General methods and materials

Commercial regeants were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AVANCE III HD spectrometer (400 MHz and 100 MHz) in the indicated solvents at 25 °C. Chemical shifts were referenced to the residual solvent peaks. Dynamic light scattering (DLS) and zeta potentional experiments were conducted on a Malvern Zetasizer Nano ZS90. Isothermal calorimetric (ITC) experiments were conducted on a Malvern MicroCal iTC200. APTT assays were exanimated on a full-automatic blood coagulation analyzer (UP3000, Shanghai Sun Biotech Co. Ltd. (Shanghai, China). TEG assays were carried on a Haema T4 from Medcaptain Medical Technology Co., LTD.

Bovine platelet poor plasma, 5% red blood cells (RBCs) in Alserver's solution from rats and human was purchased from Guangzhou Hongquan Biological Science and Technology Co., Ltd (Guangzhou, China). Human blood and Human platelet poor plasma was provided by Shanghai Blood Center. APTT (Ellagic Acid Activator) kits with 0.025 mol L^{-1} and Kaolin Activation Reagent Kits for thromboelastography (TEG) and TEG cups were bought from Shenzhen Medcaptain Medical Technology Co. Ltd. (Shenzhen, China). Unfractionated heparin sodium, dalteparin sodium, enoxaparin sodium and nadroparin calcium were purchased from Shanghai Macklin Biochemical Co.,Ltd, and Protamine sulfate was purchase from Sigma-Aldrich. 4-(4-Pyridinyl)benzaldehyde, 3-pyrid-4-ylbenzaldehyde, 3-pyridinecarboxaldehyde were purchased from ENERGY chemical. Nicotinohydrazide, Isoniazid were purchased from Sigma-Aldrich. Compounds **1**[1] and **A1**[1] were prepared according to the reported method.

Animals. ICR mice for tail transection assay and acute toxicity assay were purchased from Laboratory Animal Center of the Shanghai Institute of Planned Parenthood Research. The mice were bred in a 12 h light/dark cycle in a room with temperature and humidity controlled, grouped cages as appropriate, and allowed to have ad libitum access to sterilized tap water and standard chow. All the experimental protocols were in agreement with the guidelines of the Institutional Animal Care and Use Committee of Shanghai.

DLS experiments. For size experiments, the instrument test mode is set to Number (%), the solutions of heparins, DCPs or their mixture were left to stand for 24 h before being measured.1.5 mL solution was stand by for equillibrium for two minutes before the test.

Fluorescence titration measurements. Because the heparin did not retain any conjugated function group,the heparins (1.0 mM in saline) were added to $DCPA_1H_1$ or $DCPA_2H_1$ (2.0 mL,5 μM in saline) every two minutes with sonication.The normalization intensity was based on the ratio of final and initial fluorescence intensity of $DCPA_1H_1$ and $DCPA_2H_1$. Initial fluorescence intensity was set as 1.0. The concentration of heparin was based on the disaccharide repeating unit, and the polymer concentration is consistent with that of the precursor.

Isothermal titration calorimetry (ITC) experiments. The DCP and heparin solutions were prepared in saline (pH = 7.4). An aqueous solution of **DCPA$_1$H$_1$** or **DCPA$_2$H$_1$** (0.06 mM) was placed in the sample cell (200 uL). Solution of heparins (0.5 mM) was dropped in a series of the first injections (0.5 μL) followed by 19 injections (2 μL), the heat evolved was recorded at T = 298.15 K, the stirring speed was 750 rpm, and the interval between each drop was two minutes. Binding stoichiometry (N), enthalpy (ΔH), entropy (ΔS), and equilibrium association constants (K_a), were determined by fitting the corrected data to 1:1 binding model in Malvern MicroCal iTC200 analysis software.

Activated partial thromboplastin time (APTT) assays. The following procedure was carried out for APTT measurements: bovine and human platelet poor plasmas (PPP) with 3.8% sodium citrate anticoagulated were used to study the neutralization activity of the DCPs and protamine on a full-automatic blood coagulation analyzer. Different type of DCPs and protamine sulfate solutions were prepared in 0.150 mol/L saline. UFH, Dalte, Enoxa, Nadro (2 IU/mL) were prepared with platelet poor human or bovine plasma at the ratio of 1:99. The DCPs or protamine was added to heparinized plasma to observe the antagonistic efficiency of the heparins. Protamine sulfate was used as the positive control and Salinized PPP with the addition of saline was used as the blank control. Generally, 18 μL of the solution with the concentration ranging from 0-0.09 mg/mL stock DCPs or protamine solution in saline and the heparinized plasma (0.16 mL) composed the test sample (10%, v/v). To estimate the neutralization efficacy from APTT time, the standard curves were first established to fit the assays. Heparinized PPP (4 IU/mL) was first prepared and then doubly diluted to obtain samples with heparin of gradient concentrations, (0.078-4.0 IU/mL) for the aPTT test. In this way, standard curves were obtained, by which the neutralization efficacy of each text was calculated. Test procedure: the full-automatic blood coagulation analyzer was warmed up for half an hour to reach 37 °C. Before the test, quality control tests were conducted to calibrate the analyzer. After starting the test, samples (0.15 mL) were manually added into the sample cup and the automatic program was started. Automatically, every 50 μL of sample was sucked from the sample cup and added into the test cup by sampling probe. Then, the sample was incubated at 37 °C for 50 seconds. Subsequently, 50 μL of preheated (37 °C) aPTT reagent was added and incubated for 190 seconds. Finally, 50 μL of 25 mM preincubated $CaCl_2$ solution was added and the clotting time was recorded. The analyzer showed very stable reports for the same samples, so the experiments were conducted singly.

Thromboelastography (TEG) assays. Human whole blood from healthy consented donors was collected into 200 mL whole blood collection bags at Shanghai Blood Center (Shanghai, China), or collected into 3.8 wt% sodium citrate tube with a blood/anticoagulant ratio of 9:1. Blood coagulation were measured on a Haema T4 from Medcaptain Medical Technology Co., LTD. Human whole blood with 3.8 wt% sodium citrate tubes was used to study the TEG assays. All heparin UFH, Dalte, Enoxa, Nadro (2 IU/mL) had the same concentration for the aPTT assays. Test procedure: Whole bloods (1.0 mL) with heparin (10.1 μL) were incubated at 37 °C for 5 mins. Then, 112.2 μL antidote stock solutions in saline were mixed with the heparinized whole blood to make the final concentrations of **DCPA$_1$H$_1$** (0.028 mg/mL to UFH, 0.036 mg/mL to

Dalte, 0.063 mg/mL to Nadro), **$DCPA_2H_1$** (0.036 mg/mL to UFH, 0.045 mg/mL to Dalte, 0.090 mg/mL to Nadro). After incubated for 5 minutes, a vial containing buffered stabilizers and Kaolin® (phospholipids) was added into blood-antidote suspension, then the sample was mixed up for another five minutes. The TEG cup within 340 μL mixture and 20 μL calcium chloride solution was used to carry on the assays and the measurement time was more than 60 minutes. Saline-incubated whole blood without heparin was used as normal control for this experiment. At the same time, heparinized blood incubated with saline was used as negative control.

Mouse tail transection model and bleeding assay. Fifty ICR mice (male and female, 18-24g) were randomly divided into five groups. For the experiment group, the first injection was heparin (**UFH**, 200 IU/kg or **Dalte**, 200 IU/kg). After 5 minutes the second injection of the antidote (**$DCPA_1H_1$**, 3.1 mg/kg or **$DCPA_2H_1$**, 3.5 mg/kg) was conducted. The dose for antidotes was chosed as the one obtained by the *in vitro* APTT assays that reached over 80% antagonistic efficiency. Control group was given 2 injections of saline. Negative control group was given saline for the second injection, whereas positive control was given protamine (2.6 mg/kg) as the second injection. *General test procedure:* a) conducting the injection via tail intravenous vein at 0 minute (saline or heparins (30 IU/mL for both UFH and Dalte),0.1-0.2 mL, injection volume increased with mouse mass). After five minutes, second injection (saline or antidotes, 0.1-0.2 mL, injection volume increased with mouse mass) were given. Two minutes after the second injection, the mice were anesthetized by inhaling a mixture of 5% isoflurane in air and subsequently decreased 3% to maintain the anesthesia status. In the tenth minute of the experiment, the scalpel was cleaned and disinfected, then the tail of each mice was transected at a site 2.5 mm from the end of tail with scalpel and immediately used 1 cm 1cm filter paper to collect bleeding blood. The tail bleeding time was counted until there was no blood spot on the filter paper for 1 min continuously. The filter papers were then treated with 2 mL 10 wt% NaOH aqueous solution in 5 mL centrifuge tubes. Total blood loss was measured according to reported method.2 The total blood volume in each tube was quantified by spectrophotometry (absorbance at 405 nm) from a standard curve that was constructed with accurate volumes of blood hemoglobin concentration and corresponding absorbance value.

Cell cytotoxicity. In vitro cytotoxicity was evaluated by cell counting kit-8 (CCK-8) assay. H9C2 cells and L02 cells were seeded in 96-well plate (8×10^3 cells and 100 μL culture medium in per well) and incubated for 24 h. The culture medium was removed and 100 μL culture medium containing **$DCPA_1H_1$**, **$DCPA_2H_1$**, **$DCPA_2H_2$** or **$DCPA_3H_1$** of different concentrations was added (0.7-90 μg/mL). The culture was removed after 24 h and 100 μL fresh culture medium containing 10% CCK-8 was added. The cells were incubated for another 1 h and the cell viability was evaluated by absorbance at 450 nm using Allsheng AMR-100 microplate reader.

Hemolysis experiment. 5% Human and mouse red blood cells preserved in Alsever's solution were centrifuged in a 1000 r/min centrifuge for 10 minutes to abtain blood samples. Blood samples were diluted with equal volume of isotonic saline. The solution obtained (140 μL) were mixed respectively with saline (560 μL, negative control),

deionized water (560 μL, positive control), **$DCPA_1H_1$**, **$DCPA_2H_1$**, **$DCPA_2H_2$** or **$DCPA_3H_1$** solution of different concentrations (8-256 μg/mL). After incubation for 1 h at 37 ℃, the samples were centrifugated at 3000 r/min for 10 minutes and the supernatants were obtained. The hemolysis ratio of the samples was evaluated with the absorbance at 545 nm using Allsheng AMR-100 microplate reader.

Maximum tolerated dose (MTD) evaluations for $DCPA_1H_1$ and $DCPA_2H_1$. For the safety profiles of **$DCPA_1H_1$** and **$DCPA_2H_1$**, 30 ICR mice (18-24 g, n = 6, half female and male) were individually weighed and randomly divided into five groups. In the control group, mice were i.v. injected within 0.5 mL normal saline. For the another four experimental groups, **$DCPA_1H_1$** was i.v. injected with a concentration gradient of 3.1, 5.5 and 8.0 mg/kg, whereas **$DCPA_2H_1$** was injected with a concentration gradient of 3.5, 6.0 and 8.5mg/kg. Body weight was monitored twice a day at defined time and their general behaviors were observed and recorded. After 14 days, the mice were euthanized and organs collected for both control group and medium dose experiment group. The histopathological sections of collected organs were prepared and stained with hematoxylin and eosin (H&E), which was followed by imaging with optical microscopy.

Table S1. Dose tolerance of **$DCPA_1H_1$** in ICR mice.

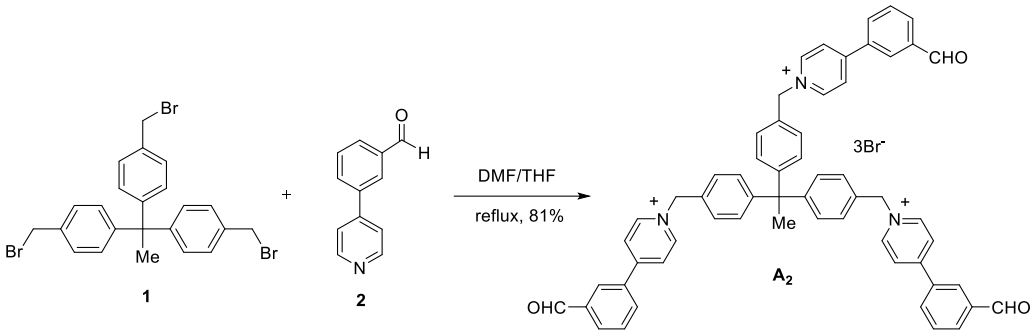
Group	$DCPA_1H_1$ Dose (mg kg^{-1})	Survived mice/Total mice		Death rate/%		
	Mice	female	Male	female	Male	overall
1	3.1	3/3	3/3	0	0	0
2	5.5	3/3	3/3	0	0	0
3	8.0	3/3	3/3	0	0	0
4	9.2	3/3	2/3	0	33.3	16.7
5	10.0	2/3	1/3	33.3	66.7	50.0

Table S2. Dose tolerance of **$DCPA_2H_1$** in ICR mice.

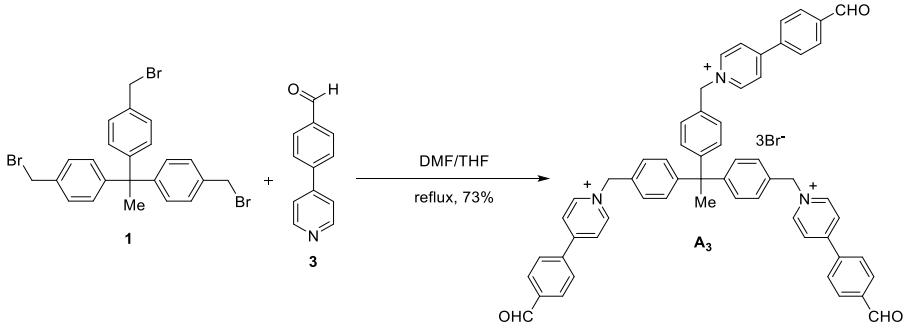
Group	$DCPA_2H_1$ Dose (mg kg^{-1})	Survived mice/Total mice		Death rate/%		
	Mice	female	Male	female	Male	overall
1	3.5	3/3	3/3	0	0	0
2	6.5	3/3	3/3	0	0	0
3	8.0	3/3	3/3	0	0	0
4	9.2	2/3	2/3	33.3	33.3	33.3
5	10.0	1/3	1/3	66.7	66.7	66.7

Statistical Analysis. Statistical analysis of the data was carried out by upaired two-tailed t-test (IBM SPSS Statistics 22 Software), and results are presented as either means ± SD or means ± SEM. *P* values of ≤ 0.05 were considered significant, *$p < 0.05$, ***$p < 0.01$ ****$p < 0.005$, and ns represents "no significant difference". The statistical test and P values are included in the figures and tables. LD_{50} values of **SOF1** and **POP1** were calculated using SPSS probit model (IBM SPSS Statistics 22 Software).

Statement for Ethical Approval. Scientific research with human platelet poor plasma and human whole blood was approved by Shanghai Municipal Commission of Health and Family Planning. Animal experiments were performed in agreement with the guidelines of the Animal Care and Use Committee of Fudan University (2020-Department of Chemistry-JS-003).

