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Electronic Supporting Information (ESI)

Molecular design of peptide amphiphiles for controlled self-assembly and drug release

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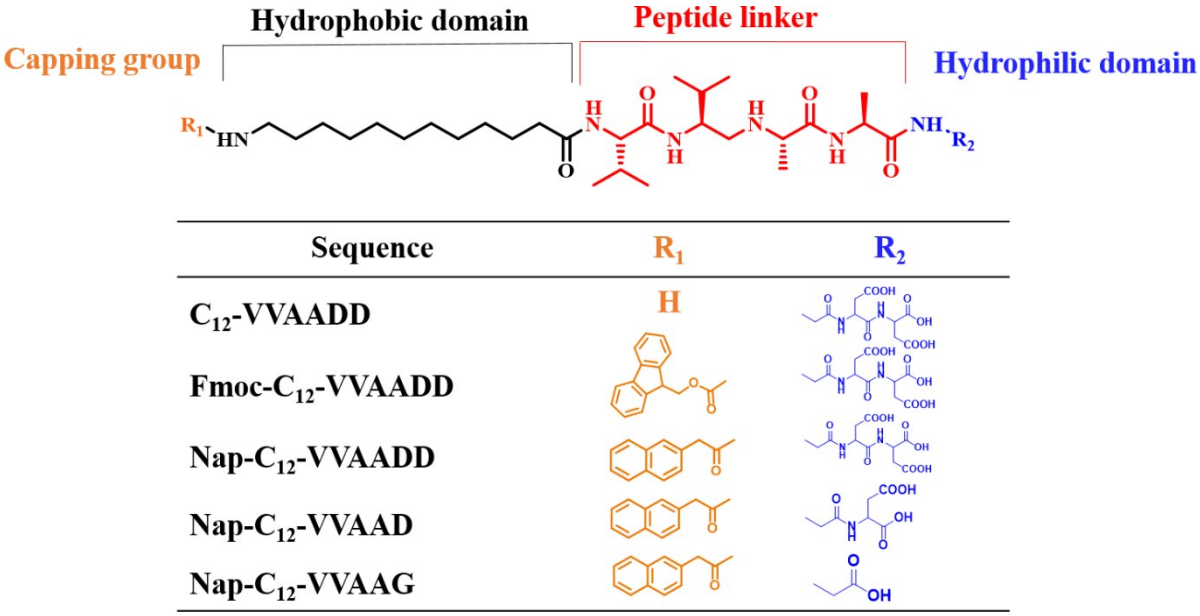


Scheme S1. Chemical structures of peptide amphiphiles (PAs) with different capping groups and hydrophilic domains.

Table S1. Values of MGC and CAC of PA molecules with varying capping groups

Sequence	MGC (%)	CAC (μM)
C_{12}-VVAADD	2.8	378.4
Fmoc-C_{12}-VVAADD	2.2	131.7
Nap-C_{12}-VVAADD	2.0	107.3

Note: MGC: minimal gelation concentration; CAC: critical aggregation concentration.

