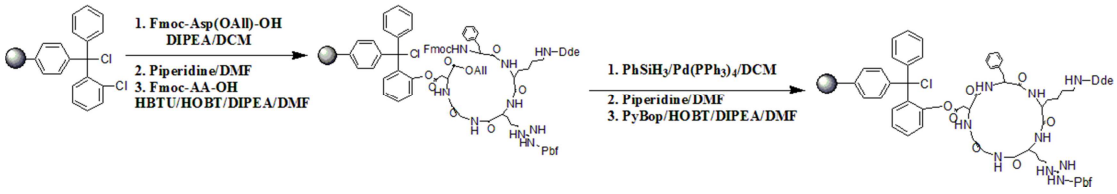
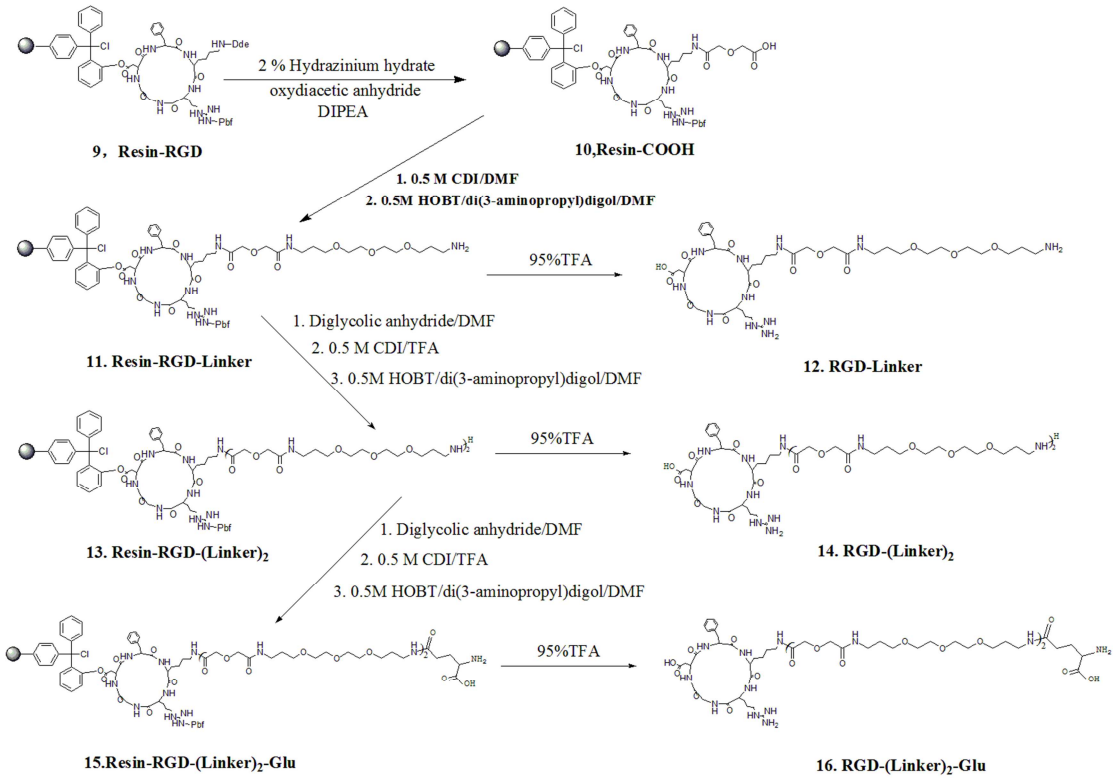
Supporting information

1. Synthesis of cRGD, cRGD-Linker, cRGD-$(Linker)_2$ and cRGD-$(Linker)_2$-Glu



Scheme S1. Synthetic procedure of the resin-bonded cyclized cRGDfK peptide



Scheme S2. Synthetic procedure of cRGD, cRGD-Linker, cRGD-$(Linker)_2$ and cRGD-$(Linker)_2$-Glu

1.1. Materials

Diglycolic anhydride, diisopropylethylamine (DIPEA) and benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) were

purchased from Heowns (Tianjin, China). Fmoc-Asp(OAll)-OH, Fmoc-Gly-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Lys(Dde)-OH, Fmoc-Dphe-OH, 1-hydroxybenzotriazole anhydrous (HOBT) and 2-(1H-benzotriazol-1-YL)-1.1.3,3-tetramethyluronium hexafluorophosphate (HBTU) were purchased from GL Biochem Ltd. (Shanghai, China).

1.2. Synthetic procedure of the resin-bonded cyclized cRGDfK peptide

Assembly of fully protected peptides was carried out manually in a sealed tube using a solid phase strategy. The syntheses were carried out on 2-chlorotrityl chloride resin (loading, 0.5 mmol/g). The resins were swollen in dichloromethane for 1 h prior to synthesis. Fmoc-Asp(OAll)-OH (1.0 g, 1.0 mmol) and DIPEA (680 μL, 4.0 mmol) were dissolved in 10 mL DMF and added to the resin. The mixture was agitated for 5 h in the sealed tube. Afterward, the sealing agent ($V_{CH_2Cl_2} : V_{MEOH} : V_{DIPEA} = 17:1:2$) was used for sealing the unreacted chlorine group. The Fmoc protecting group was removed by treatment with 20% piperidine in DMF for 30 min. Coupling reactions of four amino acids (Fmoc-Gly-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Lys(Dde)-OH and Fmoc-D-Phe-OH) were performed using 1.5 equiv of a Fmoc-protected derivative activated in situ with HBTU (2.0 equiv), HOBt (1.5 equiv), and DIPEA (4 equiv) in DMF for 5 h. Every step included three washes with DMF. Before the final Fmoc deprotection, selective α-carboxyl deprotection of the Asp residue from the allyl group was carried out by treatment of the peptidyl resin with $PhSiH_3$ (24 equiv) and $Pd(PPh_3)_4$ (0.25 equiv) in dichloromethane for 1.5 h. The cyclisation between α-NH of D-Phe and α-CO of Asp was performed with PyBOP (1.5 equiv)/HOBt (1.5 equiv)/

DIPEA (2 equiv) in DMF overnight.

