(6-aminohexanamido)propoxy)benzamido)-4-(4-(3-((4-methoxypyridin-2-yl)amino)propoxy)phenyl)butanoic acid (3)

The linear peptide was synthesized according GP1 – GP3 and GP9 on solid support starting with Fmoc-Gly-OH following standard Fmoc-strategy. After cleavage according GP4 and cyclisation according GP5 the Dde-group of lysine was cleaved according GP10. Coupling of Boc-Ahx-OH according GP7 followed by a general deprotection according GP8. The final compound 3 was isolated after purification via preparative RP-HPLC (10-60% buffer B, 10 min, Waters) and lyophilization as a white solid.

$^1$H-NMR (500 MHz, DMSO-d$_6$): δ = 12.28 (s, 1H), 8.83 (t, J = 5.7 Hz, 1H), 8.64 (d, J = 8.6 Hz, 1H), 7.83 – 7.72 (m, 2H), 7.63 (s, 4H), 7.49 (t, J = 5.9 Hz, 1H), 6.81 (d, J = 7.9 Hz, 1H), 4.73 – 4.64 (m, 2H), 4.58 (td, J = 7.8, 6.1 Hz, 1H), 4.47 (q, J = 7.1 Hz, 1H), 4.38 (dd, J = 7.9, 6.3 Hz, 1H), 3.75 (dd, J = 15.1, 5.3 Hz, 1H), 3.41 (dd, J = 15.0, 6.0 Hz, 1H), 3.08 (dt, J = 12.5, 6.7 Hz, 2H), 3.01 (s, 3H), 3.05 – 2.98 (m, 2H), 2.88 – 2.80 (m, 1H), 2.78 (s, 3H), 2.77 – 2.71 (m, 2H), 2.49 – 2.44 (m, 1H), 2.20 – 2.08 (m, 1H), 2.04 (t, J = 7.4 Hz, 3H), 1.76 – 1.66 (m, 2H), 1.66 – 1.57 (m, 1H), 1.57 – 1.44 (m, 4H), 1.44 – 1.33 (m, 3H), 1.33 – 1.22 (m, 5H), 1.20 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.4 Hz, 3H), 0.71 (d, J = 6.8 Hz, 3H).

$^{13}$C($^1$H)-NMR (126 MHz, DMSO-d$_6$): δ = 172.12, 172.05, 171.73, 171.69, 171.6, 169.7, 169.3, 168.7, 156.6, 60.7, 57.3, 51.0, 49.1, 45.9, 43.1/43.0, 40.3, 38.7, 38.1, 35.1, 34.6, 32.8, 30.3, 30.0, 29.1, 27.6, 26.9, 25.7, 25.5, 24.9, 24.8, 23.7, 20.3, 18.4, 16.5.

RP-HPLC (5-95%, 5 min): $t_R$ = 1.98 min.

MS (HESI): $m/z$ = 325.94 [M+2H]$^2$+, 650.32 [M+H]$^+$.

HRMS (ESI) calc. for C$_{34}$H$_{62}$N$_{11}$O$_{9}$: $m/z$ = 768.47320; found: 768.47140; $\delta$ = -0.7 ppm.
Synthesis of \(4\)

Scheme S2. Preparation of peptide \(4\) as solution synthesis.

- **tert-butyl-4-(3-((benzyloxy)carbonyl)amino)propoxy)-2,6-dimethylbenzoate (SI-2)**

  Compound SI-2 was prepared as described in the literature\(^5\) and isolated as a white solid (5.29 g, 12.8 mmol, 81%) after flash chromatography [SiO\(_2\), 900 mL, CyHex/EtOAc = 3/1 \(\rightarrow\) 2/1].

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.39 - 7.28\) (m, 5H), 6.52 (s, 2H), 5.10 (s, 2H), 4.98 (s, 1H), 4.00 (t, \(J = 5.9\) Hz, 2H), 3.39 (q, \(J = 6.4\) Hz, 2H), 2.31 (s, 6H), 1.98 (p, \(J = 6.2\) Hz, 2H), 1.58 (s, 9H).

\(^{13}\)C\(^{(1)}\)H-NMR (101 MHz, CDCl\(_3\)): \(\delta = 169.3, 158.8, 156.6, 138.9, 128.7, 128.5, 128.2, 113.7, 81.5, 66.8, 65.8, 38.7, 29.5, 28.4, 20.2.