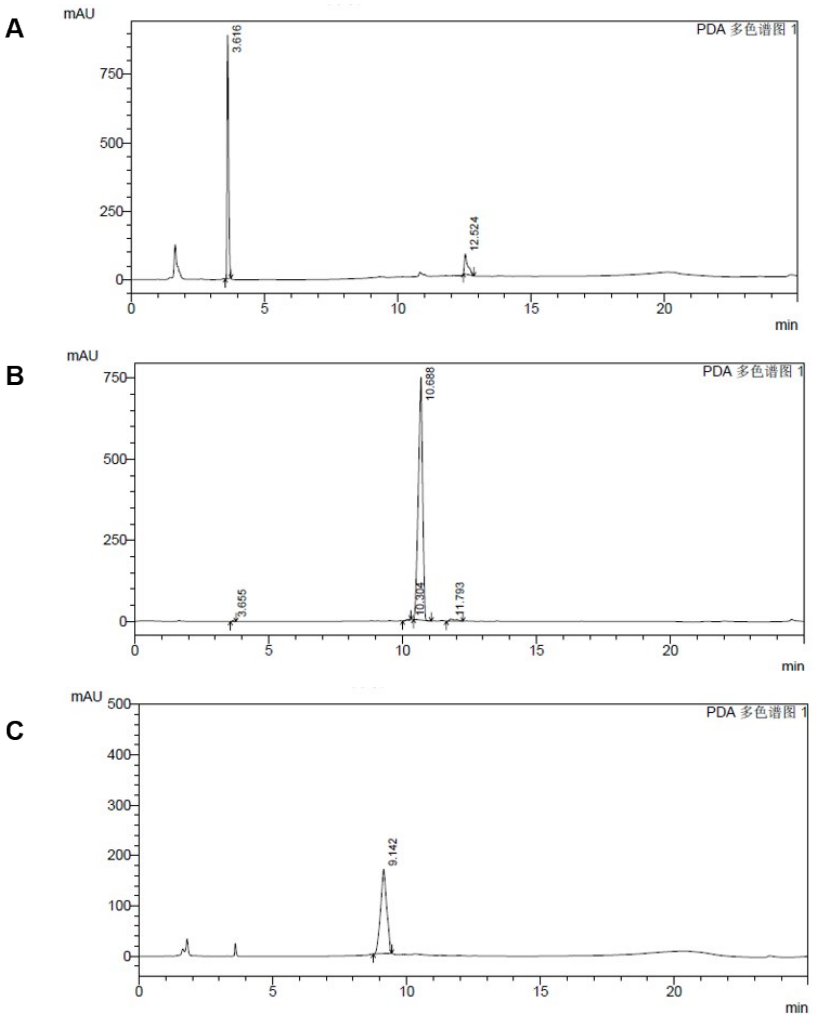


Fig. S1. HPLC elution curves of C_{12}-VVAADD (A), Fmoc-C_{12}-VVAADD (B), and