1.3．Synthesis of cRGD

The protected, resin-bonded cRGD peptide (1.0 g, 0.5 mmol) was deprotected in 2% hydrazine hydrate and then washed with DMF and dichloromethane before being dried under vacuum. Cleavage and deprotection were performed by treatment of the dried resin with 500 μL of the cleavage solution (TFA/Tris/water = 95:2.5:2.5) for 1 h at room temperature. The product was precipitated and washed three times with anhydrous ether (1.5 mL) and dried at room temperature to produce cRGD (0.16 g, 52%). HRMS-ESI: m/z calculated for $C_{27}H_{41}N_9O_7$ $[M+H]^+$ 604.3202, found 604.3202.

1.4．Synthesis of cRGD-Linker

The Dde deprotected, resin-bonded cRGD peptide (1.0 g, 0.5 mmol) was reacted with diglycolic anhydride (116.1 mg, 1.0 mmol) in 5 mL DMF for 5 h to yield resin-COOH. Then, resin-COOH was activated twice by 0.5 M CDI for 1 h. The activated resin-COOH, 0.5 M HOBt, and di(3-aminopropyl)digol (1.1 g, 5 mmol) were agitated for 5 h and washed with DMF and dichloromethane before being dried under vacuum. Cleavage and deprotection were performed by treatment of the dried resin with 500 μL of the cleavage solution (TFA/Tris/water = 95:2.5:2.5) for 1 h at room temperature. The product was precipitated and washed three times with anhydrous ether (1.5 mL) and dried at room temperature to produce RGD-Linker (0.18 g, 39%). HRMS (ESI): m/z calculated for m/z $C_{41}H_{67}N_{11}O_{13}$ $[M + H]^+$ 922.4993, found 922.4987.

1.5. Synthesis of RGD-$(Linker)_2$

The Fmoc group of the resin-RGD-Linker (1.0 g, 0.5 mmol) was deprotected in 20% Piperidine. Then, diglycolic anhydride (116.1 mg, 1 mmol) dissolved in 5 mL DMF was added to the resin. The mixture was agitated for 5 h to yield resin-COOH after washing with DMF and dichloromethane. Then, resin-COOH was activated twice by 0.5 M CDI for 1 h. The activated resin-COOH, 0.5 M HOBt, and di(3-aminopropyl)digol (1.1 g, 5 mmol) were agitated for 5 h and washed with DMF and dichloromethane before being dried under vacuum. Cleavage and deprotection were performed by treatment of the dried resin with 500 μL of the cleavage solution (TFA/Tris/water = 95:2.5:2.5) for 1 h at room temperature. The product was precipitated, washed three times with anhydrous ether (1.5 mL) and dried at room temperature to produce RGD-$(Linker)_2$ (0.18 g, 30%). HRMS (ESI): m/z calculated for $C_{55}H_{93}N_{13}O_{19}$ $[M + H]^+$ 1240.6783, found 1240.6788, $[M + Na]^+$ 1262.6603, found 1262.6603.

1.6. Synthesis of RGD-$(Linker)_2$-Glu

The Fmoc group of resin-RGD-$(Linker)_2$ (1.0 g, 0.5 mmol.) was deprotected in 20% Piperidine. Fmoc-Glu(OtBu)-OH (0.32 g, 0.75 mmol), HBTU (0.38 g, 0.1 mmol), HOBt (0.1 g, 0.75 mmol) and DIPEA (0.26 g, 2 mmol) dissolved in 5 mL DMF were added to the resin. The mixture was agitated for 5 h to yield resin-RGD-$(Linker)_2$-Glu after being washed with DMF and dichloromethane, followed by drying under vacuum. Cleavage and deprotection were performed by treatment of the dried resin with 500 μL of the cleavage solution (TFA/Tris/water = 95:2.5:2.5) for 1 h at room temperature. The product was precipitated and washed three times with anhydrous ether (1.5 mL) and dried at room temperature to produce RGD-$(Linker)_2$-Glu (0.15 g,

22%). HRMS (ESI): m/z calculated for m/z $C_{60}H_{100}N_{14}O_{22}$ $[M + H]^+$ 1369.7209, found 1369.7180.

2. HPLC analysis

HPLC analysis was performed using a C-18 column (150 × 4.6 mm) with a 0.6 mL/min flow rate and checked at λ = 668 nm. The column was initially held at 20% CH_3CN (1.4‰ TFA) - 80% H_2O (1.4‰ TFA). The concentration of CH_3CN was ramped to 40% in 10 min and then to 100% in 20 min. This concentration was maintained for 5 min and returned to 20% over 30 min; this concentration was maintained 10 min. Before the first injection, the column was washed with 100% CH_3CN for 30 min and allowed to equilibrate to the initial mobile phase conditions for 30 min before the next injection.