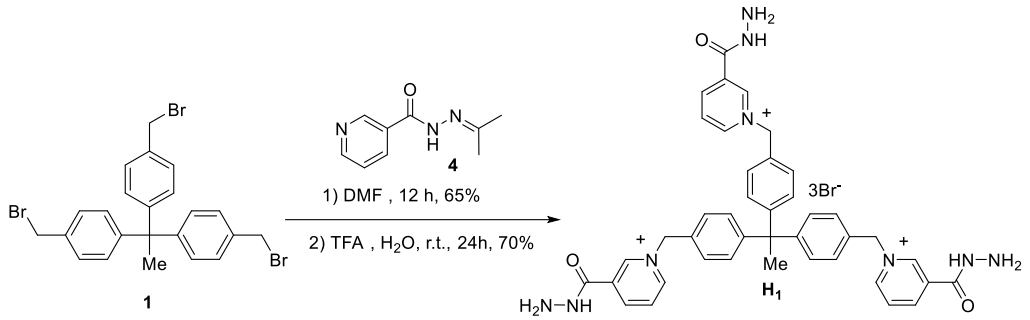


Compound A_2. A mixture of compounds **1** (0.30 g, 0.56 mmol) and **2** (0.41 g, 2.2 mmol) in THF (10 mL) and DMF (20 mL) was stirred under reflux for 12 h and then cooled to room temperature. To the mixture was added acetone (30 mL) and the precipitate formed filtrated, washed with acetone and dried under vacuum. The resulting solid was further recrystallized from acetonitrile to give $\mathbf{A_2}$ as bromide salt as a taupe solid (0.49 g, 81%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 3H), 9.35 (s, 6H), 8.76 – 8.53 (m, 8H), 8.41 (d, J = 19.1 Hz, 3H), 8.19 (d, J = 7.4 Hz, 3H), 7.88 (t, J = 7.6 Hz, 3H), 7.52 (s, 6H), 7.11 (d, J = 7.6 Hz, 6H), 5.89 (s, 6H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 193.03, 154.46, 149.54, 146.34, 137.56, 134.94, 134.30, 132.88, 130.99, 129.72, 128.93, 125.87, 62.40, 51.58, 30.15. HRMS (ESI): Calcd for $C_{59}H_{48}N_3O_3$: 846.3698 $[M-3Br]^{3+}$. Found: 846.3627.

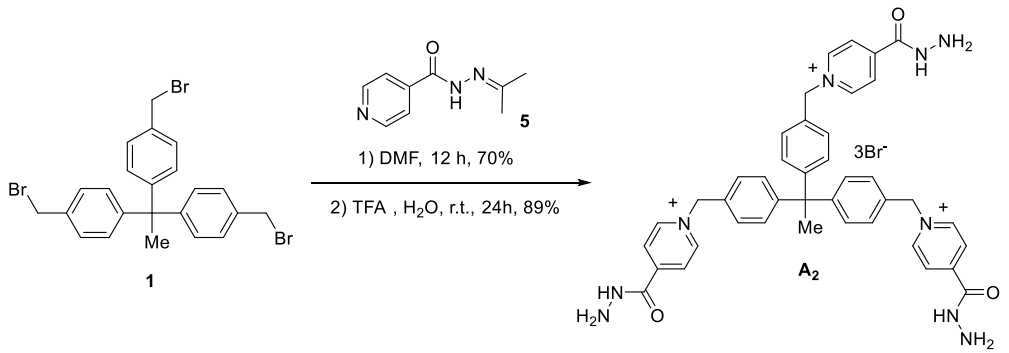


Compound A_3. A mixture of compounds **1** (0.30g, 0.56 mmol) and **3** (0.41g, 2.24 mmol) in THF (10 mL) and DMF (20 mL) was stirred under reflux for 12 h and then cooled to room temperature. To the mixture was added acetone (30 mL). The precipitate formed thereafter was filtrated and washed with acetone and dried under vacuum. The resulting solid was further recrystallized from acetonitrile to give $\mathbf{A_3}$ as bromide salt as a light yellow solid (0.42 g, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 3H), 9.33 (d, J = 39.1 Hz, 6H), 8.69 – 8.52 (m, 6H), 8.26 (d, J = 31.9 Hz, 6H), 8.16 (d, J = 19.7 Hz, 6H), 7.50 (d, J = 8.1 Hz, 6H), 7.10 (d, J = 8.1 Hz, 6H), 5.85 (s, 6H), 1.97 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 194.15, 154.32, 150.20, 145.51, 139.16, 138.02, 132.80, 130.70, 129.53, 129.43, 128.97, 126.66, 62.84, 52.08, 30.15. HRMS (ESI): Calcd for

$C_{59}H_{48}N_3O_3$: 846.3698 $[M–3Br]^{3+}$. Found: 846.3681.



Compound H_1. To a refluxed solution of compound **4** (0.71 g,2.0 mmol) in acetone (42 mL) was added a solution of compound **1** (0.30 g, 0.56 mmol) in DMF (42 mL). The mixture was heated under 65 ºC for 12 h and then cooled to room temperature. The precipitate formed was then filtrated and washed with hot acetone (50 mL) and then dried in vacuo as a faint yellow solid (0.42 g, 60 %). The yellow solid was dissolved in water (23 mL). To the solution was added 10 μL TFA. After stirring for 24 h at room temperature, the solvent was removed under reduced pressure and then dried in vacuo to give $\mathbf{H_1}$ as a bright yellow solid (0.32 g, 62%). ^{1}H NMR (400 MHz, D_2O) δ 9.24 (s, 3H), 8.98 (d, J = 6.0 Hz, 3H), 8.77 (d, J = 7.9 Hz, 3H), 8.26–7.98 (m, 3H), 7.36 (d, J = 7.9 Hz, 3H), 7.21 (d, J = 8.0 Hz, 3H), 5.81 (s, 6H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, D_2O) δ 162.43, 150.10, 146.95, 144.34, 144.22, 131.84, 130.25, 129.65, 129.05, 128.78, 117.69, 114.78, 64.71, 52.21, 29.25. HRMS (ESI): Calcd for $C_{41}H_{42}N_3O_3$: 708.3411 $[M–3Br]^{3+}$. Found: 708.3468.



Compound H_2. To a refluxed solution of compound **5** (0.71 g,2.0 mmol) in acetone (42 mL) was added a solution of compound **1** (0.30 g, 0.56 mmol) in DMF (42 mL). The mixture was heated under 65 ºC for 12 h and then cooled to room temperature. The precipitate was then filtrated and washed with hot acetone (50 mL) and then dried in vacuo as a faint yellow solid (0.42 g, 60 %). The yellow solid was dissolved in water (23 mL). To the solution was added 10 μL TFA. After stirring for 24 h at room temperature, the solvent was removed under reduced pressure and then dried in vacuo to give $\mathbf{H_2}$ as a faint yellow solid (0.13 g, 25%). ^{1}H NMR (400 MHz, D_2O) δ 9.00 (d, J = 8.1 Hz, 6H), 8.25 (d, J = 6.7 Hz, 6H), 7.31 (d, J = 6.8 Hz, 6H), 7.17 (d, J = 6.6 Hz, 6H), 5.75 (s, 6H), 2.04 (s, 3H). ^{13}C NMR (100 MHz, D_2O) δ 163.75, 150.16, 145.58, 130.37, 129.72, 129.16, 126.93, 125.50. HRMS (ESI): Calcd for $C_{41}H_{42}N_3O_3$: 708.3411 $[M–3Br]^{3+}$. Found: 708.3426.

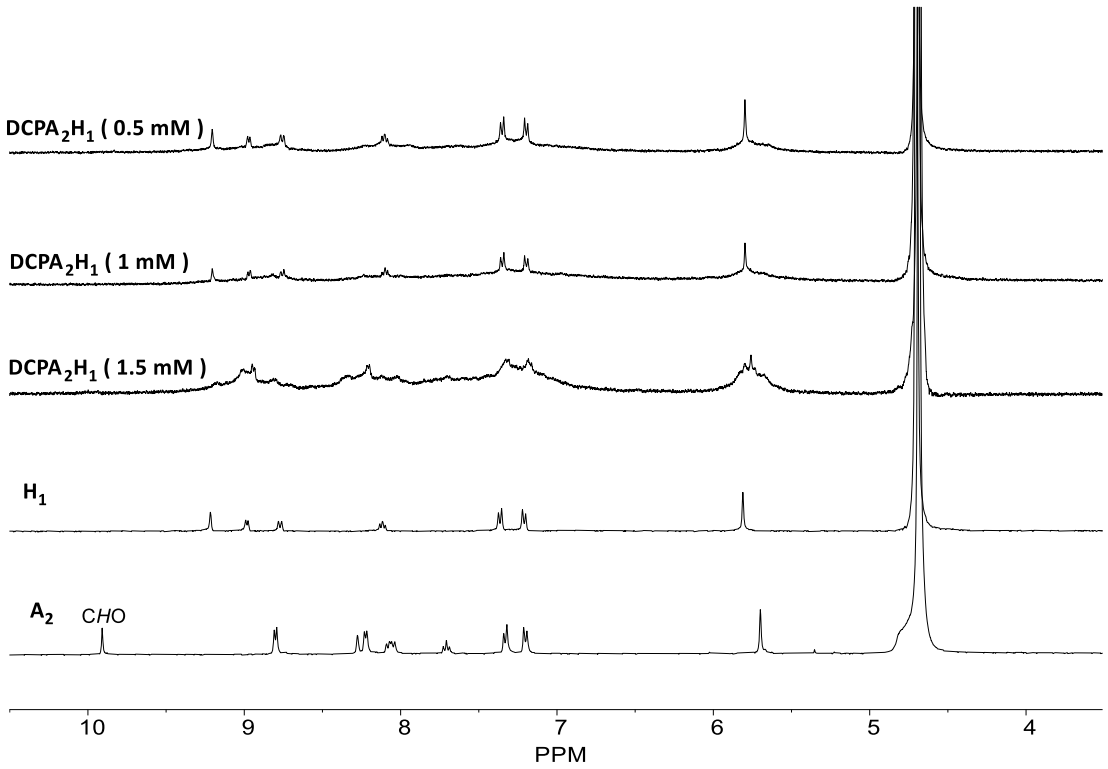


Fig. S1 ^{1}H NMR spectra (400 MHz, D_2O) of **A_2** (10 mM), **H_1** (10 mM) and **$DCPA_2H_1$** of different concentrations, represented by [**H_1**], at 25 °C.

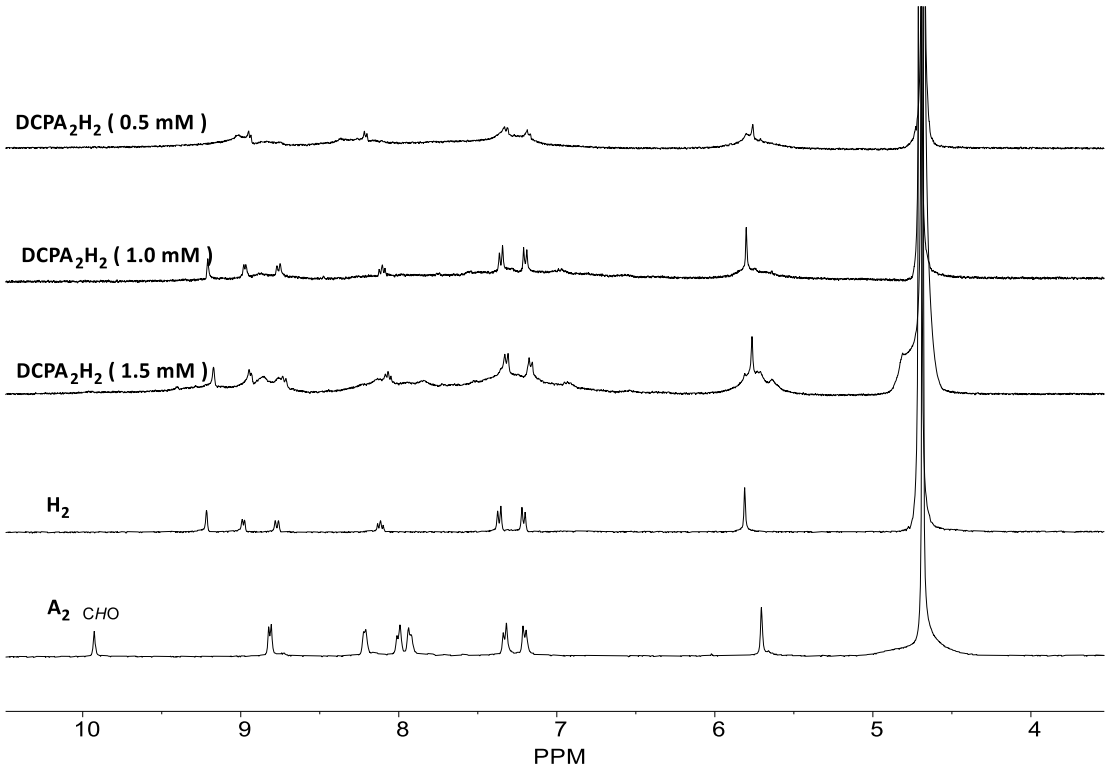


Fig. S2 ^{1}H NMR spectra (400 MHz, D_2O) of **A_2** (10 mM), **H_2** (10 mM) and **$DCPA_2H_2$** of different concentrations, represented by [**H_2**], at 25 °C.

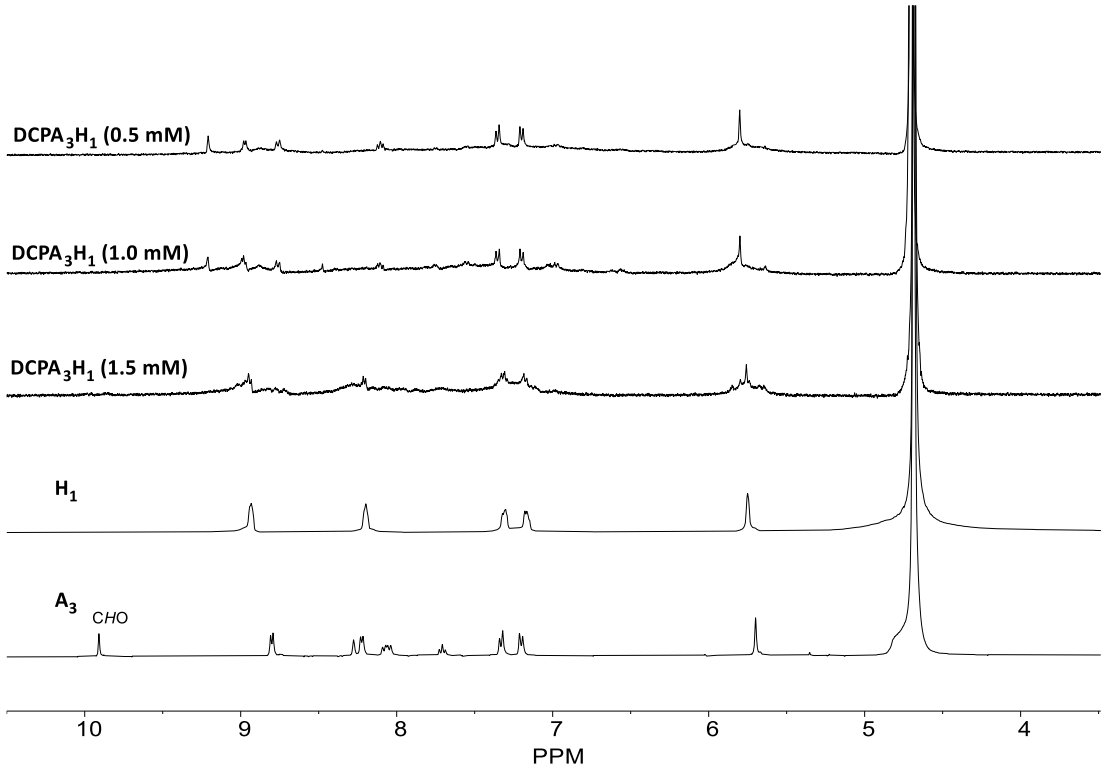


Fig. S3 ^{1}H NMR spectra (400 MHz, D_2O) of **A_3** (10 mM), **H_1** (10 mM) and **$DCPA_3H_1$** of different concentrations, represented by [**H_2**], at 25 °C.

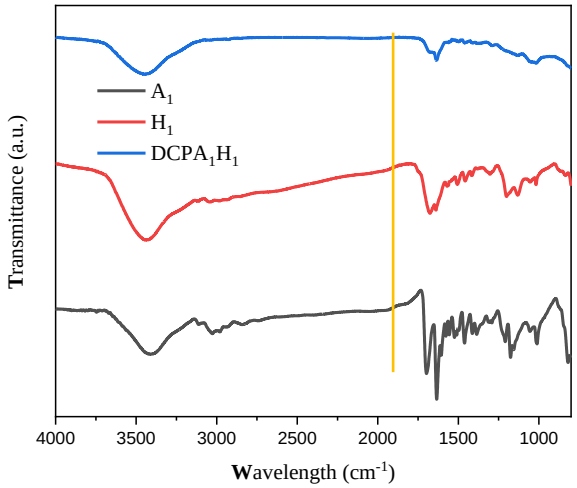


Fig. S4 FT-IR spectrum of **A_1**, **H_1** and **$DCPA_1H_1$** (solid KBr tabletting).