Nap-C_{12}-VVAADD (C). Purity > 90%.

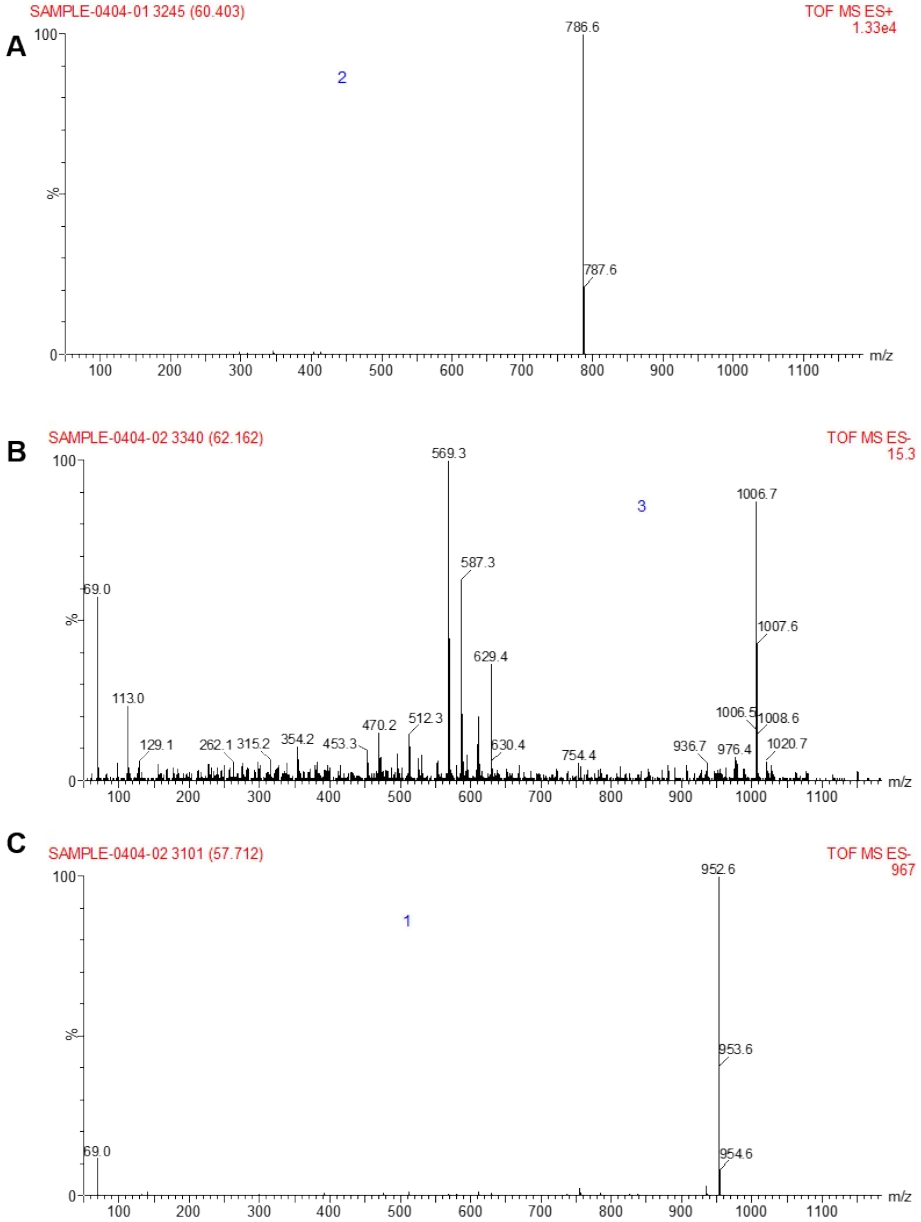
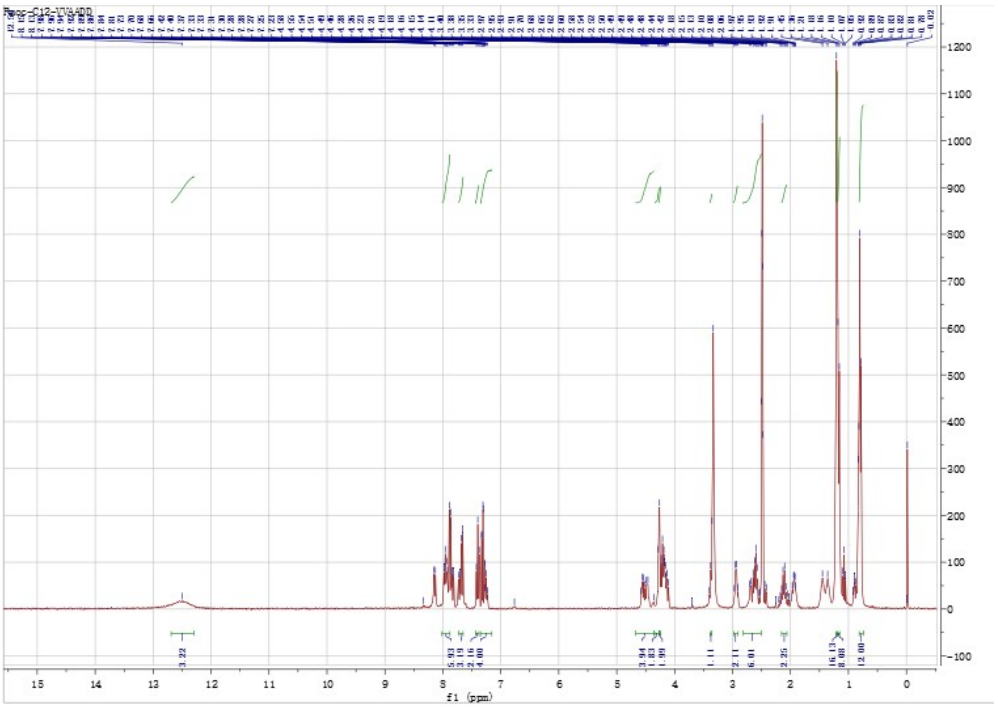