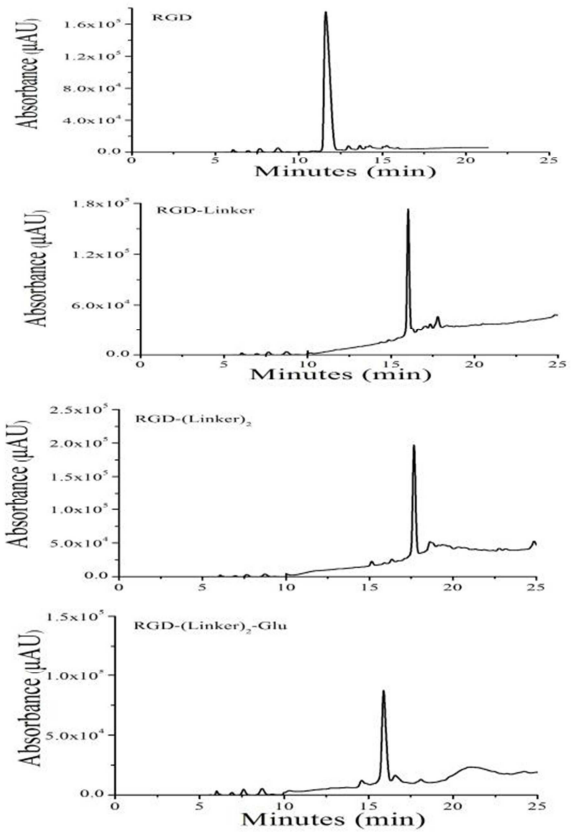


Fig. S1. HPLC analysis of cRGD, cRGD-Linker, cRGD-$(Linker)_2$ and cRGD-$(Linker)_2$-Glu. Wavelength for detection: 220 nm. cRGD (t_R = 11.6 min), cRGD-Linker (t_R = 16.0 min), cRGD-$(Linker)_2$ (t_R = 17.7 min), cRGD-$(Linker)_2$-Glu (t_R = 16.0 min).

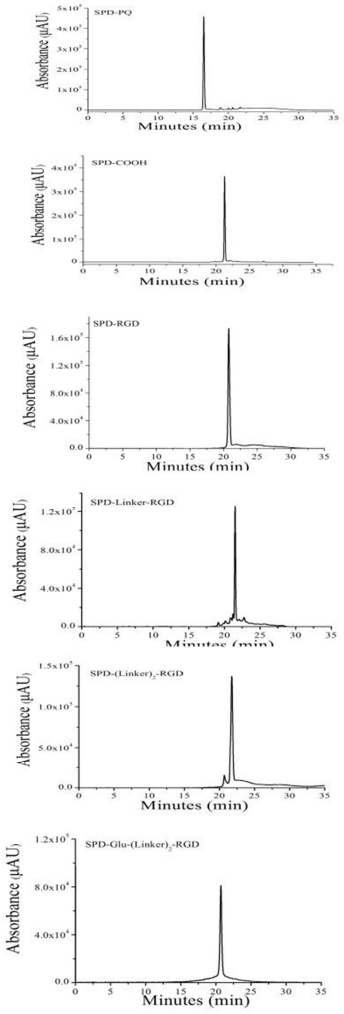


Fig. S1. HPLC analysis of SiPc-PQ **2**, SiPc-COOH **3**, RGD-SiPc **4**, RGD-Linker-SiPc **5**, RGD-$(Linker)_2$-SiPc **6** and RGD-$(Linker)_2$-Glu-SiPc **7**. Wavelength for detection: 668 nm. SiPc-PQ **2** (t_R = 16.5 min), SiPc-COOH **3** (t_R = 21.3 min), RGD-SiPc **4** (t_R = 20.8 min), RGD-Linker-SiPc **5** (t_R = 21.5 min), RGD-$(Linker)_2$-SiPc **5** (t_R = 21.8 min) and RGD-$(Linker)_2$-Glu-SiPc **7** (t_R = 20.7 min).