RP-HPLC (5-95%, 7 min): \(t_R = 4.13\)

MS (HESI): \(m/z = 413.76\) [M+H]\(^+\), 430.97 [M+NH\(_4\)]\(^+\), 436.12 [M+Na]\(^+\), 826.61 [2M+H]\(^+\).

The spectral data correspond to those given in the literature.\(^5\)

- **tert-butyl-4-(3-((benzyloxy)carbonyl)amino)hexanamido)propoxy)-2,6-dimethylbenzoate (SI-3)**
Compound SI-2 (1.00 g, 2.42 mmol 1.00 eq.) was converted according to the GP6 and GP7 with Cbz-Ahx-OH (770 mg, 2.90 mmol, 1.20 eq.) to the Cbz-protected Amin SI-3. After removal of the solvent in vacuo the crude product was purified via preparative RP-HPLC (30-80% buffer B, 10 min, Waters) and after lyophilization SI-3 was obtained as a white solid (0.91 g, 1.74 mmol, 72% over 2 steps).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ = 7.26 (s, 5H), 6.44 (d, $J = 0.8$ Hz, 2H), 5.94 (d, $J = 6.1$ Hz, 1H), 5.00 (s, 2H), 4.87 – 4.71 (m, 1H), 3.91 (t, $J = 5.8$ Hz, 2H), 3.35 (q, $J = 6.3$ Hz, 2H), 3.08 (q, $J = 6.7$ Hz, 2H), 2.23 (t, $J = 0.6$ Hz, 6H), 2.17 – 2.02 (m, 2H), 1.89 (p, $J = 6.2$ Hz, 2H), 1.61 – 1.48 (m, 2H), 1.50 (s, 9H), 1.48 – 1.33 (m, 2H), 1.25 (qd, $J = 7.3$, 6.5, 4.1 Hz, 2H).

$^{13}$C($^1$H)-NMR (75 MHz, CDCl$_3$): $\delta$ = 173.5, 169.3, 158.7, 156.6, 136.9, 136.7, 128.6, 128.6, 128.2, 128.2, 113.6, 81.6, 66.7, 66.2, 40.9, 37.5, 36.6, 29.8, 29.0, 28.4, 26.3, 25.3, 20.1.

$^1$H-NMR (5-95%, 5 min): $t_R = 3.88$ min.

MS (HESI): $m/z = 526.91$ [M+H]$^+$, 1052.98 [2M+H]$^+$.

HRMS (ESI) calc. for C$_{30}$H$_{43}$N$_2$O$_6$ $^+$ [M+H]$^+$: 527.31121; found: 527.31147; $\delta = 1.2$ ppm.

**methyl-(S)-2-(4-(3-(((benzyloxy)carbonyl)amino)hexanamido)propoxy)-2,6-dimethylbenzamido)-3-((tert-butoxycarbonyl)amino)propanoate (SI-4)**

The tert-butyl protected carboxylic acid SI-3 (914 mg, 1.74 mmol, 1.05 eq.) was dissolved in CH$_2$Cl$_2$ (3 mL) and TFA (12 mL) was added at room temperature. After stirring for 30 min, the reaction mixture was processed according to GP8. The crude carboxylic acid was coupled according to GP7 with methyl-(S)-2-amino-3-((tert-butoxycarbonyl)amino)propanoate hydrochloride (421 mg, 1.65 mmol, 1.00 eq.). After removal of the solvent in vacuo the crude reaction mixture was purified via RP-HPLC (30-80% buffer B, 10 min, Waters) and after lyophilization the product SI-4 was obtained as a white solid (832 mg, 1.23 mmol, 75% over 2 steps).

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ = 7.26 (s, 5H), 6.99 – 6.84 (m, 1H), 6.44 (s, 2H), 6.10 (t, $J = 5.7$ Hz, 1H), 5.03 (d, $J = 7.2$ Hz, 1H), 4.99 (s, 2H), 4.87 (d, $J = 6.1$ Hz, 1H), 4.69 (q, $J = 5.9$ Hz, 1H), 3.91 (t, $J = 5.8$ Hz, 2H), 3.71 (s, 3H), 3.52 (t, $J = 5.8$ Hz, 2H), 3.34 (q, $J = 6.3$ Hz, 2H), 3.04 (q, $J = 6.7$ Hz, 2H), 2.22 (s, 6H), 2.14 – 2.05 (m, 2H), 1.89 (p, $J = 6.2$ Hz, 2H), 1.53 (p, $J = 7.6$ Hz, 2H), 1.38 (q, $J = 7.5$ Hz, 2H), 1.32 (s, 9H), 1.28 – 1.19 (m, 2H).