Fig. S2. TOF-MS spectra of C_{12}-VVAADD (A), Fmoc-C_{12}-VVAADD (B), and Nap-C_{12}-VVAADD (C). C_{12}-VVAADD: Calc. MW = 785, obsvd. $[M+H]^+$ = 786.6; Fmoc-C_{12}-VVAADD: Calc. MW = 1007, obsvd. $[M-H]^-$ = 1006.7; Nap-C_{12}-VVAADD: Calc. MW = 953, obsvd. $[M-H]^-$ = 952.6.

A



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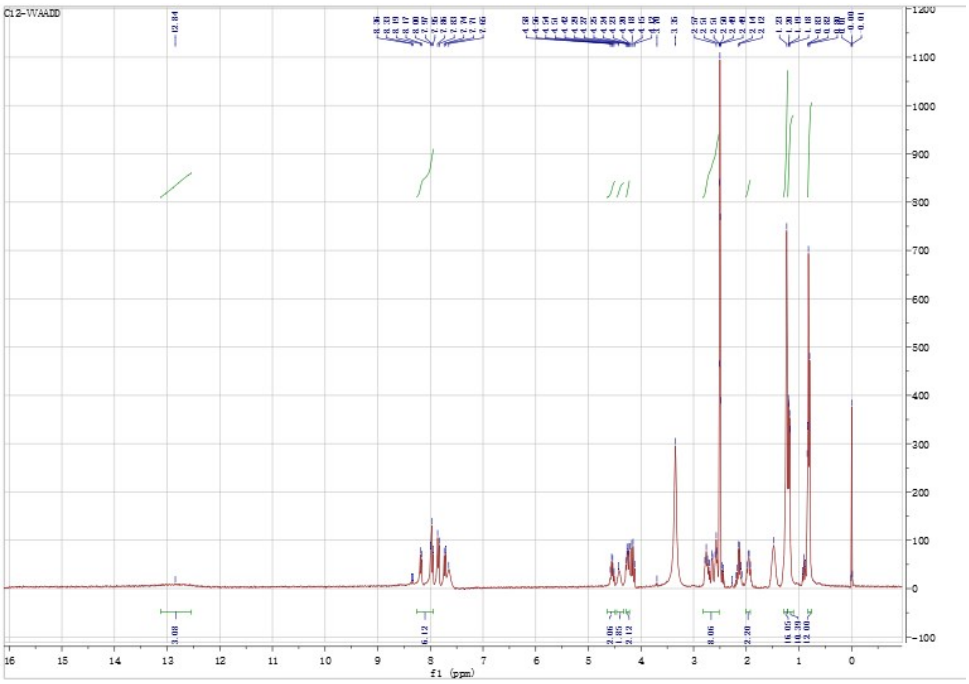

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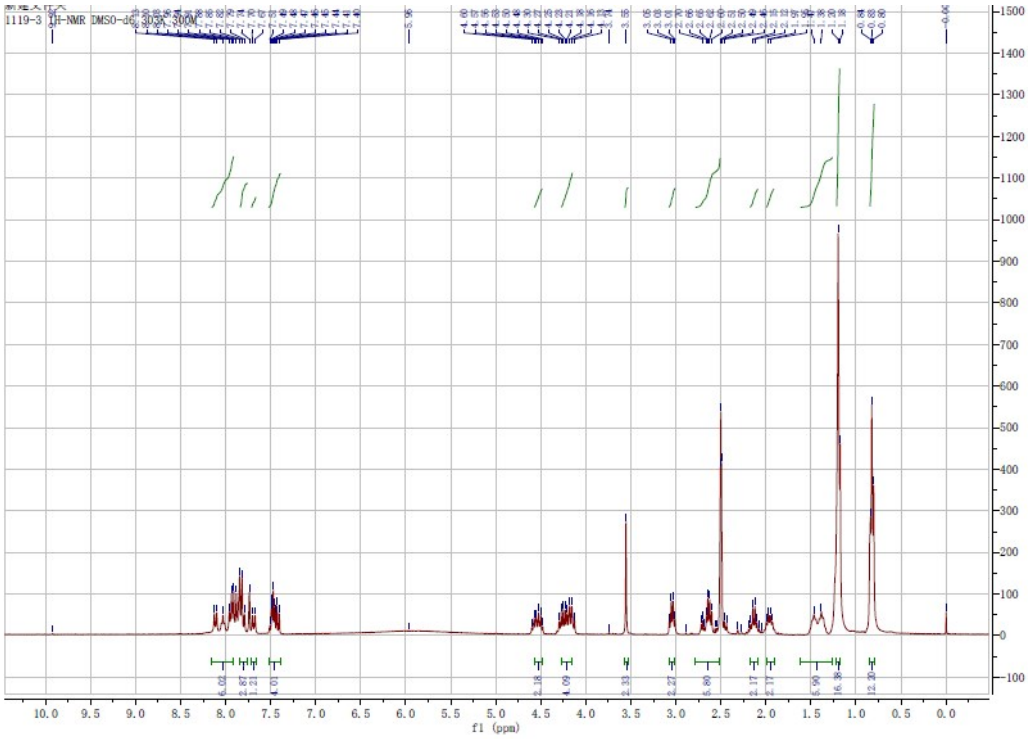


Fig. S3. (A) ^{1}H NMR spectrum of C_{12}-VVAADD (300 MHz, DMSO).

^{1}H NMR (300 MHz, DMSO) δ 12.84 (s, 3 H), 8.26 – 7.94 (m, 6 H), 4.55 (dd, *J* = 13.5, 7.8 Hz, 2 H), 4.42 (s, 2 H), 4.25 (dd, *J* = 7.1, 4.9 Hz, 2 H), 2.82 – 2.52 (m, 8 H), 2.01 – 1.92 (m, 2 H), 1.23 (s, 16 H), 1.18 (dd, *J* = 7.0, 2.1 Hz, 10 H), 0.81 (d, *J* = 6.8 Hz, 12 H).

(B) ^{1}H NMR spectrum of Fmoc-C_{12}-VVAADD (300 MHz, DMSO).