3. Absorbance spectra in DMSO

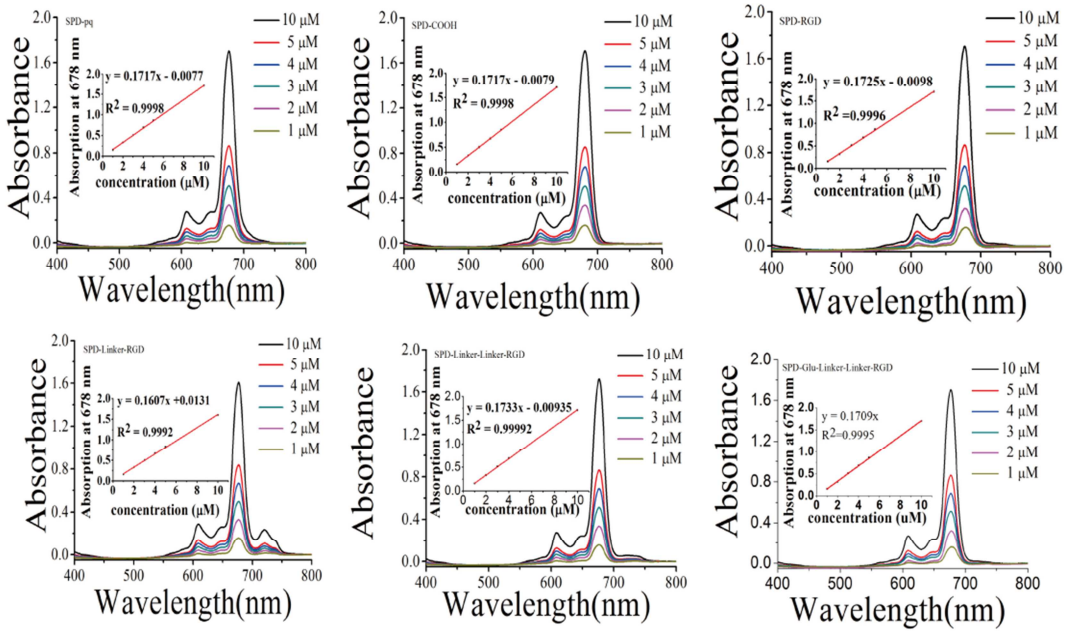


Fig. S3. Absorbance spectra of SiPc-PQ **2**, SiPc-COOH **3**, RGD-SiPc **4**, RGD-Linker-SiPc **5**, RGD-(Linker)$_2$-SiPc **6** and RGD-(Linker)$_2$-Glu-SiPc **7** at various concentrations in DMSO. The insets show plots of the intensity at 678 nm versus the concentration of the corresponding compounds.

4. The Absorbance spectra of singlet oxygen determination in DMSO

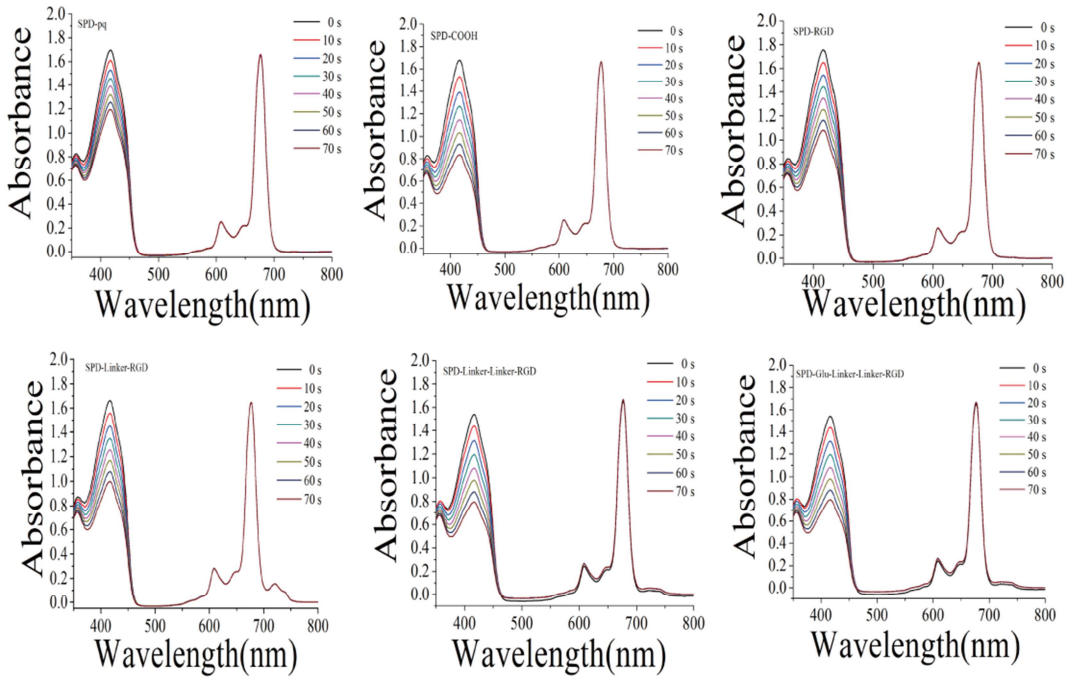


Fig. S4. Typical spectra for determination of the singlet oxygen quantum yield of SiPc-PQ **2**, SiPc-COOH **3**, RGD-SiPc **4**, RGD-Linker-SiPc **5**, RGD-$(Linker)_2$-SiPc **6** and RGD-$(Linker)_2$-Glu-SiPc **7** in DMSO using DPBF as a singlet oxygen quencher. DPBF concentration = 2×10^{-5} M.