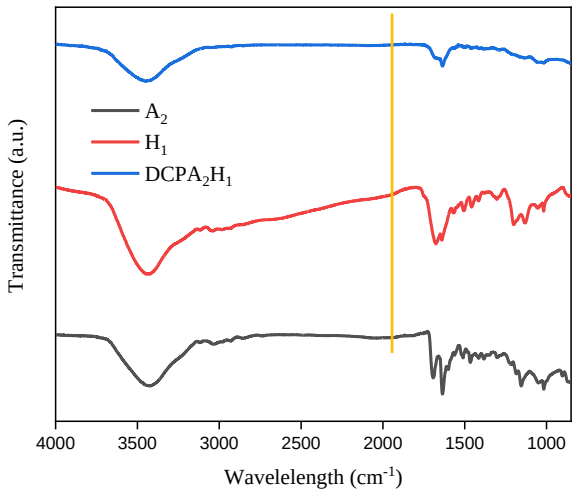


Fig. S5 FT-IR spectrum of **A_2**, **H_1** and **$DCPA_2H_1$** (solid KBr tabletting).

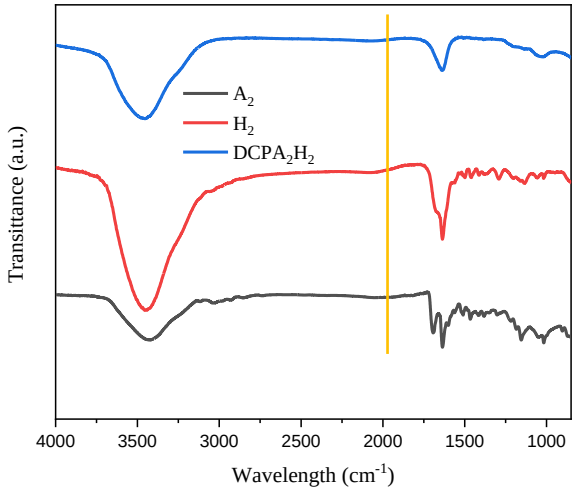


Fig. S6 FT-IR spectrum of **A_2**, **H_2** and **$DCPA_2H_2$** (solid KBr tabletting).

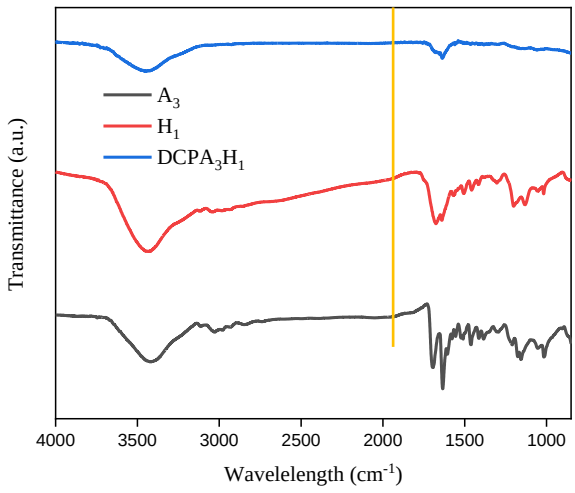


Fig. S7 FT-IR spectrum of **A_3**, **H_1** and **$DCPA_3H_1$** (solid KBr tabletting).

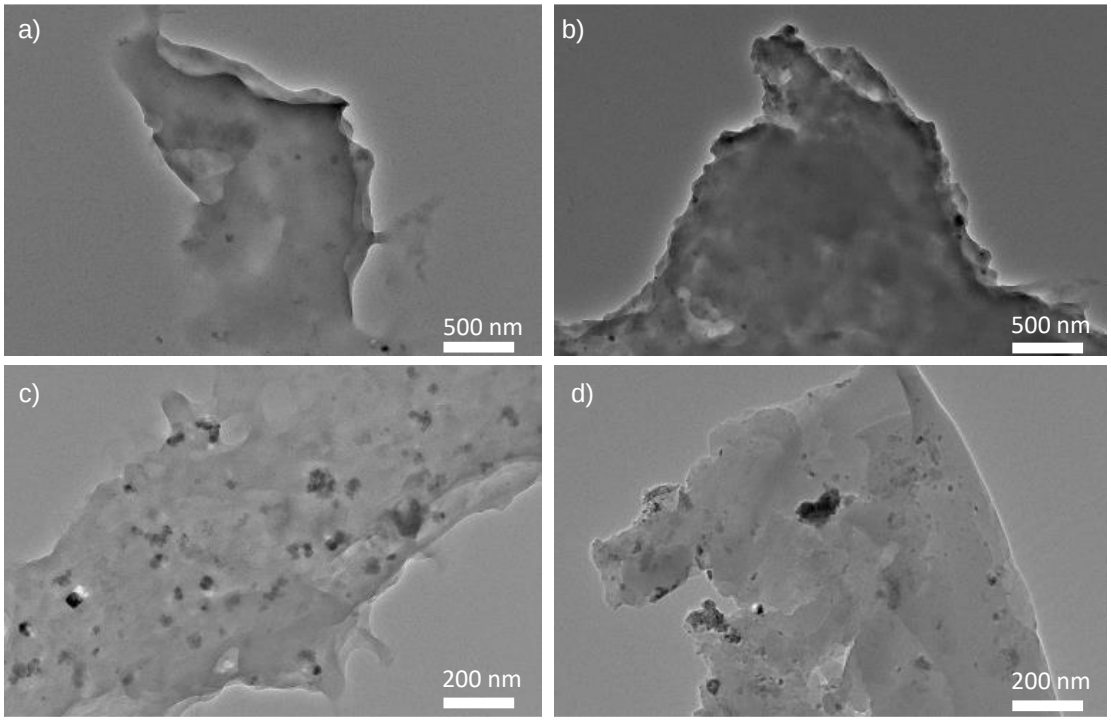


Fig. S8 Transmission electron miscroscope images of the solid samples of a) **DCPA$_1$H$_1$**, b) **DCPA$_2$H$_1$**, c) **DCPA$_2$H$_2$** and d) **DCPA$_3$H$_1$**, prepared by spin-coating their aqueous solution.

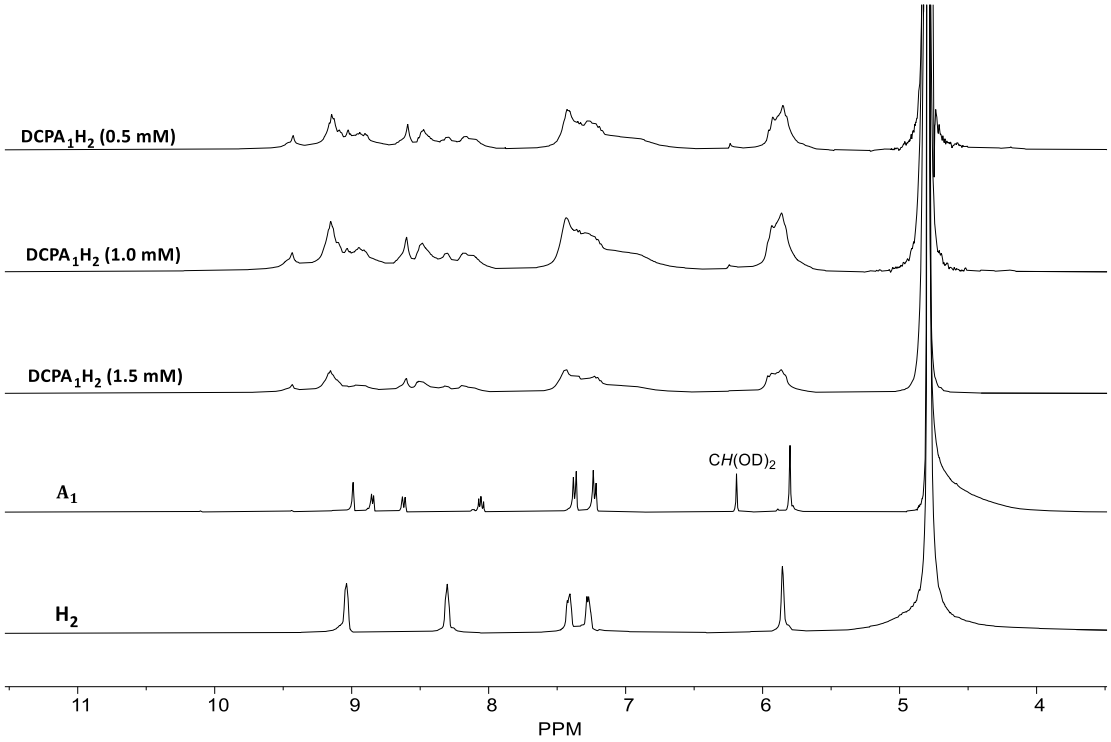


Fig. S9 ^{1}H NMR spectra (400 MHz, D_2O) of **A$_1$** (10 mM), **H$_2$** (10 mM) and **DCPA$_1$H$_2$** of different concentrations, represented by [**H$_2$**], at 25 °C.

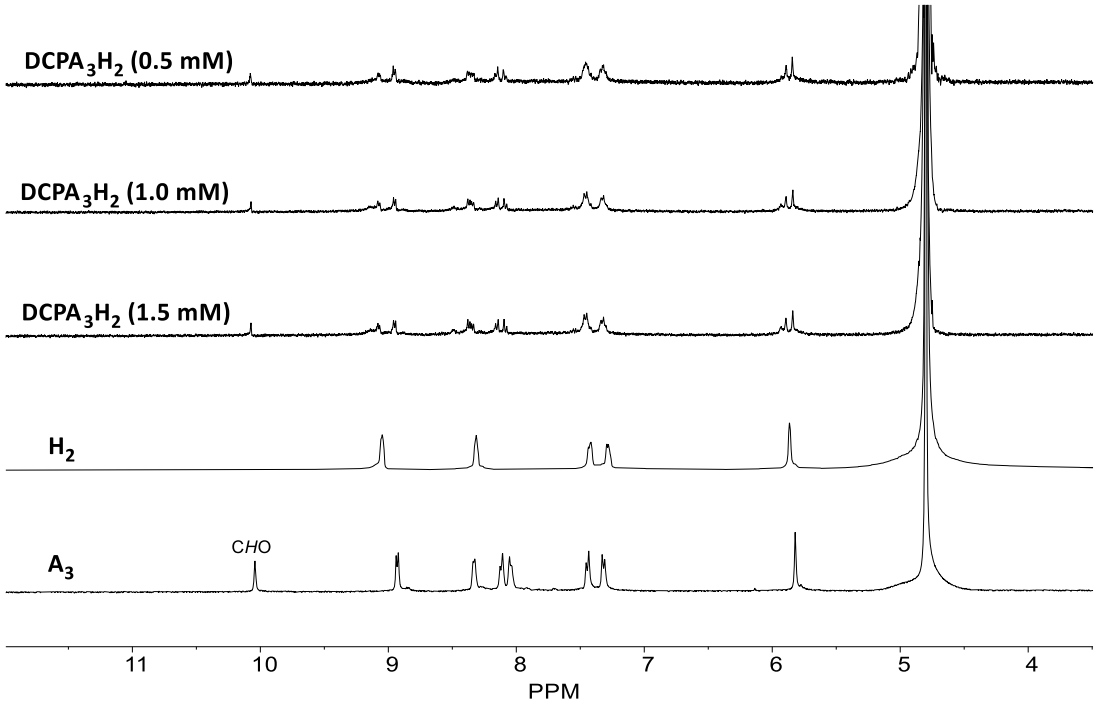


Fig. S10 ^{1}H NMR spectra (400 MHz, D_2O) of **A3** (10 mM), **H2** (10 mM) and **DCPA3H2** of different concentrations, represented by [**H2**], at 25 °C.

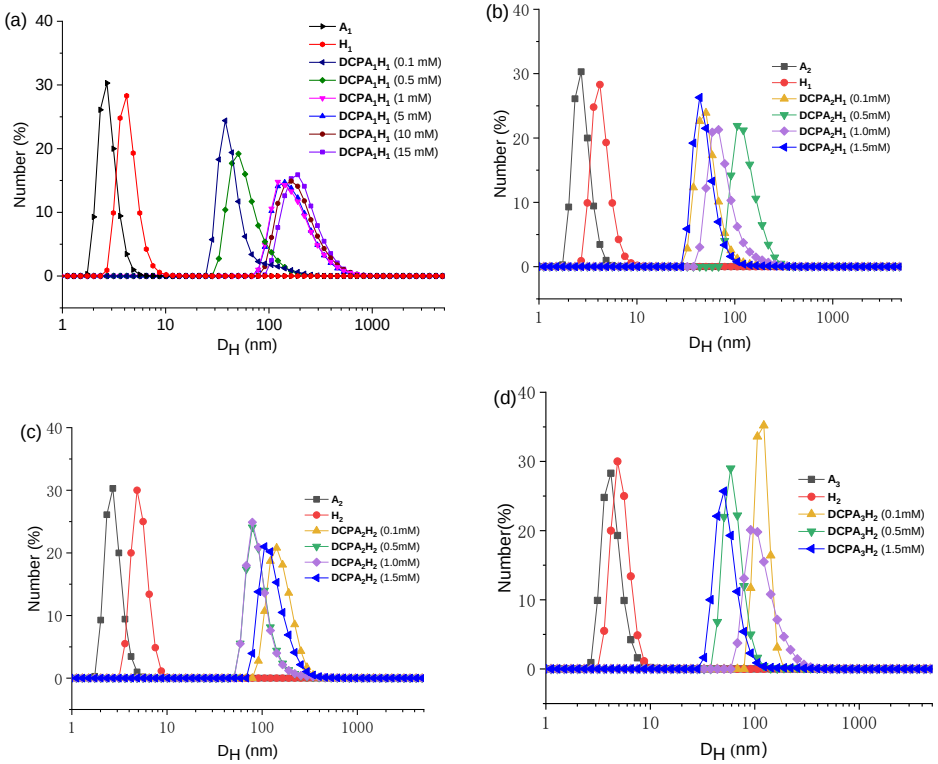


Fig. S11 The DLS profile of (a) **DCPA1H1**, (b) **DCPA2H1**, (c) **DCPA2H2** and (d) **DCPA3H1** of different concentrations in water at pH = 7. All the solutions were left to stand for 24 h before being measured.