^{1}H NMR (300 MHz, DMSO) δ 12.50 (s, 3 H), 8.01 – 7.88 (m, 6 H), 7.73 – 7.65 (m, 3 H), 7.41 (d, *J* = 7.2 Hz, 2 H), 7.35 – 7.16 (m, 4 H), 4.67 – 4.36 (m, 4 H), 4.28 (s, 2 H), 4.26 (s, 2 H), 3.38 (s, 1 H), 2.98 – 2.92 (m, 2 H), 2.61 (qd, *J* = 16.8, 5.8 Hz, 6 H), 2.12 (dd, *J* = 15.0, 7.2 Hz, 2 H), 1.21 (s, 16 H), 1.17 (d, *J* = 7.0 Hz, 8 H), 0.80 (d, *J* = 6.8 Hz, 12 H).

(C) ^{1}H NMR spectrum of Nap-C_{12}-VVAADD (300 MHz, DMSO).

^{1}H NMR (300 MHz, DMSO) δ 8.15 – 7.91 (m, 6 H), 7.80 (d, *J* = 8.1 Hz, 3 H), 7.69 (d, *J* = 8.6 Hz, 1 H), 7.52 – 7.39 (m, 4 H), 4.57 – 4.48 (m, 2 H), 4.27 – 4.15 (m, 4 H), 3.55 (s, 2 H), 3.08 – 3.01 (m, 2 H), 2.78 – 2.51 (m, 6 H), 2.13 (dd, *J* = 14.5, 7.3 Hz, 2 H), 1.99 – 1.91 (m, 2 H), 1.43 (d, *J* = 24.6 Hz, 6 H), 1.20 (s, 16 H), 0.82 (t, *J* = 5.4 Hz, 12 H).

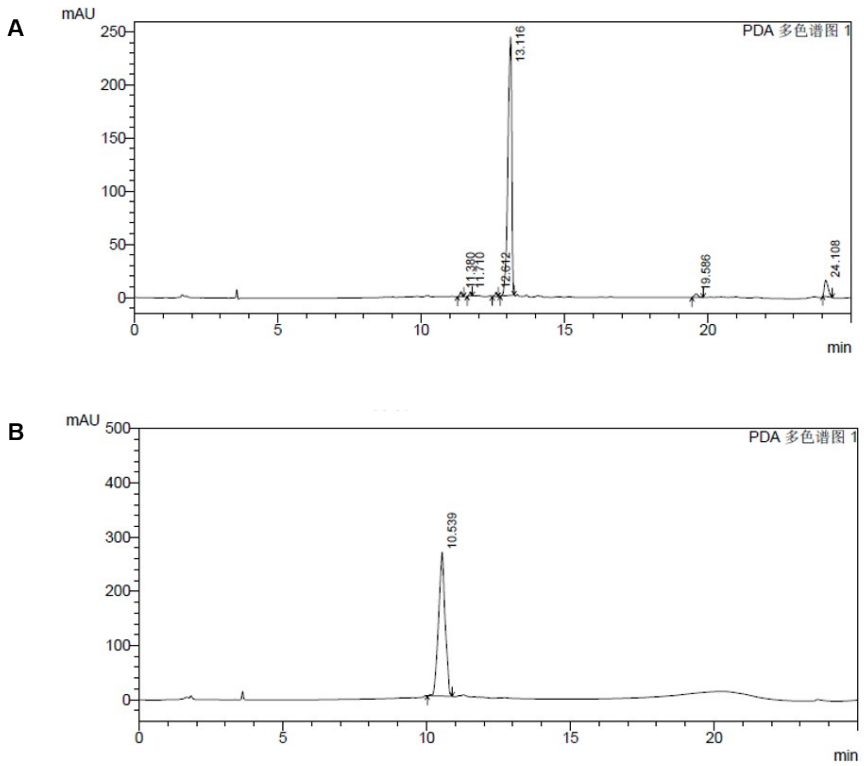


Fig. S4. HPLC elution curves of Nap-C_{12}-VVAAG (A) and Nap-C_{12}-VVAAD (B). Purity > 90%.