5. Absorption, excitation, and emission spectra in DMSO

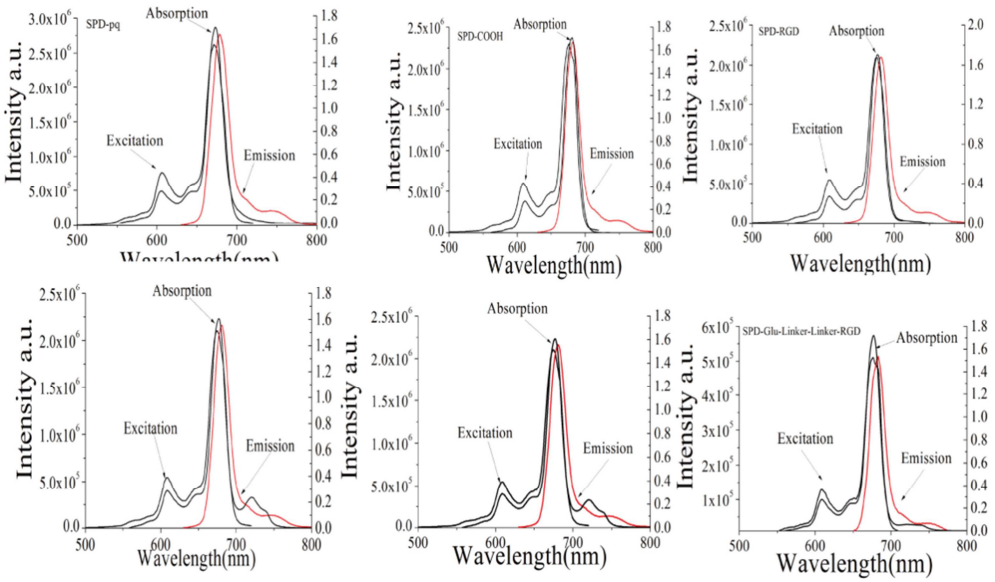


Fig. S5. Absorption, excitation, and emission spectra of SiPc-PQ **2**, SiPc-COOH **3**, RGD-SiPc **4**, RGD-Linker-SiPc **5**, RGD-$(Linker)_2$-SiPc **6** and RGD-$(Linker)_2$-Glu-SiPc **7** in DMSO. The concentration for absorption determination was 10 μM, and the concentration for fluorescence determination was 2 μM. The fluorescence emission spectra were recorded in the wavelength range of 600–900 nm upon excitation at 671 nm, and the fluorescence excitation spectra were recorded in the wavelength range of 500–900 nm upon emission at 678 nm.

6. Fluorescence spectra in DMSO

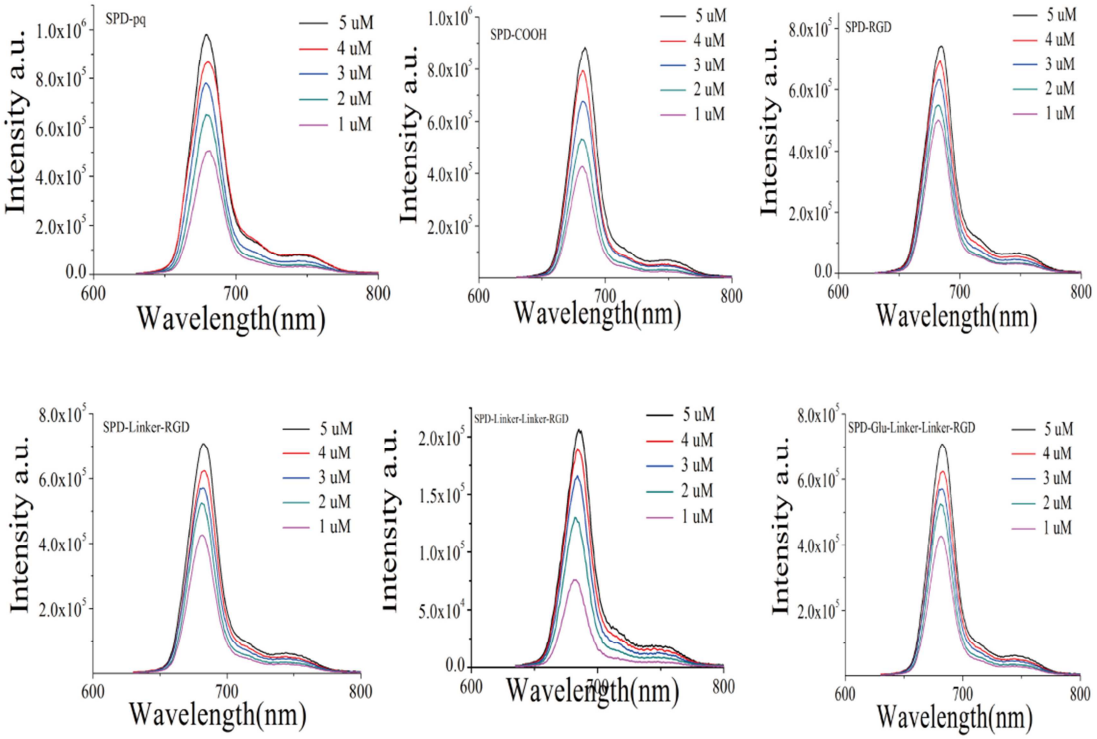


Fig. S6. Fluorescence emission spectra of SiPc-PQ **2**, SiPc-COOH **3**, RGD-SiPc **4**, RGD-Linker-SiPc **5**, RGD-$(Linker)_2$-SiPc **6** and RGD-$(Linker)_2$-Glu-SiPc **7** at various concentrations in DMSO.