$^{13}$C($^1$H)-NMR (126 MHz, CDCl$_3$): $\delta$ = 173.9, 170.9, 170.8, 158.8, 156.7, 136.7, 136.6, 129.9, 128.6, 128.2, 128.2, 113.5, 80.3, 69.6, 66.7, 66.2, 53.8, 52.8, 42.2, 40.8, 37.6, 36.5, 29.6, 28.8, 28.4, 26.3, 25.3, 19.6.

RP-HPLC (5-95%, 8 min): $t_R = 6.05$ min.


HRMS (ESI) calc. for C$_{35}$H$_{51}$N$_4$O$_9$ $^+$ [M+H]$^+$: $m/z = 671.36560$; found: 671.36482; $\delta = 1.2$ ppm.
The Boc-protected amine **SI-4** (130 mg, 194 µmol, 1.00 eq.) was converted according to GP8 for 30 min and GP7 for 1 h with Boc-Gly-OH (40.7 mg, 233 µmol, 1.20 eq.). After removal of the solvent *in vacuo* the crude product was purified by RP-HPLC (20-60% buffer B, 10 min, Waters) and after lyophilization the product **SI-5** was obtained as a white solid (112 mg, 154 µmol, 79% over 2 steps).

**1H-NMR** (500 MHz, CDCl₃): \( \delta = 7.43 – 7.28 \) (m, 5H), 6.99 (d, \( J = 7.6 \) Hz, 1H), 6.86 (t, \( J = 5.8 \) Hz, 1H), 6.52 (s, 2H), 6.09 (s, 1H), 5.12 (t, \( J = 5.6 \) Hz, 1H), 5.07 (s, 2H), 4.95 (s, 1H), 4.86 (t, \( J = 6.2 \) Hz, 1H), 4.00 (t, \( J = 5.7 \) Hz, 2H), 3.84 – 3.80 (m, 1H), 3.79 (s, 3H), 3.76 – 3.68 (m, 2H), 3.71 – 3.67 (m, 1H), 3.45 (virt. q, \( J = 6.2 \) Hz, 2H), 3.17 – 3.03 (m, 2H), 2.29 (s, 6H), 2.20 (t, \( J = 7.5 \) Hz, 2H), 1.98 (p, \( J = 6.1 \) Hz, 2H), 1.67 – 1.56 (m, 2H), 1.52 – 1.44 (m, 2H), 1.41 (s, 9H), 1.41 – 1.26 (m, 2H).

**MS** (HESI): \( m/z = 728.22 \) [M+H]+, 1454.75 [2M+H]+.

**HRMS** (ESI) calc. for C₁₇₂H₅₈N₅O₁₀⁺ [M+H]+: \( m/z = 728.38707 \); found: 728.38644; \( \delta = 0.9 \) ppm.

The spectral data correspond to those given in the literature.

**3-(2,3-bis(tert-butoxycarbonyl)guanidino)benzoic acid (SI-6)**

According to the literature,⁶ \( N,N´-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine \) (5.19 g, 16.7 mmol, 1.00 eq.) and 3-aminobenzoic acid (2.40 g, 17.5 mmol, 1.05 eq.) were suspended in MeOH (67mL, 0.25 M) and triethylamine (6.96 mL, 5.06 g, 50.0 mmol, 3.00 eq.) was added. The mixture was heated at 40°C for 16 h and after reaction control, cooled down to room temperature. The solvent was removed *in vacuo* and after addition of ethyl acetate (150 mL) the crude product mixture was washed with HCl \( \text{aq.} \) (150 mL, 1 M) and brine (150 mL). The organic phase was dried over Na₂SO₄, filtrated and the solvent removed *in vacuo*. The product **SI-6** was isolated as a white solid (5.67 g, 14.9 mmol, 90%) and used for further reactions without additional purification.

**1H-NMR** (500 MHz, DMSO-d₆): \( \delta = 12.85 \) (bs, 1H), 11.35 (bs, 1H), 10.11 (bs, 1H), 8.00 (s, 1H), 7.87 – 7.75 (m, 1H), 7.71 (d, \( J = 7.7 \) Hz, 1H), 7.48 (t, \( J = 7.9 \) Hz, 1H), 1.45 (s, 18H).