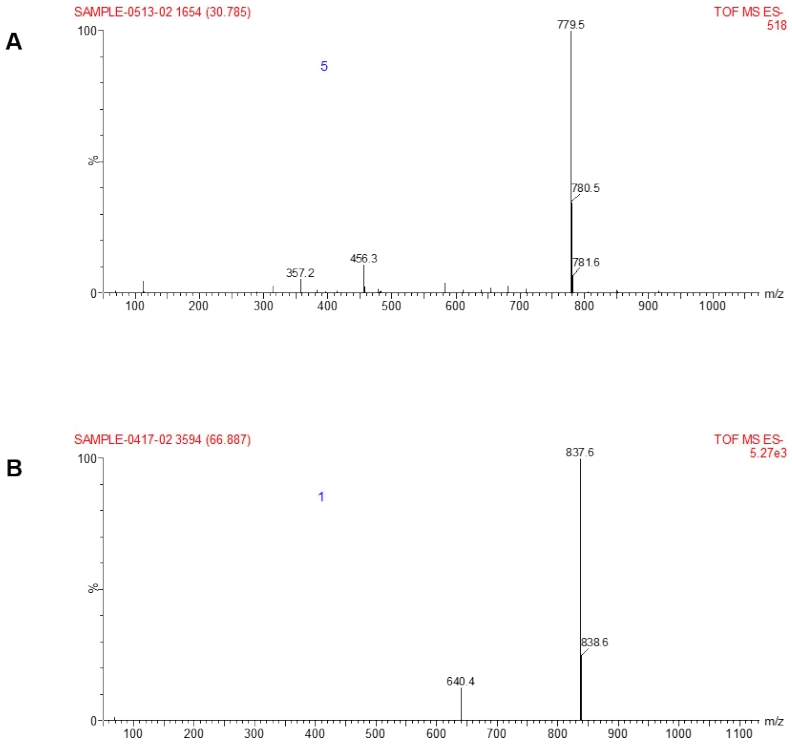


Fig. S5. TOF-MS spectra of Nap-C_{12}-VVAAG (A), and Nap-C_{12}-VVAAD (B),
Nap-C_{12}-VVAAG: Calc. MW = 780, obsvd. $[M-H]^-$ = 779.5; Nap-C_{12}-VVAAD: Calc. MW = 838, obsvd. $[M-H]^-$ = 837.6.