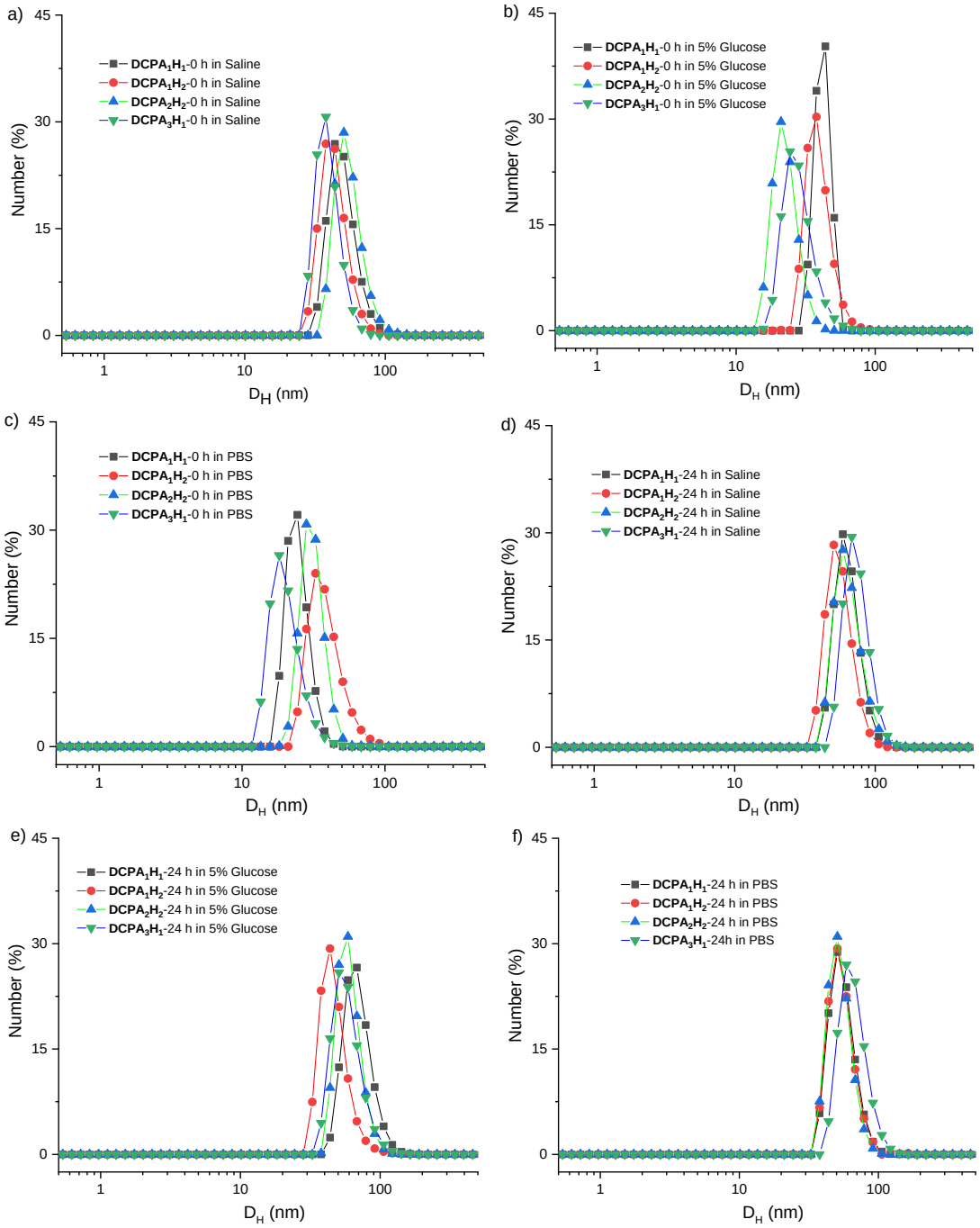


Fig. S12 DLS profiles of DCPs ([tetrahedral monomer] = 20 μM) in a,d) normal saline, b,e) 5% glucose solution and c,f) phosphate-buffered saline (PBS, pH = 7.4) at 25 °C, recorded with 24 hours' interval.

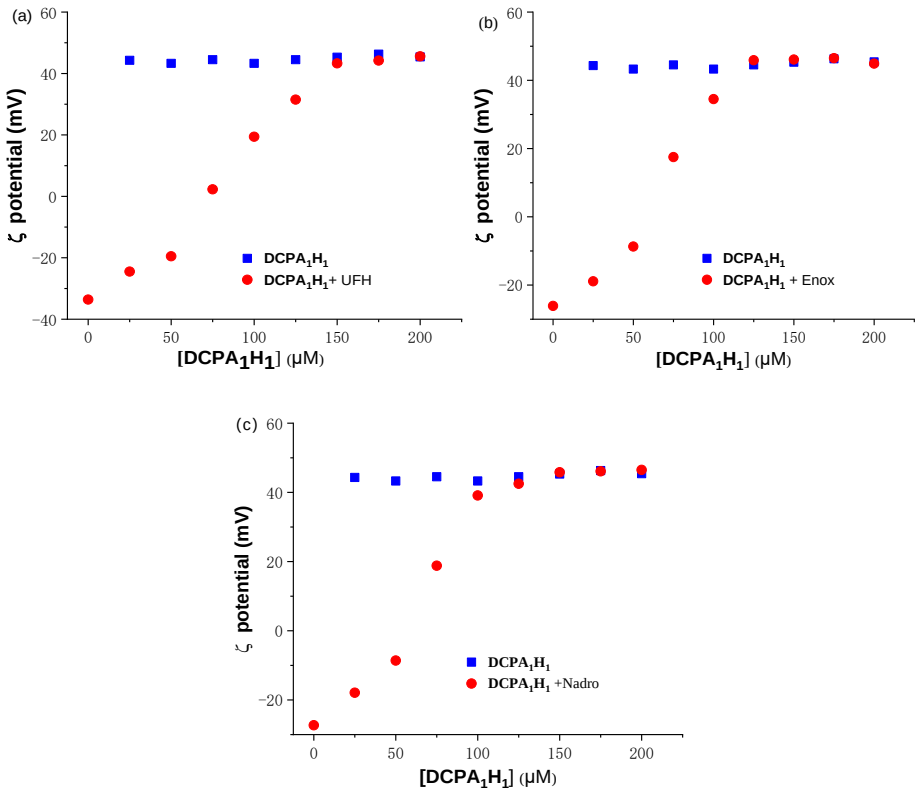


Fig. S13 Zeta potential of the solution of **DCPA$_1$H$_1$** of different concentrations, represented by the 1:1 precursors, in the absence and presence of (a) UFH, (b) Enox and (c) Nadro of different concentrations in water at 25 °C.

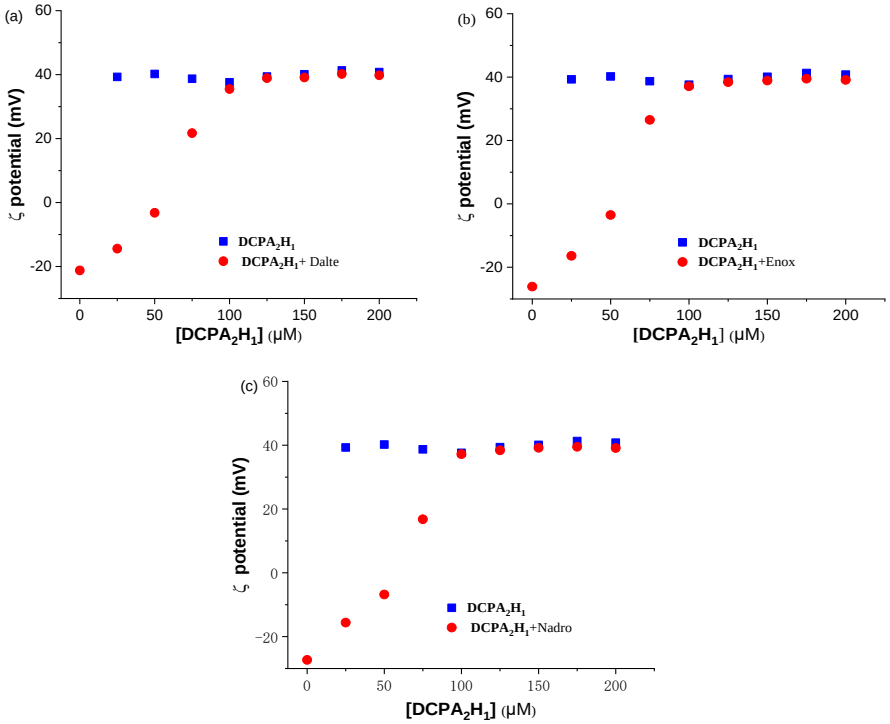


Fig. S14 Zeta potential of the solution of **DCPA$_2$H$_1$** of different concentrations, represented by the 1:1 precursors, in the absence and presence of (a) Dalte, (b) Enox and (c) Nadro of different concentrations in water at 25 °C.

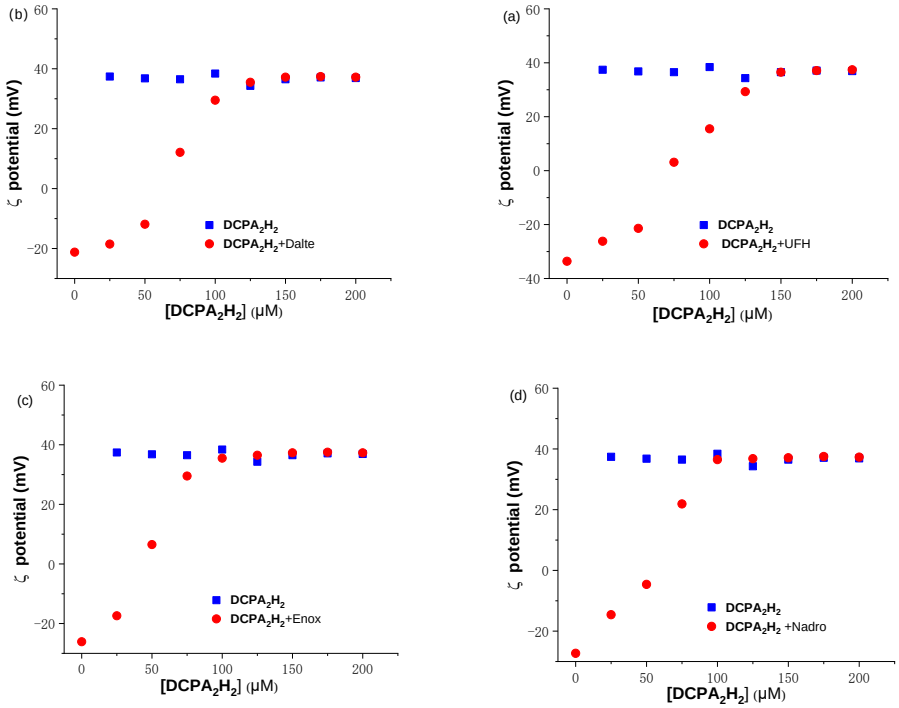


Fig. S15 Zeta potential of the solution of **$DCPA_2H_2$** of different concentrations, represented by the 1:1 precursors, in the absence and presence of (a) UFH, (b) Dalte, (c) Enox and (d) Nadro of different concentrations in water at 25 °C.

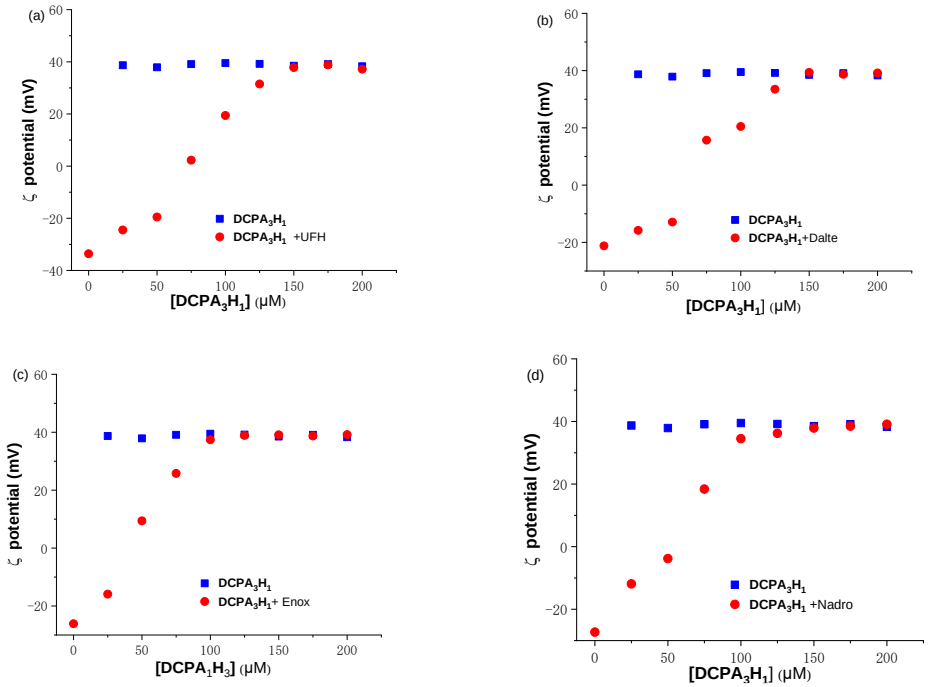


Fig. S16 Zeta potential of the solution of **$DCPA_3H_1$** of different concentrations, represented by the 1:1 precursors, in the absence and presence of (a) UFH, (b) Dalte, (c) Enox and (d) Nadro of different concentrations in water at 25 °C.

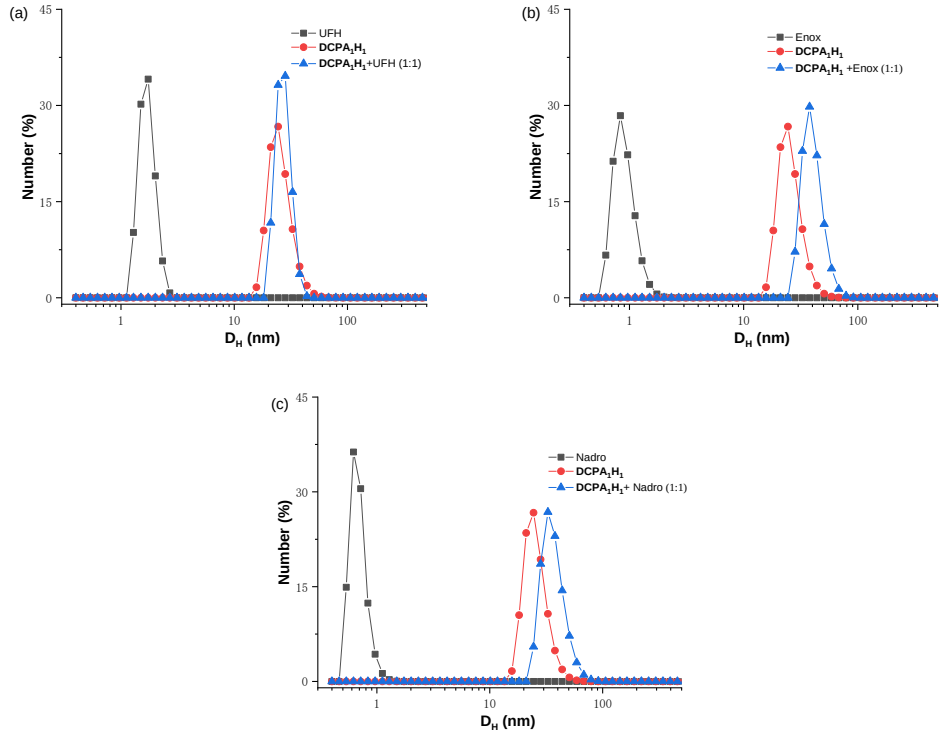


Fig. S17 DLS profile of (a) **DCPA$_1$H$_1$**, UFH, **DCPA$_1$H$_1$**/UFH (1:1); (b) **DCPA$_1$H$_1$**, Enox, **DCPA$_1$H$_1$**/Enox (1:1); (c) **DCPA$_1$H$_1$**, Nadro, **DCPA$_1$H$_1$**/Nadro (1:1).

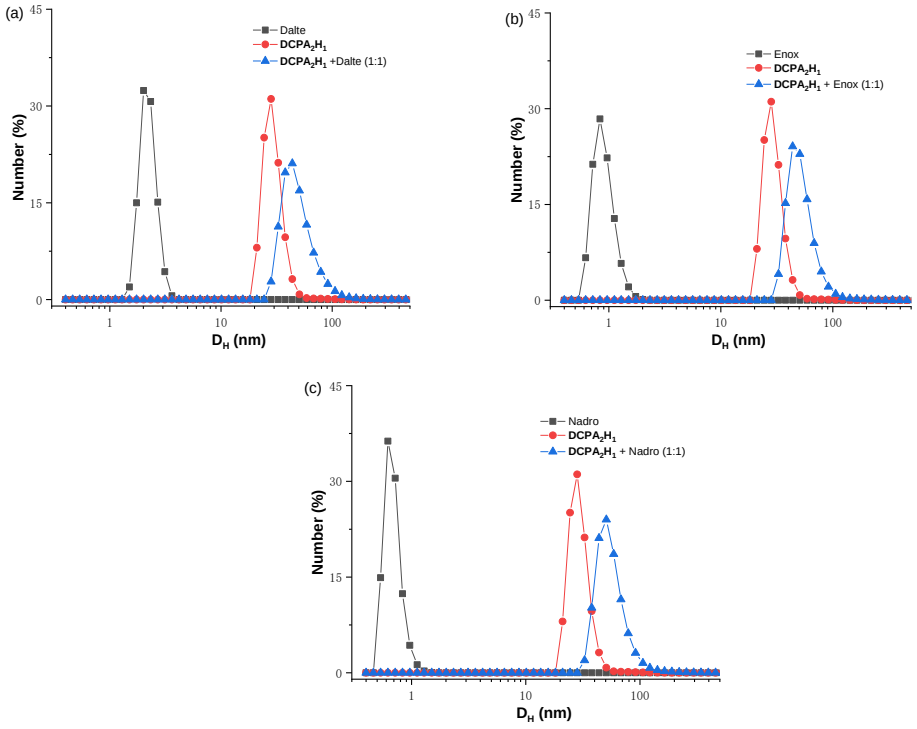


Fig. S18 DLS profile of (a) **DCPA$_2$H$_1$**, Dalte, **DCPA$_2$H$_1$**/Dalte (1:1); (b) **DCPA$_2$H$_1$**, Enox, **DCPA$_1$H$_1$**/Enox (1:1); (c) **DCPA$_1$H$_1$**, Nadro, **DCPA$_1$H$_1$**/Nadro (1:1).