**13C{1H}-NMR** (126 MHz, DMSO-d₆): \( \delta = 166.9, 158.5, 153.7, 151.1, 148.4, 131.4, 129.0, 127.2, 125.6, 123.5, 81.9, 79.0, 27.8.

**RP-HPLC** (5-95%, 5 min): \( t_R = 3.77 \) min.

**MS** (HESI) calc. for C₁₈₂H₁₀₀N₁₁O₁₂⁺ [M+H]+: \( m/z = 379.85 \) [M+H]+, 780.81 [2M+H]+.

**HRMS** (ESI) calc. for C₁₈₂H₁₀₀N₁₁O₁₂⁺ [M+H]+: \( m/z = 380.18216 \); found: 380.18155; \( \delta = 0.9 \) ppm.

The spectral data correspond to those given in the literature.⁶
• **Methyl (S)-2-(4-(3-((6-(((benzyloxy)carbonyl)amino)hexanamido)propoxy)-2,6-dimethyl benzamido)-3-(2-(3-(2,3-bis(tert-butoxycarbonyl)guanidino)benzamido)acetamido)propanoate (SI-7)**

![Chemical Structure of SI-7](image)

Chemical Formula: C_{50}H_{69}N_{8}O_{13}

Exact Mass: 988.49058

Molecular Weight: 989,13700

Compound SI-5 (480 mg, 659 µmol, 1.00 eq.) was Boc-deprotected according to GP11 and the crude product used as the amine for further coupling with compound SI-6 (300 mg, 791 µmol, 1.20 eq.) according to GP7. After removal of the solvent in vacuo the crude product was purified via RP-HPLC (20-80% buffer B, 10 min, Waters) and after lyophilization the product SI-7 was obtained as a white solid (428 mg, 435 µmol, 66% over 2 steps).

**RP-HPLC** (5-95%, 5 min): \( t_R = 3.93 \text{ min} \).

**MS** (HESI): \( m/z = 495.24 \ [M+2H]^{2+}, \ 989.23 \ [M+H]^{+} \).

**HRMS** (ESI) calc. for C_{50}H_{69}N_{8}O_{13}^{+} [M+H]: \( m/z = 989.49786; \) found: 989.49738; \( \delta = 0.5 \text{ ppm} \).

• **(S)-2-(4-(3-(6-aminohexanamido)propoxy)-2,6-dimethylbenzamido)-3-(2-(3-guanidinobenzamido)acetamido)propanoic acid (4)**

![Chemical Structure of 4](image)

Chemical Formula: C_{23}H_{44}N_{8}O_{7}

Exact Mass: 640,33330

Molecular Weight: 640,74200

Compound SI-7 (214 mg, 216 µmol, 1.00 eq.) was deprotected according to GP8 and GP6. The isolated crude product was further treated with a mixture of dioxane and aqueous solution of LiOH (1 M, 1:1, 3 mL each). After full consumption of the starting material, the solution was neutralized with an aqueous solution of HCl (1 M) and the solvents removed in vacuo. The crude product was purified via semi-preparative RP-HPLC (05-50% buffer B, 10 min, Waters) and compound 4 (85 mg, 132 µmol, 61% over 3 steps) was isolated as a white solid after lyophilization.

**\(^1\)H-NMR** (400 MHz, DMSO-d\(_6\)): \( \delta = 10.07 \ (s, \ 1H), \ 8.81 \ (\text{virt. t, } J = 5.9 \text{ Hz, } 1H), \ 8.36 \ (d, \ J = 7.7 \text{ Hz, } 1H), \ 8.03 \ (\text{virt. t, } J = 5.9 \text{ Hz, } 1H), \ 7.88 \ (\text{virt. t, } J = 5.6 \text{ Hz, } 1H), \ 7.77 \ (\text{virt. dt, } J = 7.9, \ 1.3 \text{ Hz, } 1H), \ 7.76 - 7.58 \ (m, \ 7H), \ 7.54 \ (\text{virt. t, } J = 7.9 \text{ Hz, } 1H), \ 7.39 \ (\text{ddd, } J = 7.9, \ 2.2, \ 1.0 \text{ Hz, } 1H), \ 6.58 \ (s, \ 2H), \ 4.56 - 4.44 \ (m, \ 1H), \ 3.99 - 3.86 \ (m, \ 3H), \ 3.82 \ (\text{dd, } J = 16.3, \ 5.8 \text{ Hz, } 1H), \ 3.62 - 3.35 \ (m, \ 2H), \ 3.24 - 3.09 \ (m, \ 2H), \ 2.83 - 2.68 \ (m, \ 2H), \ 2.21 \ (s, \ 6H), \ 2.06 \ (\text{virt. t, } J = 7.4 \text{ Hz, } 2H), \ 1.87 - 1.72 \ (m, \ 2H), \ 1.57 - 1.42 \ (m, \ 4H), \ 1.33 - 1.19 \ (m, \ 2H). \)**
\[ ^{13}C\{^1H\}-NMR \) (126 MHz, DMSO-\( d_6 \)): \( \delta = 172.0, 171.8, 169.4, 169.3, 165.8, 158.5 \) (q, \( J = 32.3 \) Hz, TFA), 158.1, 155.9, 136.0, 135.7, 135.5, 130.8, 129.8, 127.4, 125.2, 123.4, 116.9 (q, \( J = 297.9 \) Hz, TFA), 113.0, 65.2, 52.1, 42.6, 39.6, 38.8, 35.5, 35.2, 29.0, 26.9, 25.6, 24.8, 19.2.