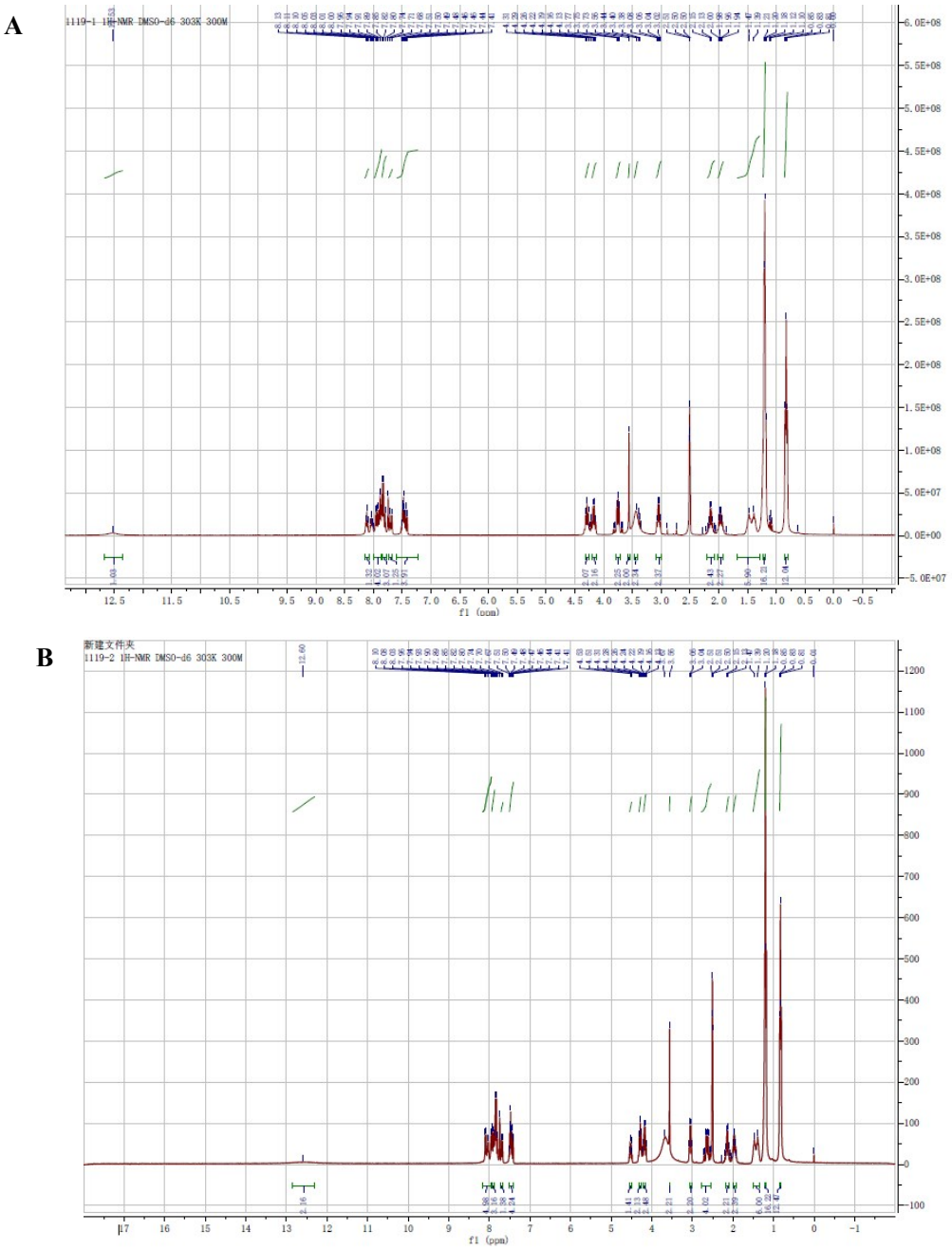


Fig. S6. (A) ^{1}H NMR spectrum of Nap-C_{12}-VVAAG (300 MHz, DMSO).

^{1}H NMR (300 MHz,) δ 12.53 (s, 1 H), 8.11 (t, *J* = 5.8 Hz, 1 H), 7.99 – 7.86 (m, 4 H), 7.81 (d, *J* = 8.3 Hz, 3 H), 7.69 (d, *J* = 8.7 Hz, 1 H), 7.47 (ddd, *J* = 15.2, 10.3, 6.3 Hz, 4 H), 4.32 – 4.25 (m, 2 H), 4.21-4.13(m, 2 H), 3.79 – 3.71 (m, 2 H), 3.56 (s, 2 H), 3.44 (s, 2 H), 3.05 (dd, *J* = 12.7, 6.6 Hz, 2 H), 2.14 (dq, *J* = 13.7, 6.8 Hz, 2 H), 1.97 (dd, *J* = 13.1, 6.6 Hz, 2 H), 1.39 (t, *J* = 27.3 Hz, 6 H), 1.21 (d, *J* = 3.4 Hz, 16 H), 0.83 (t, *J* = 5.5 Hz, 12 H).

(B) ^{1}H NMR spectrum of Nap-C_{12}-VVAAD (300 MHz, DMSO).

^{1}H NMR (300 MHz, DMSO) δ 12.60 (s, 2 H), 8.04 (dd, *J* = 27.4, 14.4 Hz, 5 H), 7.91 (dd, *J* = 11.7, 3.9 Hz, 3 H), 7.69 (d, *J* = 8.7 Hz, 1 H), 7.46 (ddd, *J* = 14.3, 8.0, 2.2 Hz, 4 H), 4.52 (d, *J* = 7.7 Hz, 1 H), 4.29 (d, *J* = 7.0 Hz, 2 H), 4.17 (d, *J* = 7.1 Hz, 2 H), 3.56 (s, 2 H), 3.05 (d, *J* = 6.0 Hz, 2 H), 2.63 (qd, *J* = 16.7, 6.2 Hz, 4 H), 2.17 – 2.10 (m, 2 H), 2.00 – 1.93 (m, 2 H), 1.43 (d, *J* = 24.9 Hz, 6 H), 1.20 (s, 16 H), 0.84 (d, *J* = 4.7 Hz, 12 H).

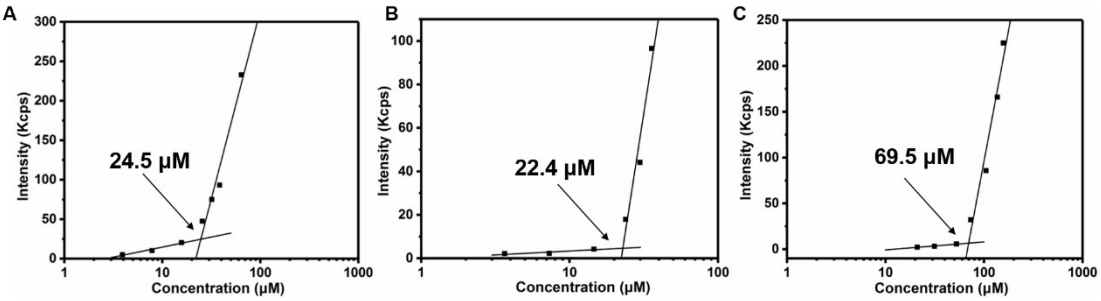
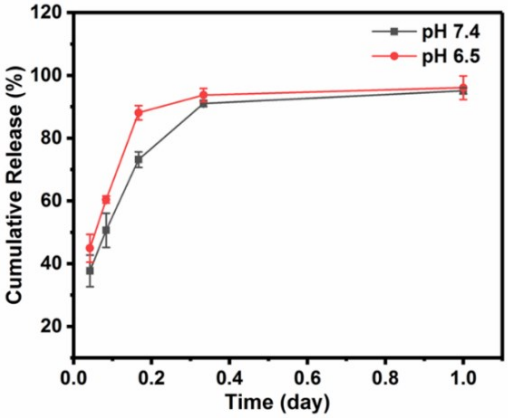