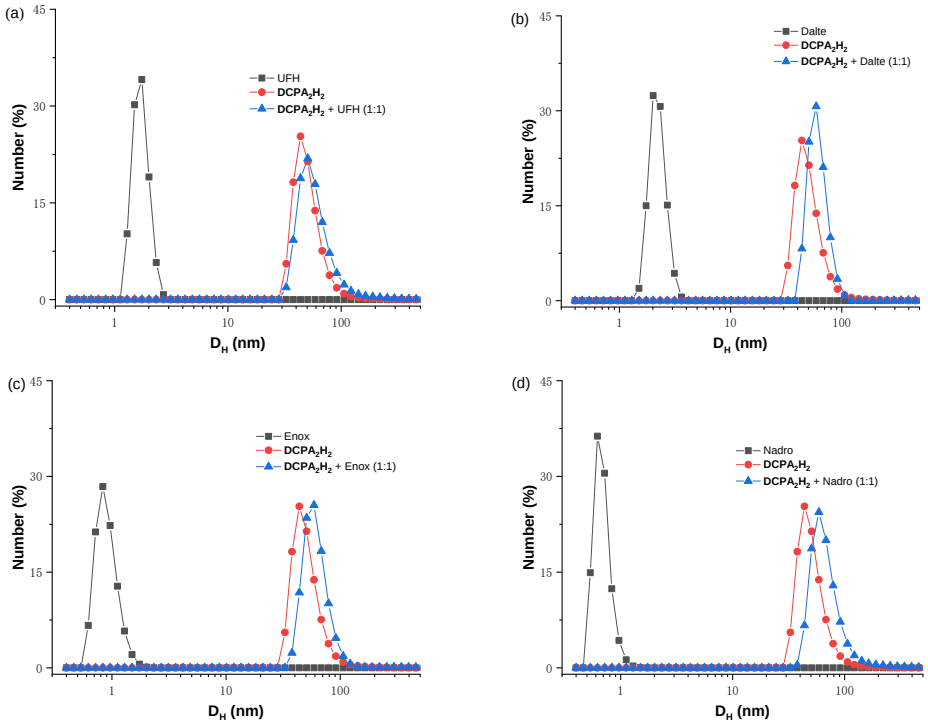


Fig. S19 DLS profile of (a) **DCPA$_2$H$_2$**, UFH, **DCPA$_2$H$_2$**/UFH (1:1); (b) **DCPA$_2$H$_2$**, Dalte, **DCPA$_2$H$_2$**/Dalte (1:1); (c) **DCPA$_1$H$_1$**, Enox, **DCPA$_1$H$_1$**/Enox (1:1); (d) **DCPA$_2$H$_2$,** Nadro, **DCPA$_2$H$_2$**/Nadro (1:1).

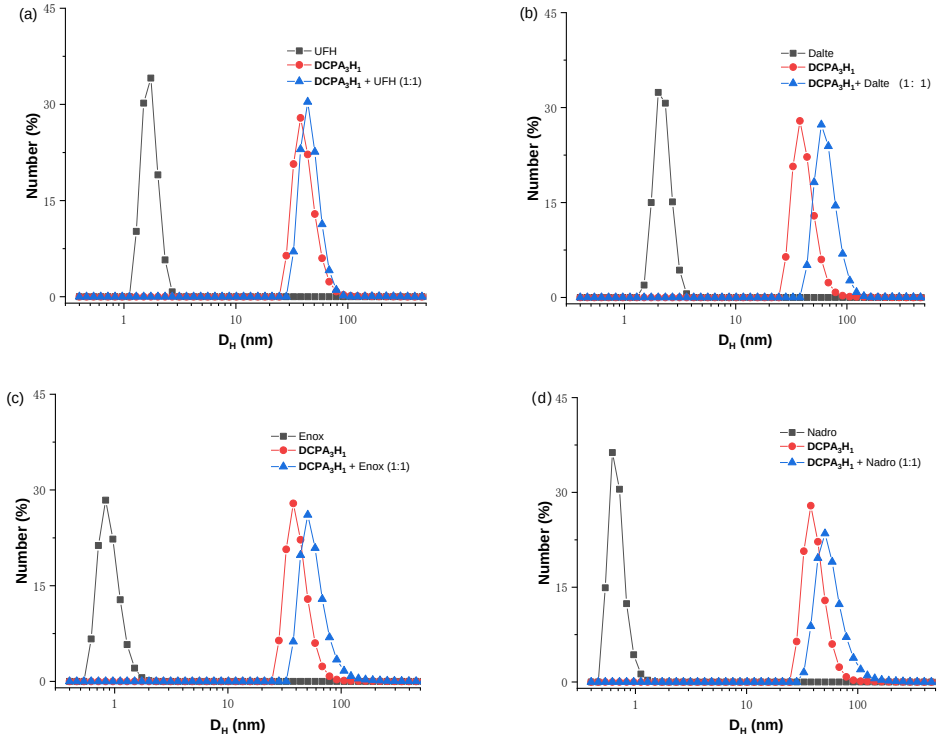


Fig. S20 DLS profile of (a) **DCPA$_3$H$_1$**, UFH, **DCPA$_3$H$_1$**/UFH (1:1); (b) **DCPA$_3$H$_1$**, Dalte, **DCPA$_3$H$_1$**/Dalte (1:1); (c) **DCPA$_3$H$_1$**, Enox, **DCPA$_3$H$_1$**/Enox (1:1); (d) **DCPA$_3$H$_1$,** Nadro, **DCPA$_3$H$_1$**/Nadro (1:1).

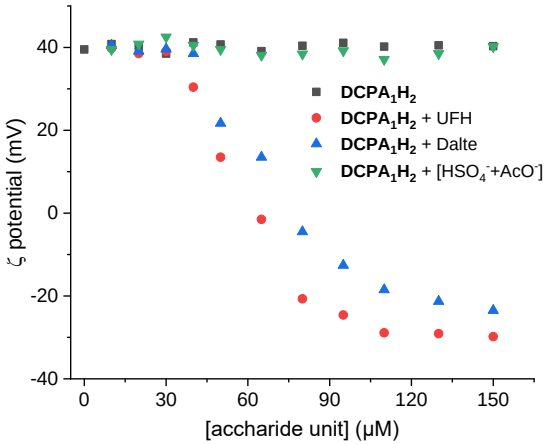


Fig. S21 Zeta potential of the solution of **DCPA$_1$H$_2$** ([monomers] = 20 μM) versus] the concentrations of UFH and Dalte, represented by those of their saccharide units.

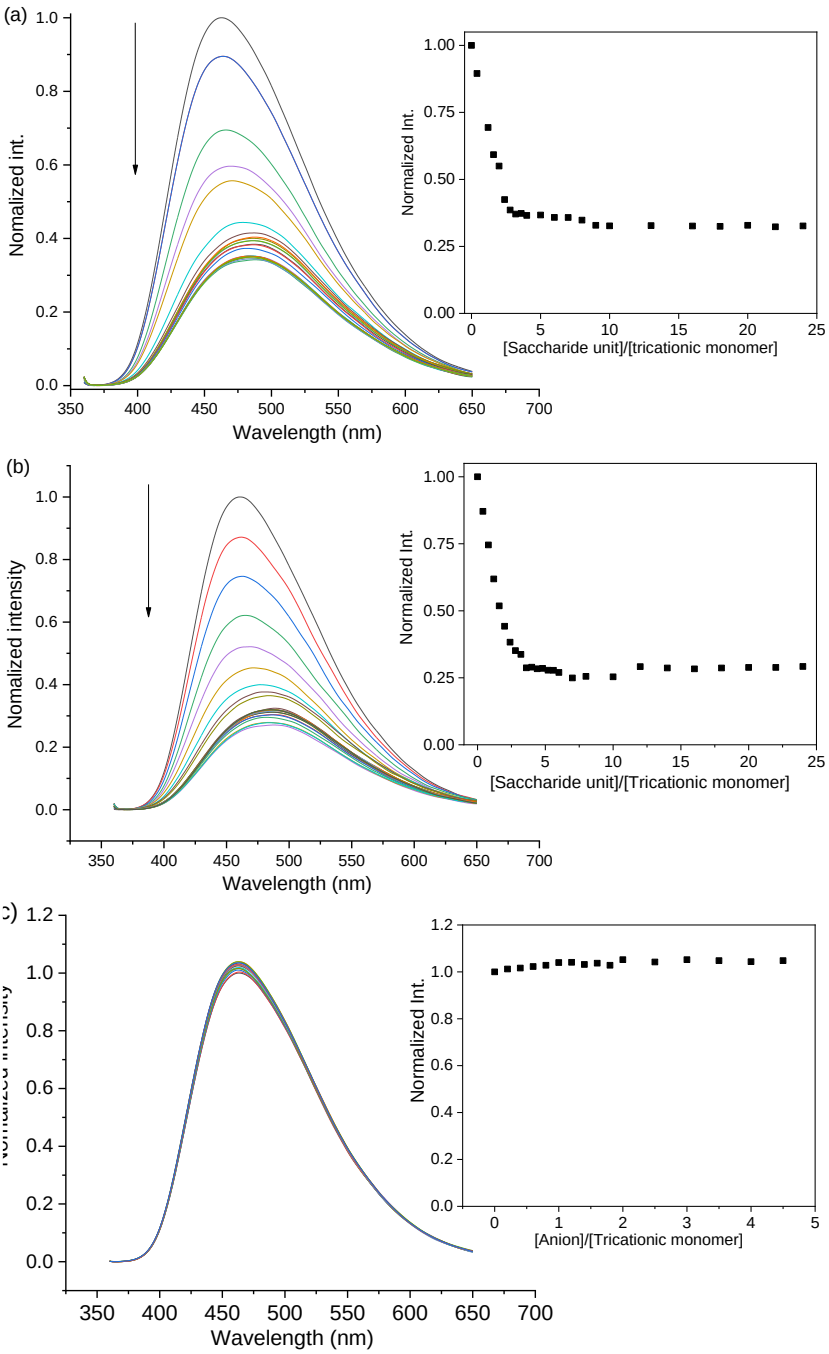


Fig. S22 Fluorescence spectra of the solution of **DCPA$_1$H$_1$** ([Tricatinic monomer] = 5.0 μM) in saline with the addition of UFH ([Saccharide unit] = 0-120 μM), b) Dalte([Saccharide unit] = 0-120 μM), and c) $NaHSO_4$ and NaOAc (3:1, 0-240 μM) in saline. The excitation and emission wavelength were 340 and 460 nm, respectively.

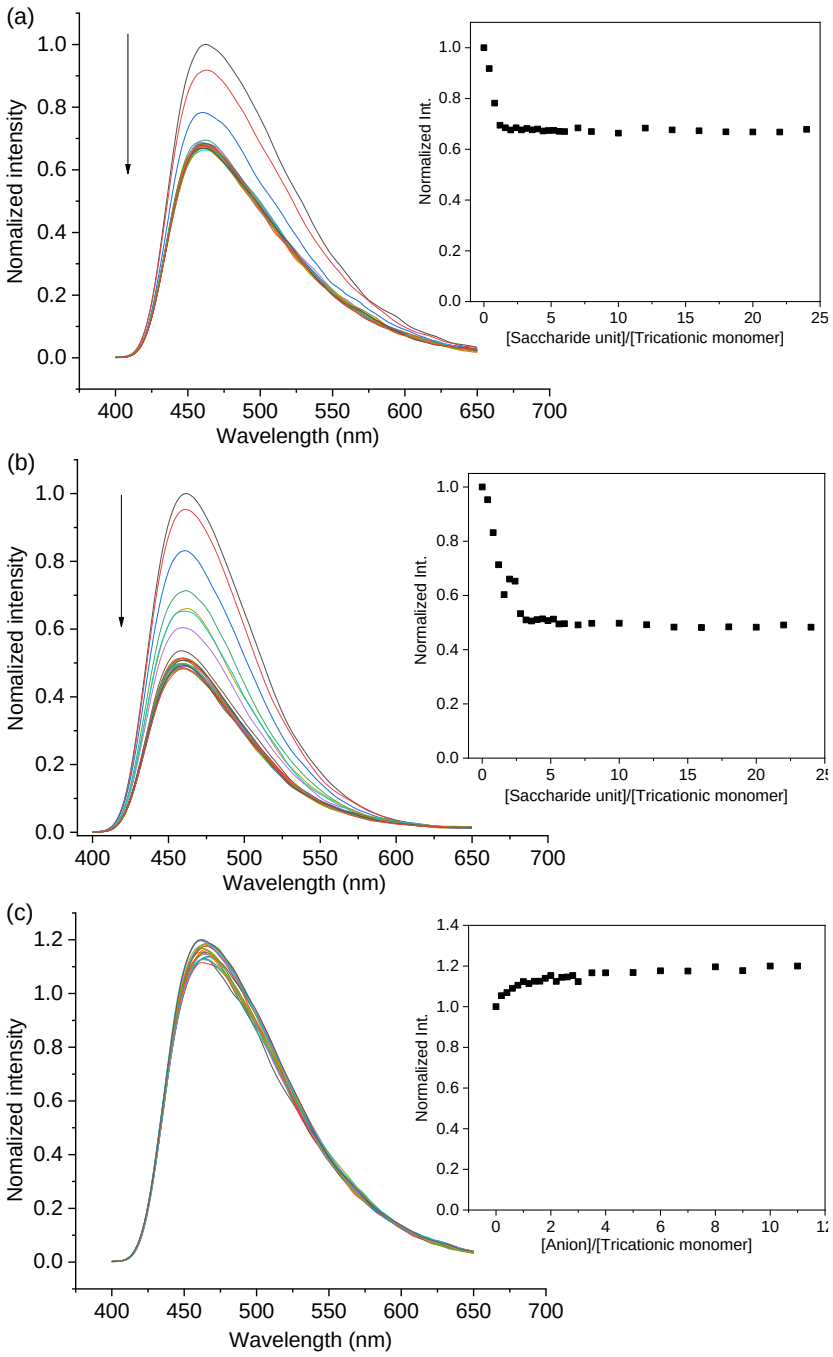


Fig. S23 Fluorescence spectra of the solution of **DCPA$_2$H$_1$** ([Tricatinic monomer] = 5.0 μM) in saline with the addition of UFH ([Saccharide unit] = 0-120 μM), b) Dalte([Saccharide unit] = 0-120 μM), and c) $NaHSO_4$ and NaOAc (3:1, 0-240 μM) in saline. The excitation and emission wavelength was 340 and 460 nm, respectively.