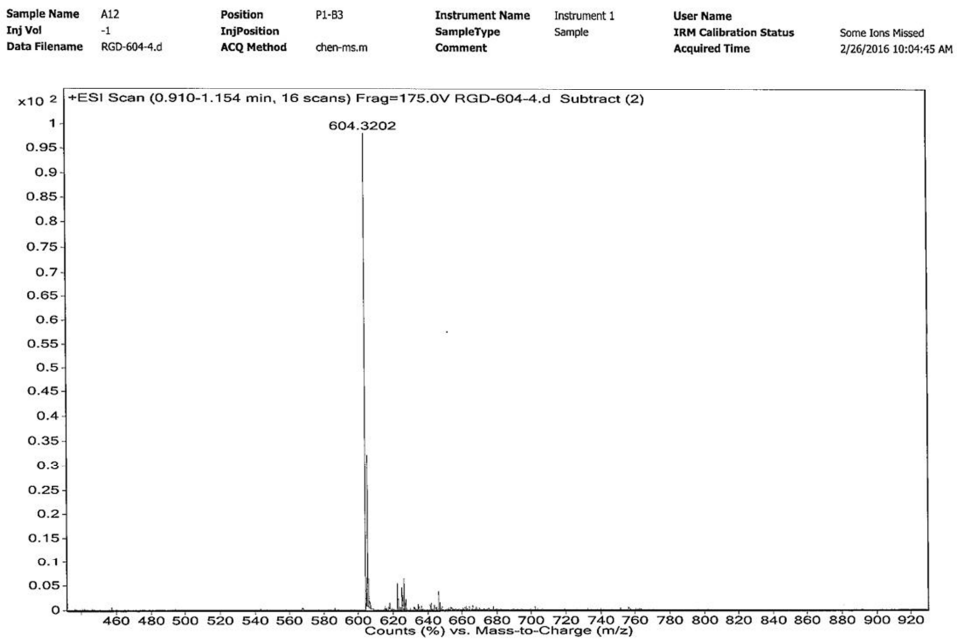


Fig. S7. Mass spectrometry analysis of of cRGD (HRMS-ESI: m/z $C_{27}H_{41}N_9O_7$ $[M+H]^+$ 604.3202, found 604.3202.)

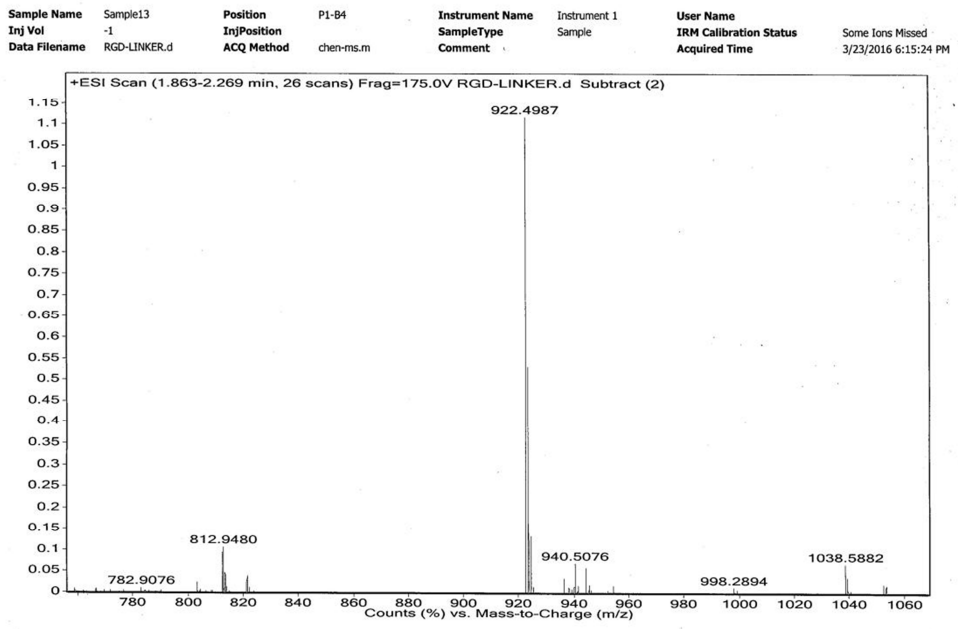


Fig. S8. Mass spectrometry analysis of cRGD-Linker (HRMS-ESI: m/z calcd for m/z $C_{41}H_{67}N_{11}O_{13}$ $[M + H]^+$ 922.4993, found 922.4987).

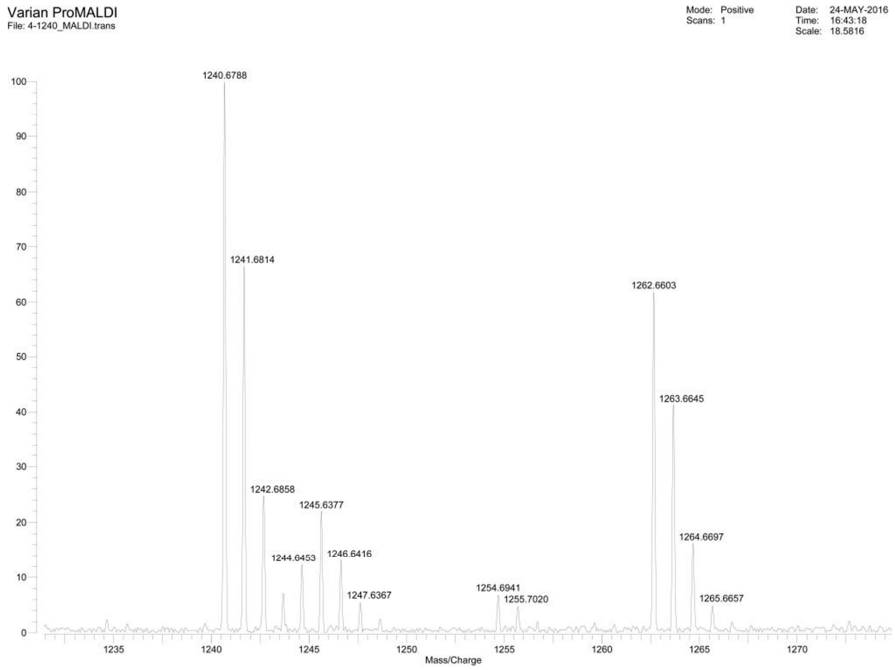


Fig. S9. Mass spectrometry analysis of RGD-(Linker)$_2$ (HRMS-ESI: m/z calcd for m/z $C_{55}H_{93}N_{13}O_{19}$ $[M+H]^+$ 1240.6783, found 1240.6788, calcd for $C_{55}H_{93}N_{13}O_{19}Zn^+$ $[M+Na]^+$1262.6603, found: 1262.6603).