Fig. S7. Values of critical aggregation concentration (CAC) of 1-G/Ca^{2+}/DOX (A), 1-D/Ca^{2+}/DOX (B), and 1-DD/Ca^{2+}/DOX (C).



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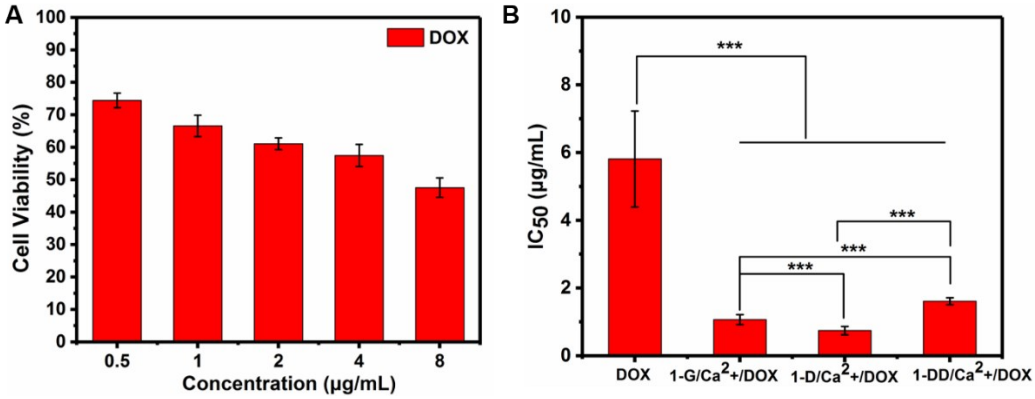

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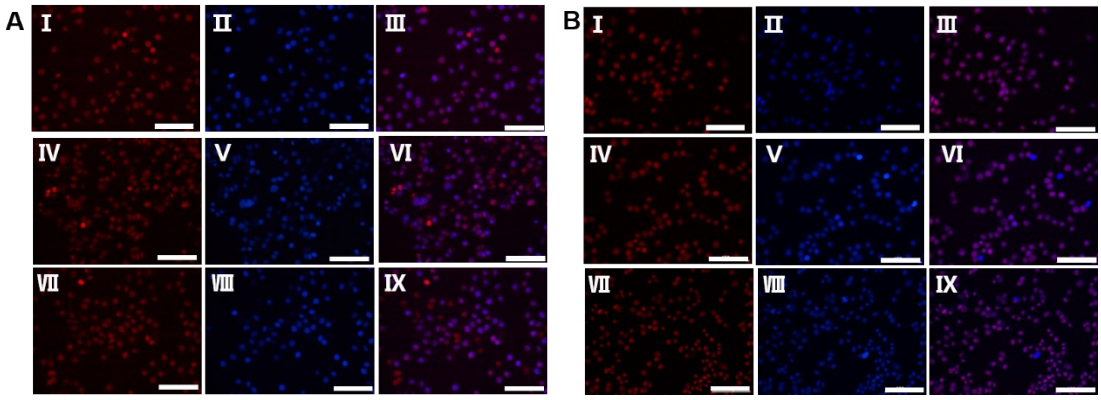

Fig. S10. Fluorescence images of HeLa cells after 2 h pre-treatment of varying endocytosis inhibitors (CPZ, CytD and Filipin III) and 2 h treatment of free DOX (10 μg/mL) (A) and 1-DD/Ca^{2+}/DOX (B) at 37 °C. Graphic labeling: CPZ (I, II, III); CytD (IV, V, VI) and Filipin III (VII, VIII, IX). Red fluorescence channel for DOX (I, IV, VII); DAPI channel for nucleus stain (II, V, VIII); and Merged images (III, VI, IX). The scale bars correspond to 100 μm in all the images.