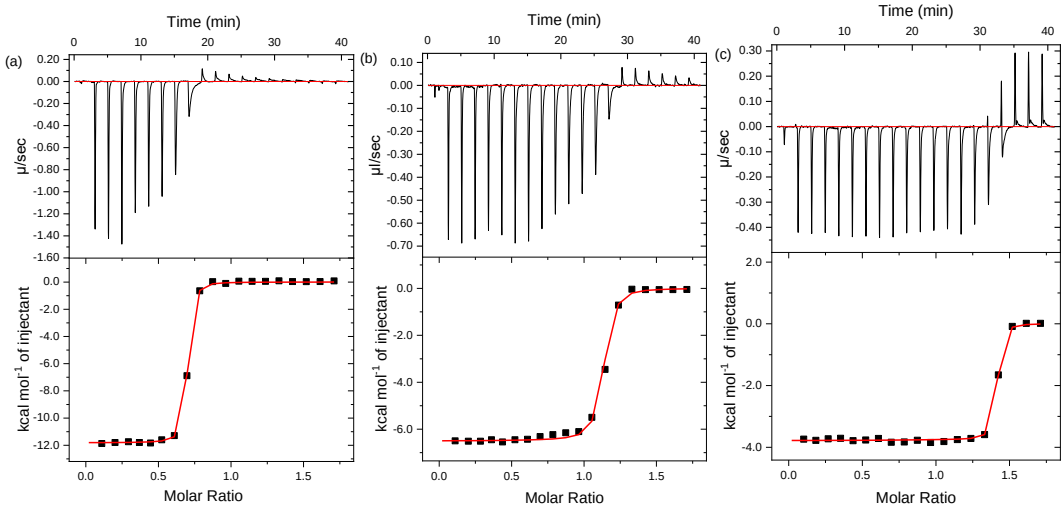


Fig. S24 Isothermal titration thermogram of **DCPA$_1$H$_1$** (0.06 mM) with (a) UHF (0.5 mM), (b) Dalte (0.5 mM) and (c) Enoxa (0.5 mM) in saline at 25 °C.

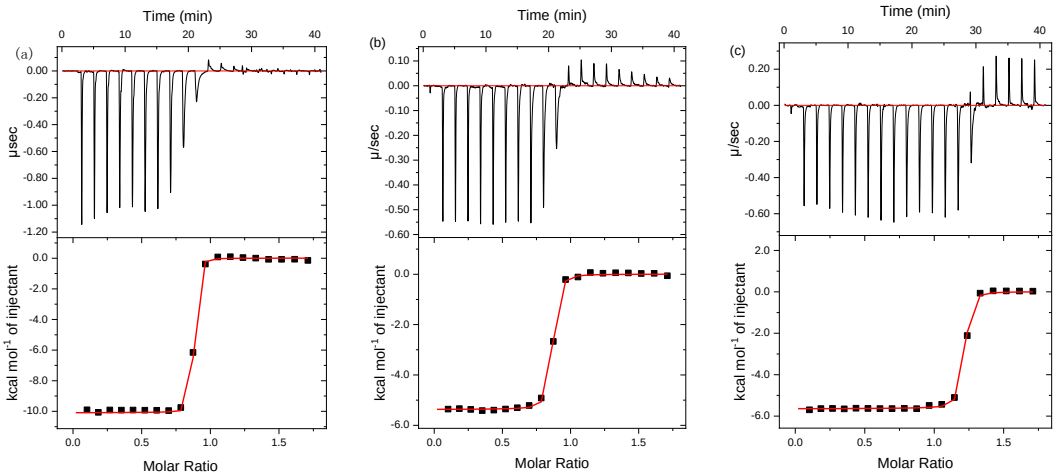


Fig. S25 Isothermal titration thermogram of **DCPA$_2$H$_1$** (0.06 mM) with (a) UHF (0.5 mM), (b) Dalte (0.5 mM) and (c) Enoxa (0.5 mM) in saline at 25 °C.

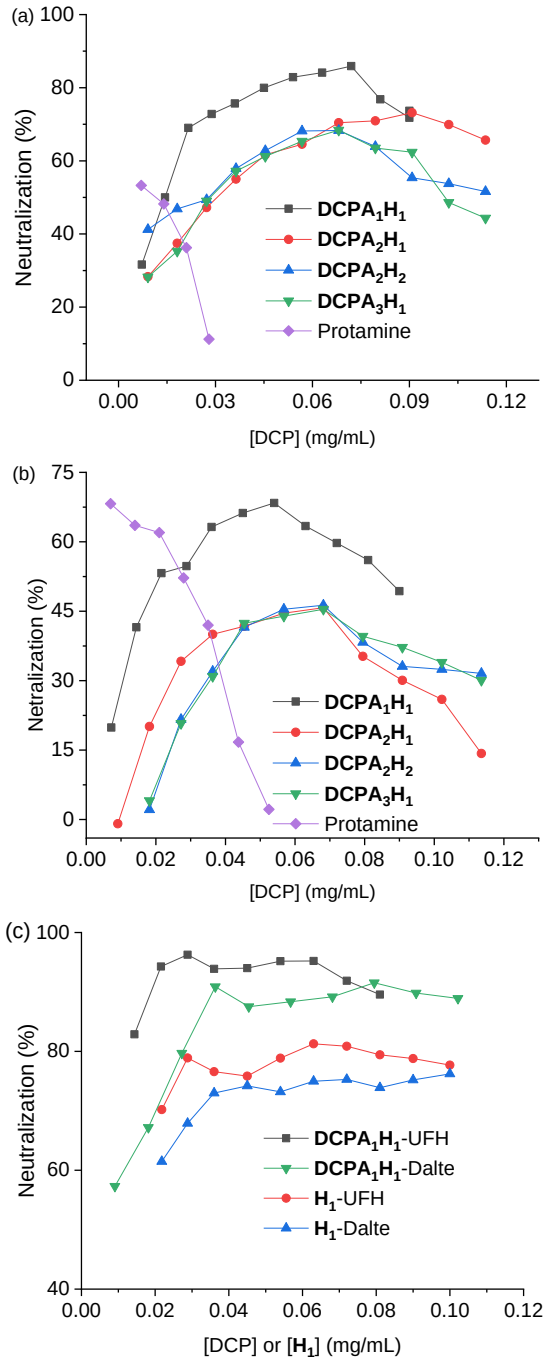


Fig. S26 APTT assays in human plasma for the neutralization of (a) Enoxa (2.0 IU/mL) and (b) Nadro (2.0 IU/mL) by DCPs and protamine of increasing amounts, and (c) UFH (2.0 IU/mL) and Dalte (2.0 IU/mL) by **H_1** of increasing amounts (For comparison, the results of **$DCPA_1H_1$** were also included).

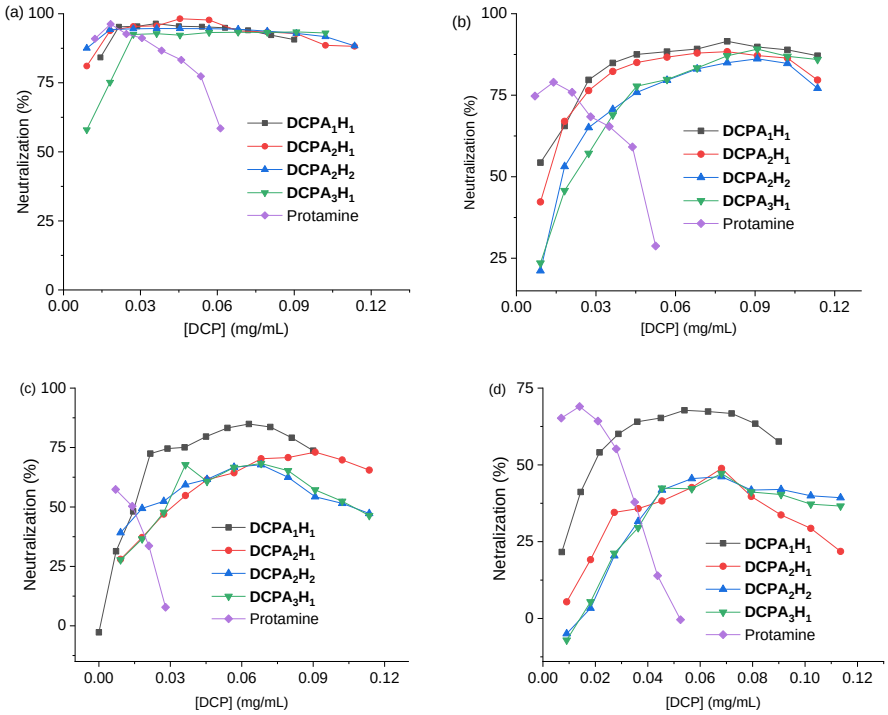


Fig. S27 APTT assays in bovine plasma for the neutralization of (a) UFH (2.0 IU/mL), (b) Dalte (2.0 IU/mL), (c) Enoxa (2.0 IU/mL), and (d) Nadro (2.0 IU/mL) by DCPs and protamine of increasing amounts.

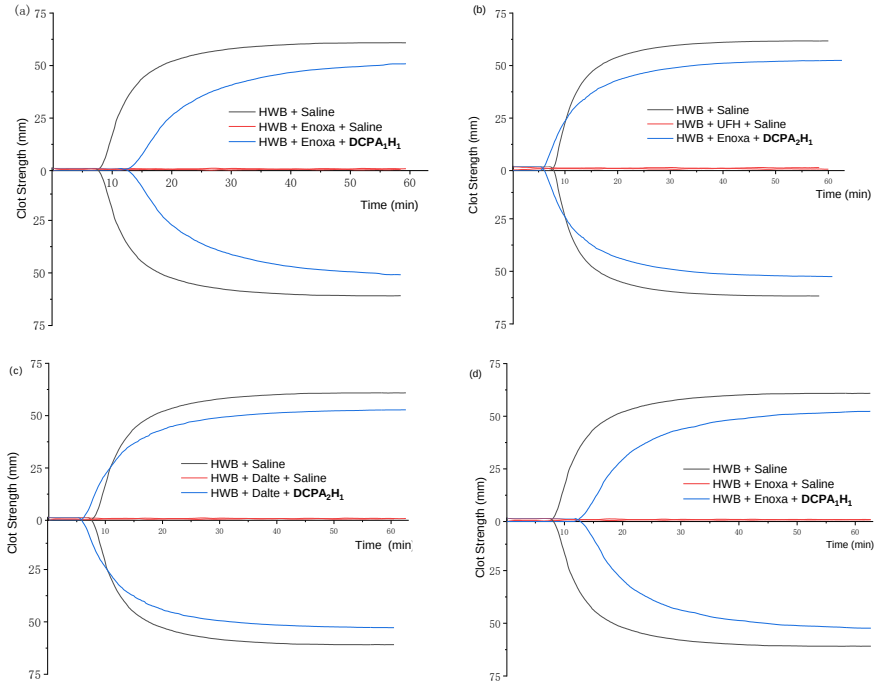


Fig. S28 Thromboelastographic tracings of human whole blood (HWB) for: (a) saline control, Enoxa (2.0 IU/mL) without or with the addition of **DCPA$_1$H$_1$** (0.063 mg/mL), (b) saline control, UFH (2.0 IU/mL) without or with the addition of **DCPA$_2$H$_1$** (0.036 mg/mL), (c) saline control, Dalte (2.0 IU/mL) without or with the addition of **DCPA$_2$H$_1$** (0.045 mg/mL), and (d) saline control, Enoxa (2.0 IU/mL) without or with the addition of **DCPA$_2$H$_1$** (0.090 mg/mL).

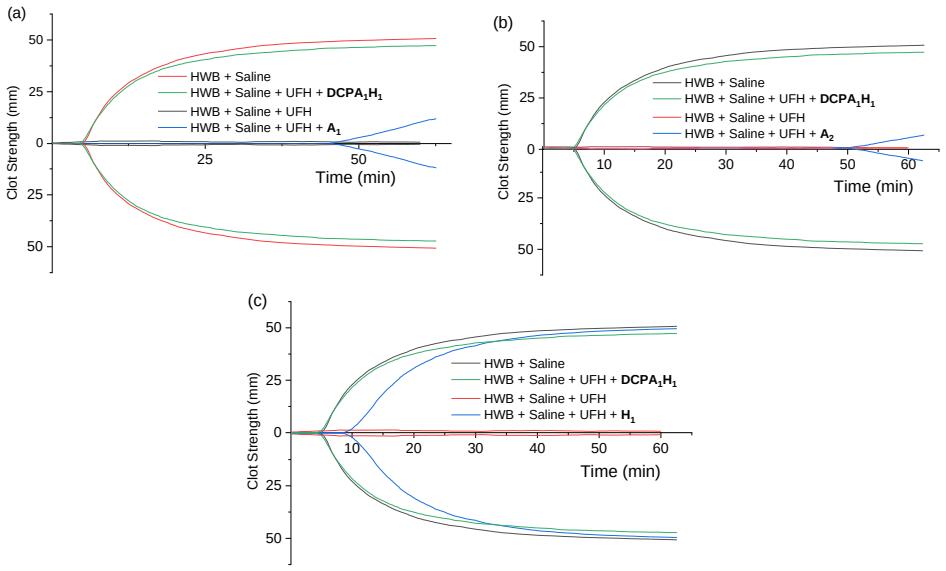


Fig. S29 Thromboelastographic (TEG) tracings of human whole blood (HWB) for (a) saline control, UFH (2.0 IU/mL) without or with the addition of **DCPA$_1$H$_1$** (0.028 mg/mL) or **A$_1$** (0.028 mg/mL), (b) control, UFH (2.0 IU/mL) without or with the addition of **DCPA$_1$H$_1$** (0.028 mg/mL) or **A$_2$** (0.028 mg/mL), and (c) saline control, UFH (2.0 IU/mL) without or with the addition of **DCPA$_1$H$_1$** (0.028 mg/mL) or **H$_1$** (0.028 mg/mL).

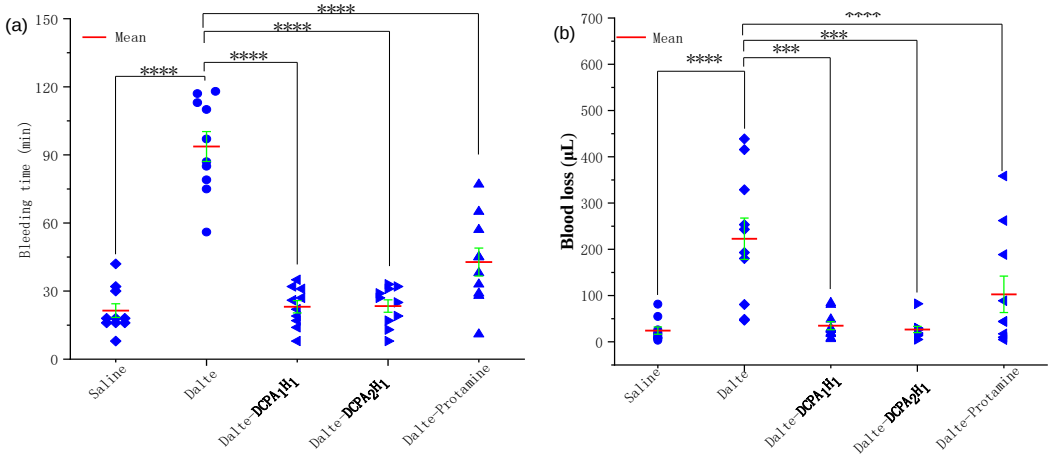


Fig. S30 *In vivo* heparin neutralization via tail bleeding model in ICR mice: (a) Total time of bleeding and (b) blood loss volume. All the models were two-time intravenous administration successively via tail intravenous vein, with the first injection of saline (normal control) or Dalte (200 IU/kg) at t = 0 min, followed by saline, **DCPA$_1$H$_1$** (2.8 mg/kg), **DCPA$_2$H$_1$** (3.6 mg/kg) or protamine (2.6 mg/kg) at t = 5 min. The mouse was anesthetized with isoflurane before tail cutting. The distal 2.5 mm of the mouse tail was transfected at t = 10 min, and then blood bleeding time and blood loss were recorded. Data presented are the mean ± S.E.M. (n = 10, 5 male and 5 female). *p < 0.05, ****p < 0.001.