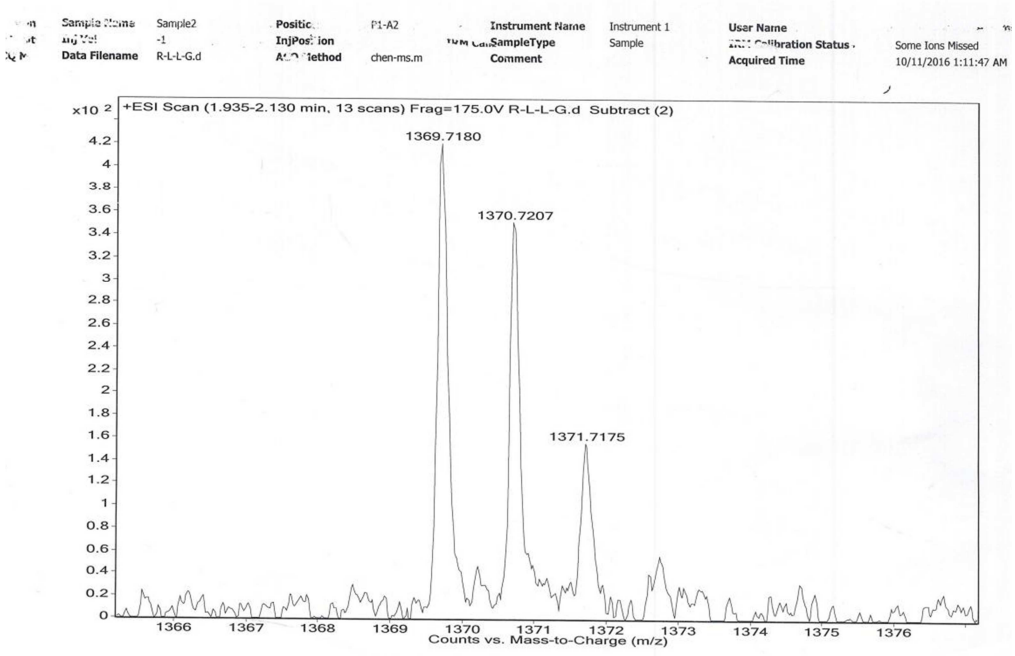


Fig. S10. Mass spectrometry analysis of RGD-(Linker)$_2$-Glu (HRMS-ESI: m/z calcd for m/z $C_{60}H_{100}N_{14}O_{22}$ $[M+H]^+$ 1369.7209, found 1369.7180).

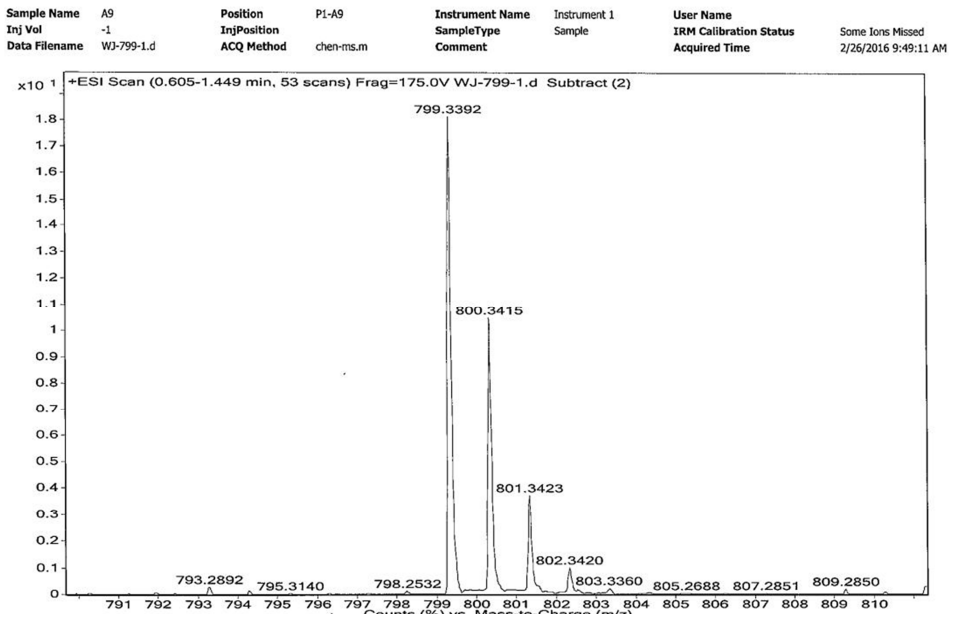


Fig. S11. Mass spectrometry analysis of SiPc-PQ **2** (HRMS-ESI: m/z calcd for m/z $C_{44}H_{42}N_{12}O_2Si$ $[M+H]^+$ 799.3396, found 799.3392).