\[ ^{13}C\{^1H\}-NMR \) (400 MHz, DMSO-\( d_6 \)): \( \delta \) \([ppm]\) = 165.9, 153.2, 151.3, 143.6, 137.9, 134.0, 133.1, 127.9, 122.9, 122.6, 93.3, 86.5.

\[ ^{11}B\{^1H\} \) NMR (128 MHz, DMSO-\( d_6 \)): \( \delta \) \([ppm]\) = -1.18.

\[ ^{19}F\{^1H\} \) NMR (376 MHz, DMSO-\( d_6 \)): \( \delta \) \([ppm]\) = -147.8.

HRMS (ESI) calcld. for \( C_{84}H_{44}N_8O_8Pd_2 \) [M-4(BF\(_4\)]^{4+} \): \( m/z = 377.5426 \); found: 377.5406; \( \delta = 5.3 \) ppm.

The spectral data correspond to those given in the literature.\(^4\)

5. Cage formation and analysis (C0, C1-C4)

![Scheme S3. Synthesis of cage C0, C1-C4 via metal-mediated self-assembly.](image)

\( ^1H \) NMR (400 MHz, DMSO-\( d_6 \)): \( \delta \) \([ppm]\) = 9.60 (s, 2H, \( H_a \)), 9.40 (d, \( J = 5.8 \) Hz, 2H, \( H_b \)), 8.35 (d, \( J = 8.8 \) Hz, 2H, \( H_c \)), 8.20 (s, 2H, \( H_d \)), 8.15 (s, 1H, \( H_e \)), 7.85 (dd, \( J = 6.1, 8.2 \) Hz, 2H, \( H_f \)).

HRMS (ESI) calcld. for \( C_{31}H_{45}N_8O_7 \) [M+2H]^{2+} \): \( m/z = 641.34057 \); found: 641.34046; \( \delta = 0.2 \) ppm.

6. Integrin binding studies

\( \alpha_v\beta_3 \)

(1) 1.0 \( \mu g/mL \) human vitronectin; Merck Millipore.

(2) 2.0 \( \mu g/mL \), human \( \alpha_v\beta_3 \)-integrin, R&D.

(3) 2.0 \( \mu g/mL \), mouse anti-human CD51/61, BD Biosciences.

(4) 2.0 \( \mu g/mL \), anti-mouse IgG-POD, Sigma-Aldrich.

\( \alpha_v\beta_5 \)

(1) 5.0 \( \mu g/mL \), human vitronectin, Merck Millipore.

(2) 3.0 \( \mu g/mL \), human \( \alpha_v\beta_5 \)-integrin, R&D.
(3) 1:500 dilution, anti-αv mouse anti-human MAB1978, Merck Millipore.
(4) 2.0 μg/mL, anti-mouse IgG-POD, Sigma-Aldrich.

αvβ6
(1) 0.4 μg/mL; LAP (TGF-β), R&D.
(2) 0.5 μg/mL, human αvβ6-integrin, R&D.
(3) 1:500 dilution, anti-αv mouse anti-human MAB1978, Merck Millipore.
(4) 2.0 μg/mL, anti-mouse IgG-POD, Sigma-Aldrich.