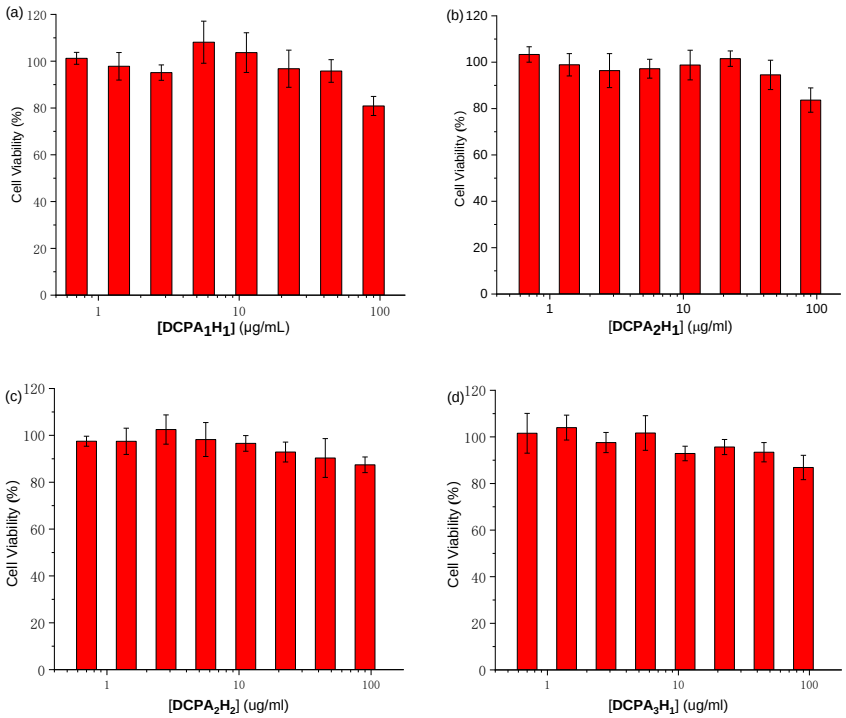


Fig. S31 CCK-8 proliferation tests for viability values (%) of H9C2 cell lines versus the incubation concentration of **DCPA$_1$H$_1$**, **DCPA$_2$H$_1$**, **DCPA$_2$H$_2$**, and **DCPA$_3$H$_1$**, which equaled to that of the precursors (1:1). The cells (2×10^4 per well) were incubated with the DCPs at 37 °C for 24 h. Error bars represent the s.d. of uncertainty for each point.

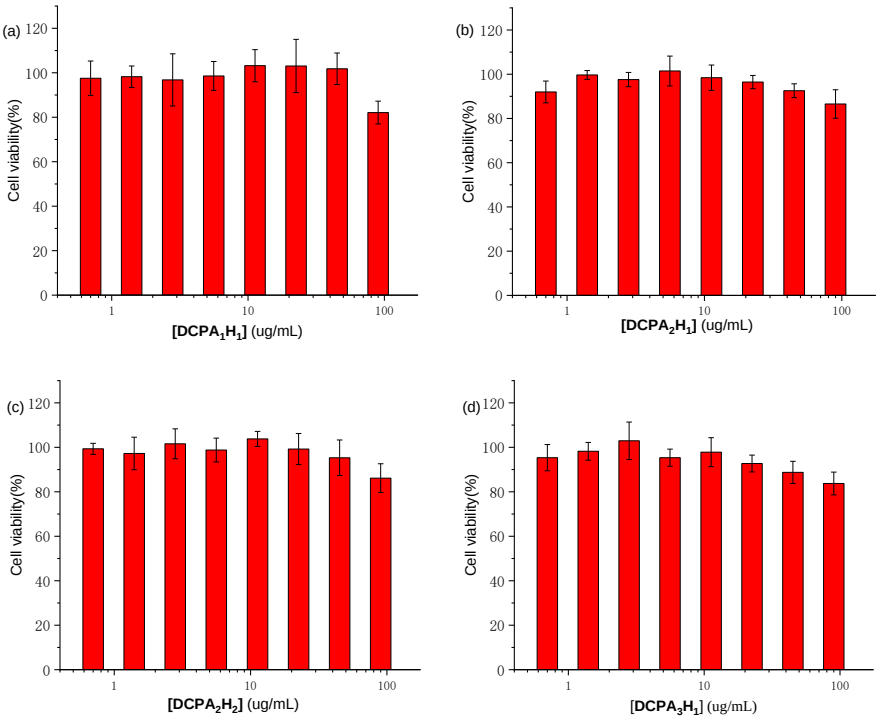


Fig. S32 CCK-8 proliferation tests for viability values (%) of L02 cell lines versus the incubation concentration of **DCPA$_1$H$_1$**, **DCPA$_2$H$_1$**, **DCPA$_2$H$_2$**, and **DCPA$_3$H$_1$**, which equaled to that of the precursors (1:1). The cells (2×10^4 per well) were incubated with the DCPs at 37 °C for 24 h. Error bars represent the s.d. of uncertainty for each point.

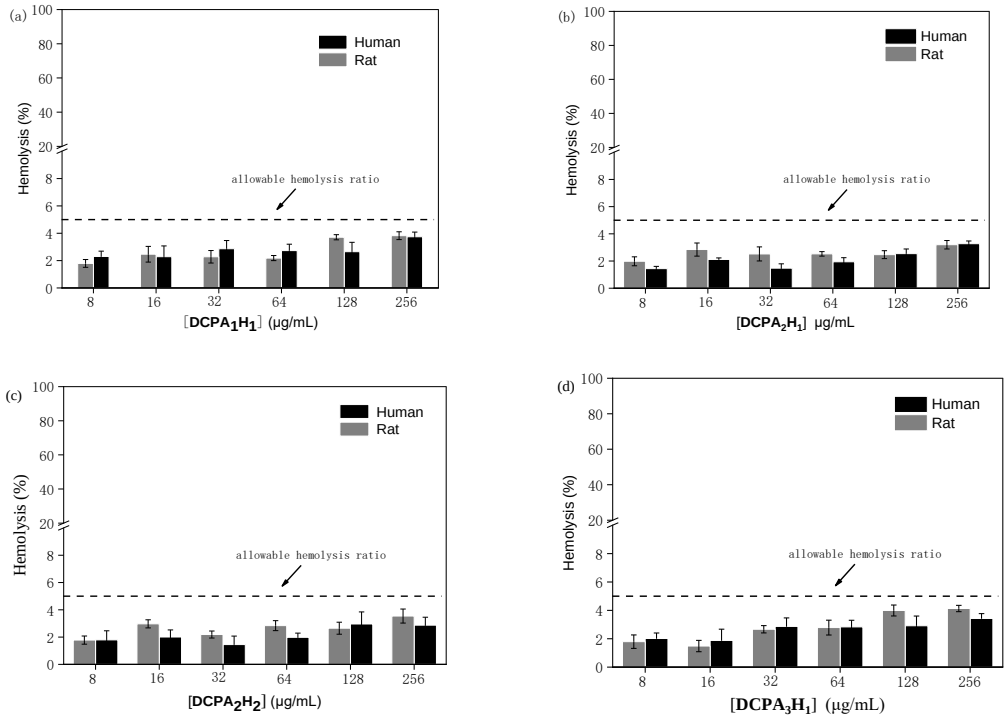


Fig. S33 Hemolytic activity of SD rat erythrocyte and human O-type erythrocyte treated with **DCPA$_1$H$_1$**, **DCPA$_2$H$_1$**, **DCPA$_2$H$_2$** and **DCPA$_3$H$_1$** of increasing concentrations, which were equal to that of their 1:1 precursors.

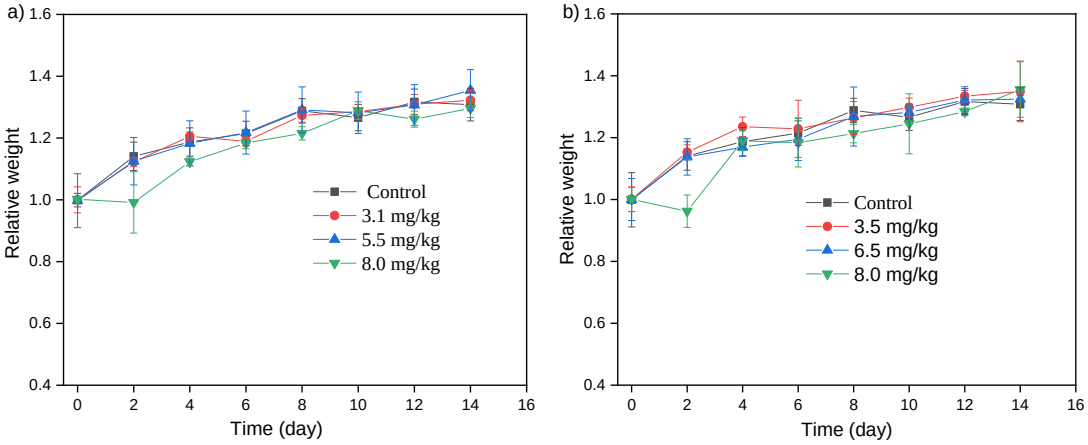


Fig. S34 Weight changes of mice (n = 6, 3 male and 3 female) versus time after iv administration of (a) **DCPA$_1$H$_1$** and (b) **DCPA$_2$H$_1$** of the indicated dose.

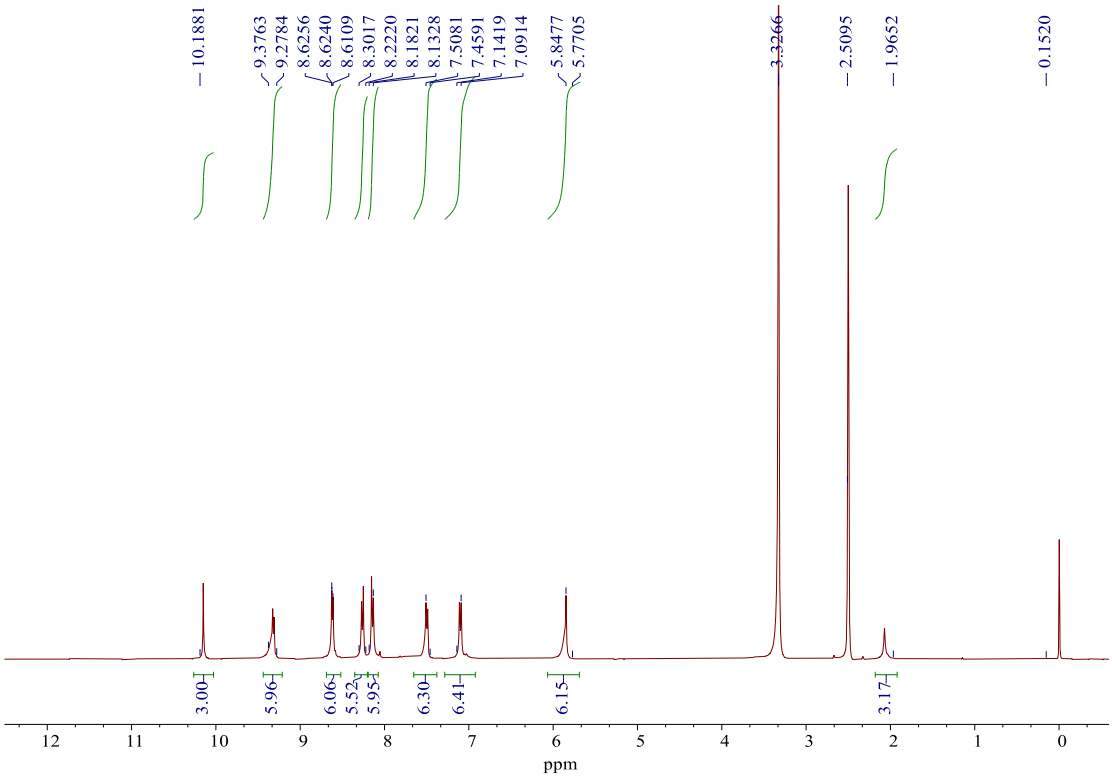


Figure S35 ^{1}H NMR spectra (400 MHz, DMSO-d_6) recorded for compound **A2**.

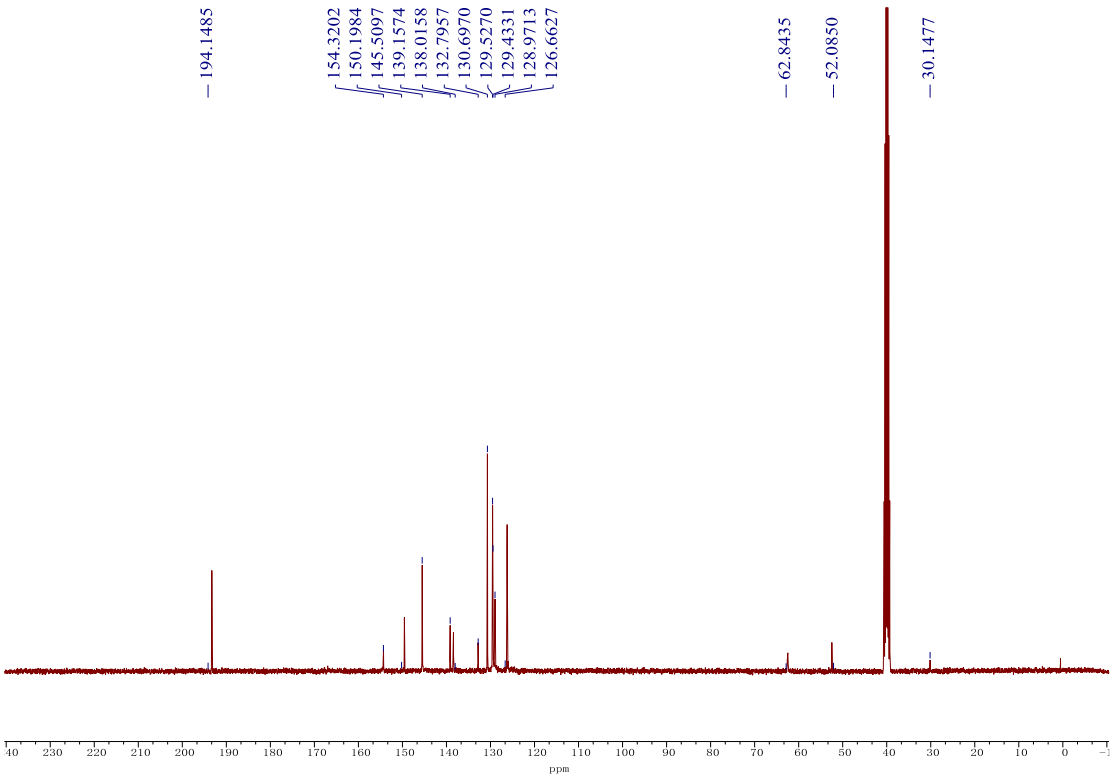


Figure S36 ^{13}C NMR spectra (100 MHz, DMSO-d_6) recorded for compound **A2**.

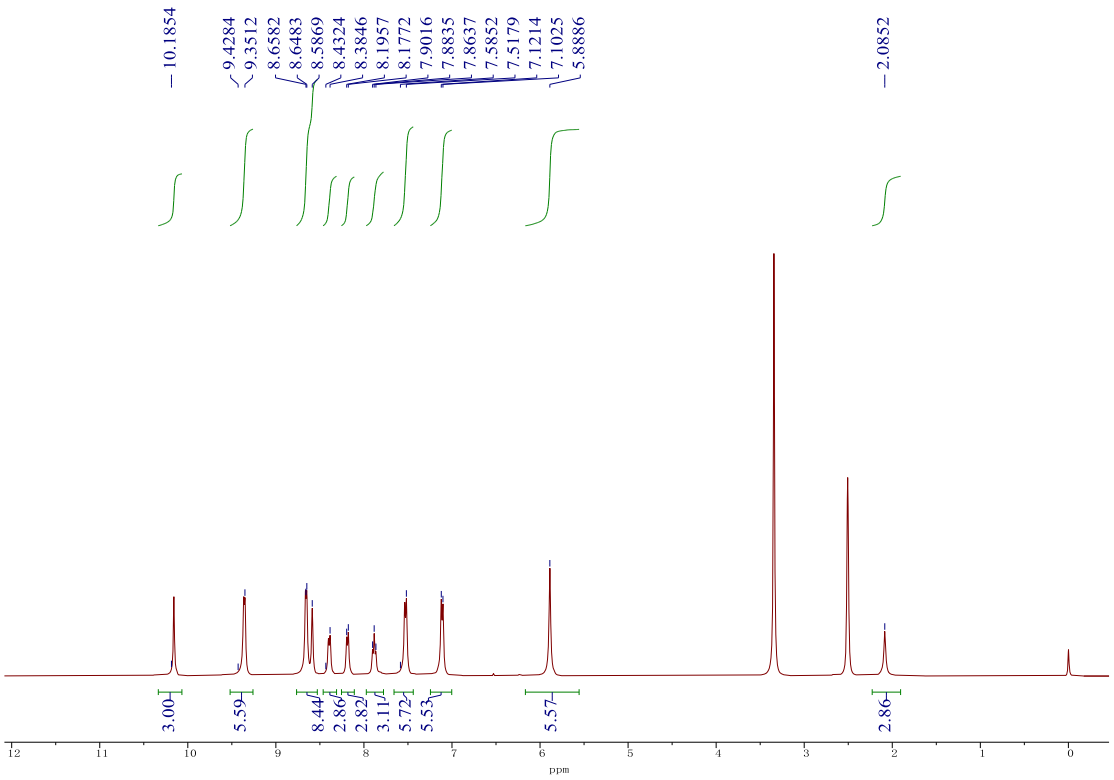


Figure S37 ^{1}H NMR spectra (400 MHz, DMSO-d_6) recorded for compound **A3**.