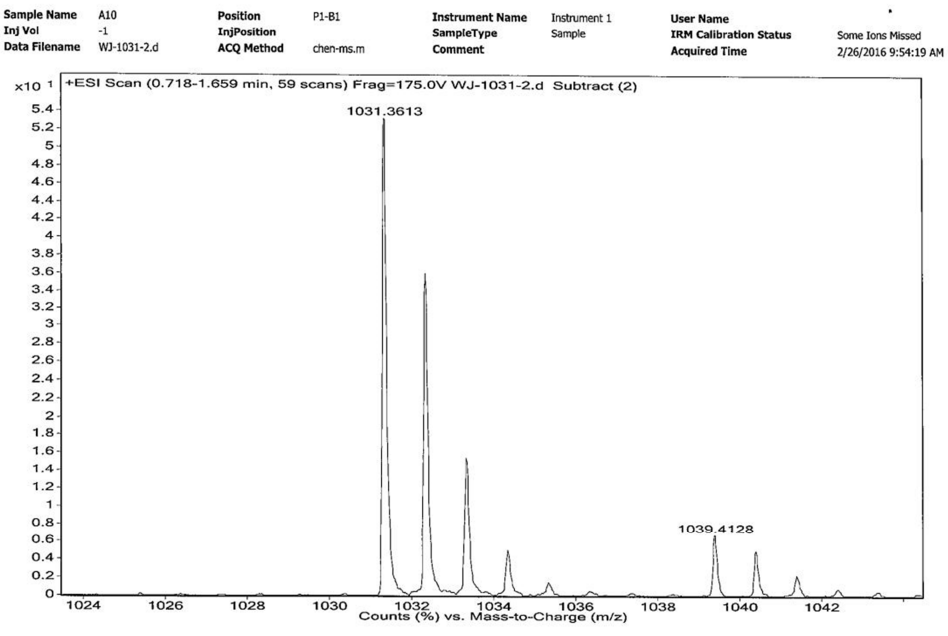


Fig. S12. Mass spectrometry analysis of SiPc-COOH **3** (HRMS-ESI: m/z calcd for m/z $C_{52}H_{50}N_{12}O_{10}Si$ $[M+H]^+$ 1031.3615, found 1031.3613).

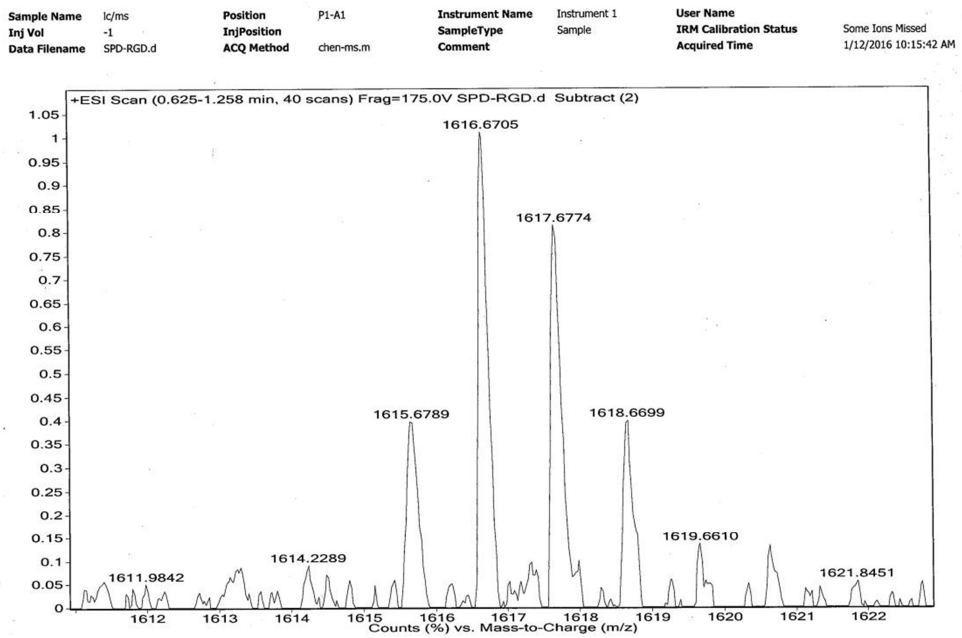


Fig. S13. Mass spectrometry analysis of RGD-SiPc **4** (HRMS-ESI: m/z calcd for m/z $C_{79}H_{89}N_{21}O_{16}Si$ $[M+H]^+$ 1616.6638, found 1616.6705).

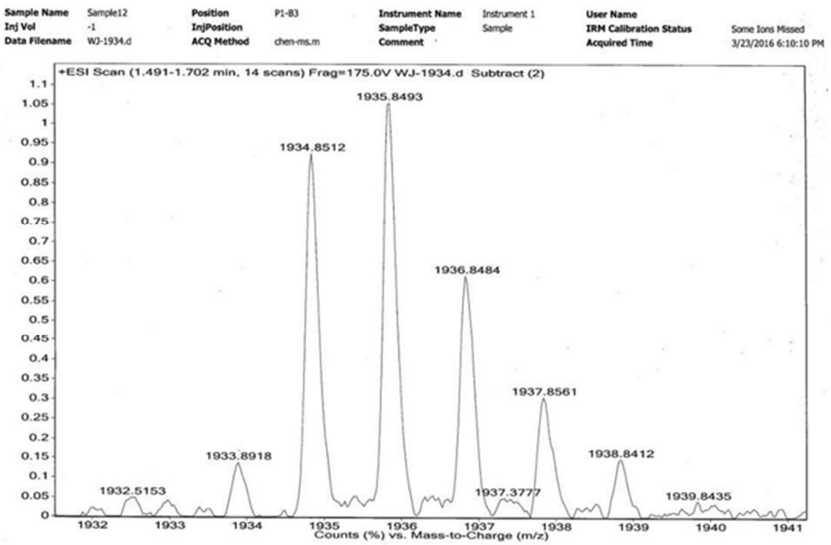


Fig. S14. Mass spectrometry analysis of RGD-Linker-SiPc **5** (HRMS (ESI): m/z calcd for $C_{93}H_{116}N_{23}O_{22}Si$ $[M + H]^+$ 1934.8429, found 1934.8512).