α5β1
(1) 0.5 μg/mL; human fibronectin, Sigma-Aldrich.
(2) 2.0 μg/mL, human α5β1-integrin, R&D.
(3) 1.0 μg/mL, mouse anti-human CD49e, BD Biosciences.
(4) 2.0 μg/mL, anti-mouse IgG-POD, Sigma-Aldrich.
7. NMR Spectroscopy

Figure S1. $^1$H NMR (400 MHz, DMSO-$d_6$, 298K) of Benzyl 3,5-bis(pyridin-3-ylethynyl)benzoate SI-1.

Figure S2. $^{13}$C($^1$H) NMR (400 MHz, DMSO-$d_6$, 298K) of Benzyl 3,5-bis(pyridin-3-ylethynyl)benzoate SI-1.
Figure S3. DEPT135-$^{13}$C NMR (400 MHz, DMSO-$d_6$, 298K) of Benzyl 3,5-bis(pyridin-3-yloethynyl)benzoate SI-1.

Figure S4. HSQC NMR (400 MHz, DMSO-$d_6$, 298K) of Benzyl 3,5-bis(pyridin-3-yloethynyl)benzoate SI-1.
Figure S5. $^1$H NMR (400 MHz, DMSO-$d_6$, 298K) of ligand L0.

Figure S6. $^{13}$C($^1$H) NMR (400 MHz, DMSO-$d_6$, 298K) of ligand L0.
Figure S7. $^1$H NMR (400 MHz, DMSO-$d_6$, 298K) of cage C0 (bottom) and related zoom (top).
Figure S8. $^{13}$C($^1$H) NMR (400 MHz, DMSO-$d_6$, 298K) of cage C0.

Figure S9. High-resolution MS spectrum of cage C0 in H$_2$O with 0.1% Formic Acid.
Figure S10. $^1$H NMR (500 MHz, DMSO-d$_6$) spectrum of ligand L1.

Figure S11. $^{13}$C($^1$H) NMR (126 MHz, DMSO-d$_6$) spectrum of ligand L1.
Figure S12. $^{1}$H NMR (400 MHz, DMSO-$d_{6}$) spectrum of cage C1.

Figure S13. $^{1}$H NMR (500 MHz, DMSO-$d_{6}$) spectrum of ligand L2.
Figure S14. $^{13}$C($^1$H) NMR (126 MHz, DMSO-d$_6$) spectrum of ligand L2.

Figure S15. $^1$H NMR (500 MHz, DMSO-d$_6$) spectrum of cage C2.
Figure S16. $^1$H NMR (500 MHz, DMSO-d$_6$) spectrum of ligand L3.

Figure S17. $^{13}$C($^1$H) NMR (126 MHz, DMSO-d$_6$) spectrum of ligand L3.
Figure S18. $^1$H NMR (500 MHz, DMSO-$d_6$) spectrum of cage C3.

Figure S19. $^1$H NMR (500 MHz, DMSO-$d_6$) spectrum of ligand L4.
Figure S20. $^{13}$C($^1$H) NMR (126 MHz, DMSO-d$_6$) spectrum of ligand L4.

Figure S21. $^1$H NMR (500 MHz, DMSO-d$_6$) spectrum of cage C4.
Figure S22. Stacked aromatic region $^1$H NMR (DMF-d$_7$) showing: Top: Free ligand. Middle: Pd$_2$L$_4$ metallacage formation. Bottom: Pd$_2$L$_4$ metallacage encapsulating two equivalents of cisplatin. Box A: Magnified region showing the downfield shift of peaks H$_a$ and H$_b$ upon cisplatin encapsulation. Box B: Peak upfield shift of peak H$_e$. 
Figure S23. $^1$H-DOSY-NMR of Cisplatin in DMF-d$_7$.

Figure S24. $^1$H-DOSY-NMR of C0-Bz in DMF-d$_7$. 
**Figure S25.** $^1$H-DOSY-NMR of 1.00 eq. C0-Bz and 1.00 eq. Cisplatin in DMF-$d_7$.

**Figure S26.** $^1$H-DOSY-NMR of 1.00 eq. C0-Bz and 2.00 eq. cisplatin in DMF-$d_7$. 
Figure S27. $^1$H-DOSY-NMR of 1.00 eq. C0-Bz and 3.00 eq. cisplatin in DMF-d$_7$.

Figure S28. $^{195}$NMR of (top) cisplatin and (bottom) 1.00 eq. C0-Bz and 2.00 eq. cisplatin in DMF-d$_7$.

8. References