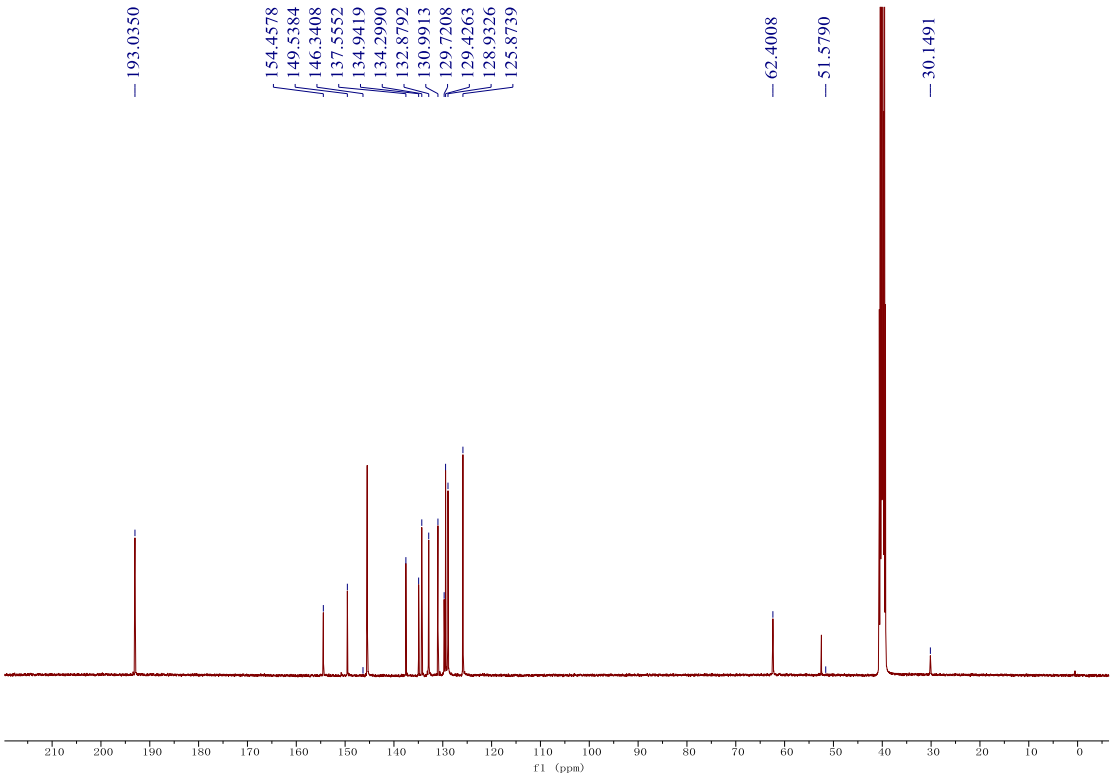


Figure S38 ^{13}C NMR spectra (100 MHz, DMSO-d_6) recorded for compound **A3**.

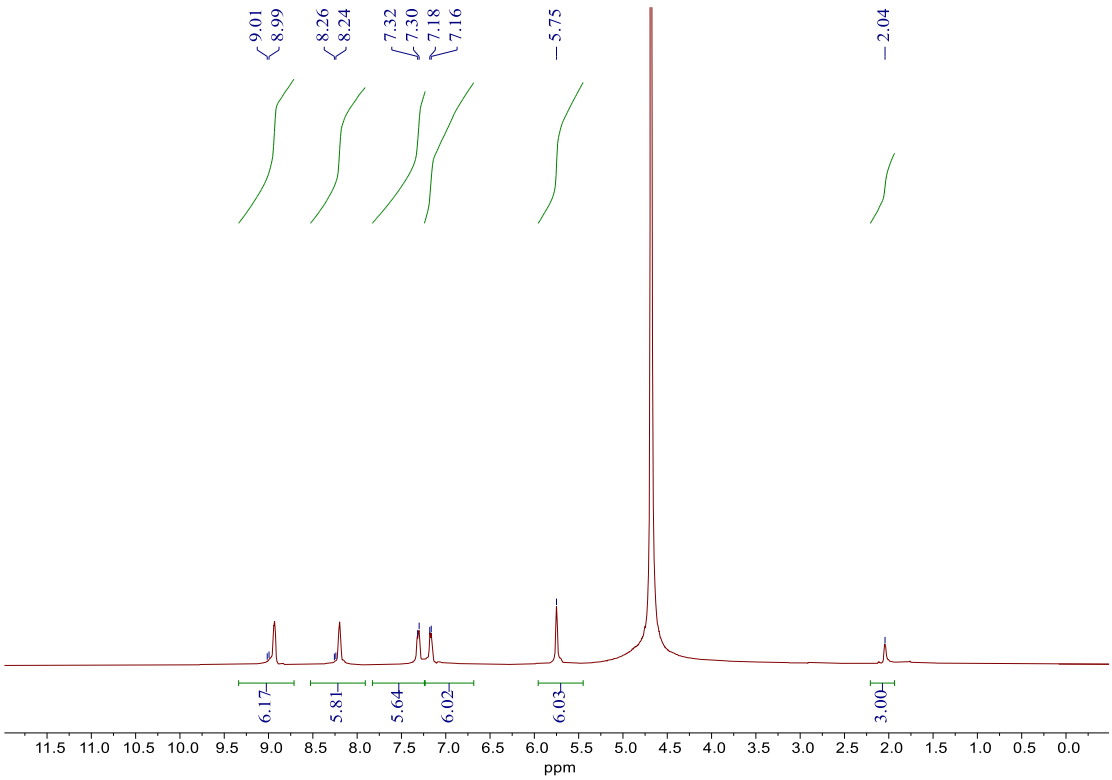
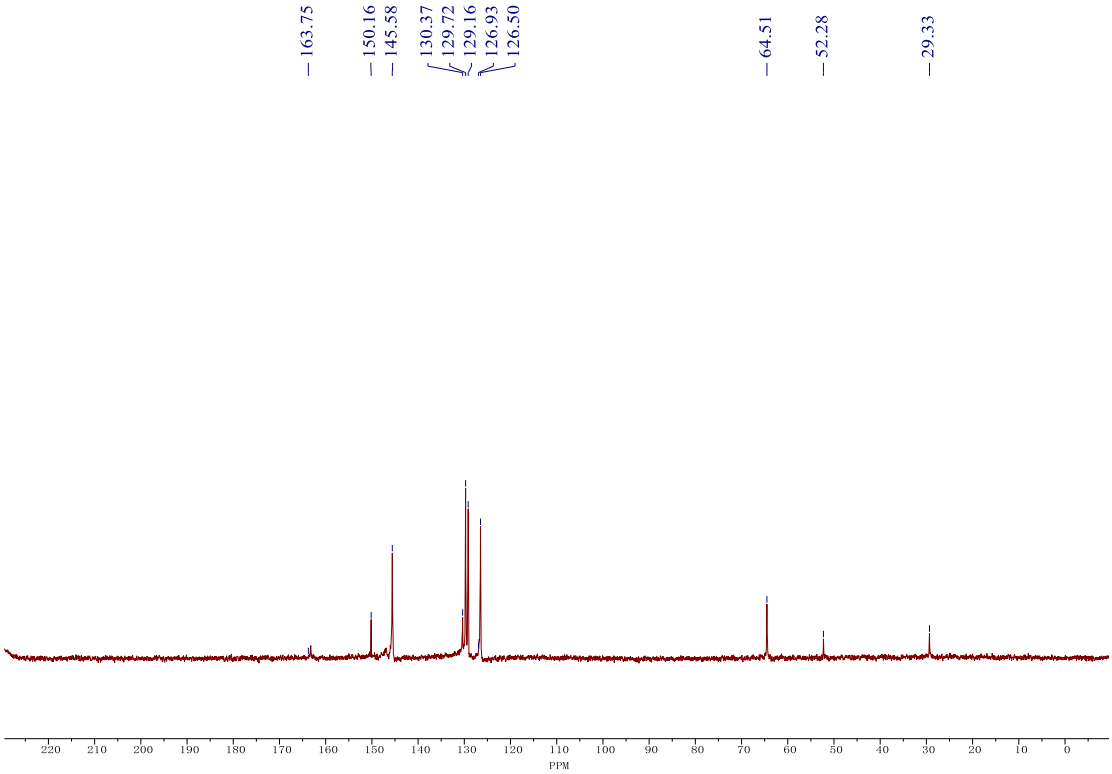


Figure S39 ^{1}H NMR spectra (400 MHz, D_2O) recorded for compound **H_1**.



Figurg S40 ^{13}C NMR spectra (100 MHz, D_2O) recorded for compound **H_1.**

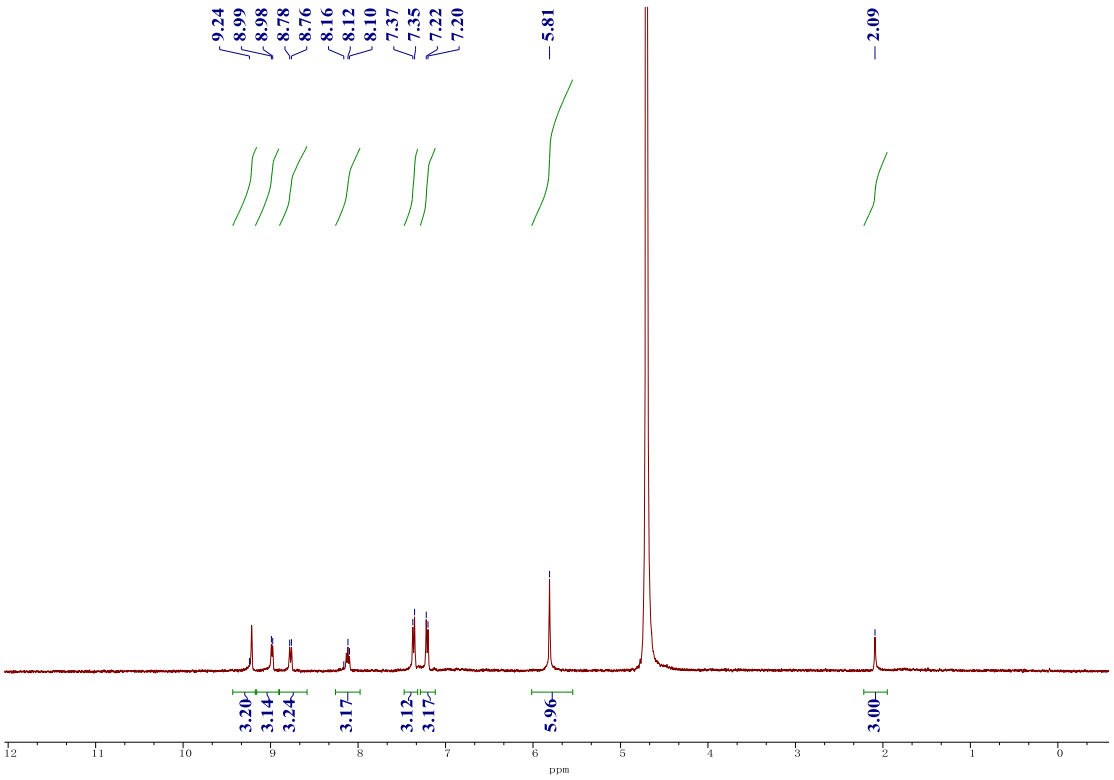


Figure S41 ^{1}H NMR spectra (400 MHz, D_2O) recorded for compound **H2**.

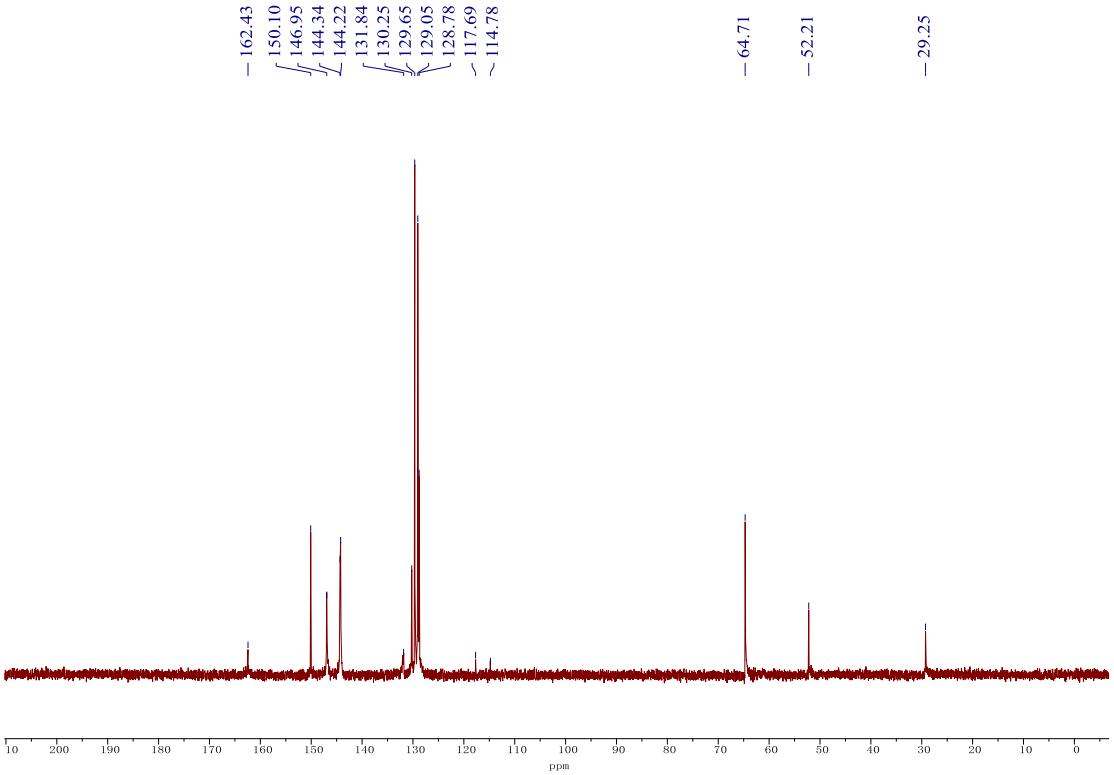


Figure S42 ^{13}C NMR spectra (100 MHz, D_2O, r.t.) recorded for compound **H2**.

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(1) Y.-Y. Xu, H.-K. Liu, Z.-K. Wang, B. Song, D.-W. Zhang, H. Wang, Z. Li, X. Li, Z.-T. Li, Olive-Shaped Organic Cages: Synthesis and Remarkable Promotion of

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(2) G. M. Lu, F. R. DeGuzman, S. J. Hollenbach, M. J. Karbarz, K. Abe, G. Lee, P. Luan, A. Hutchaleelaha, M. Inagaki, P. B. Conley, D. R. Phillips and U. Sinha, A Specific Antidote for Reversal of Anticoagulation by Direct and Indirect Inhibitors of Coagulation Factor Xa. *Nat. Med.*, 2013, **19**, 446-451.