Supporting Information

Materials and general methods:

Chemicals materials: Curcumin were purchased from Aladdin. Glutaric anhydride was come from Alfa Aesar. O-(Benzotriazol-1-yl)-N,N,N',N'–tetramethyluronium hexafluorophosphate(HBTU) and Fmoc-amino acids were obtained from GL Biochem (Shanghai). Chemical reagents and solvents were used as received from commercial sources. Commercially available reagents and solvents were used without further purification, unless noted otherwise.

General methods: ^{1}H NMR (Bruker ARX 400) was used to characterize the synthesized compounds. Drug release of succinated dexamethasone was carried out by a LCMS-20AD (Shimadzu) system. TEM was performed at the Tecnai G2 F20 system, operating at 100 kV. Rheology test was done on an AR 2000ex (TA instrument) system, 40 mm parallel plates was used during the experiment at the gap of 500 μm. All live animals' experimental procedures were conducted in conformity with institutional guidelines for the care and use of laboratory animals, and protocols were approved by the Institutional Animal Care and Use Committee in College of life sciences, Nankai University, China.

Preparation of peptide: Peptide of FFEssERGD were prepared by standard Fmoc solid-phase peptide synthesis (SPPS) by using 2-chlorotrityl chloride resin and the corresponding N-Fmoc protected amino acids with side chains properly protected. The first amino acid was loaded on the resin at the C-terminal with the loading efficiency about 1.4 mmol/g. 20% piperidine in anhydrous N,N'-dimethylf ormamide (DMF) was used to remove Fmoc group. To couple the next Fmoc-protected amino acid to the free amino group, O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluron ium-hexafluorophosphate (HBTU) was used as the coupling reagent. The peptide chain was entended according to the standard Fmoc SPPS protocol. After the last coupling step, excessive reagents were removed through five times of DMF wash for 1 min, followed by five times of washing using dichloromethane (DCM) for 1 min. To cleave the peptide derivatives from the resin, ice-cold 95% TFA was used and the mixture was stirred, filtered at room temperature, and finally poured into ice-cold diethylether, successively. The resulting precipitate was centrifuged for 10 min at 3℃ at a speed of 10,000 rpm. Afterward decanting the supernatant and the solid was dried by vacuum pump.

Preparation of Curcumin Glutaric acid (Cur-GA): Curcumin (1.107 g, 3 mmol) and Glutaric anhydride (0.353 g, 3.1 mmol) were dissolved in pyridine (23 mL), and the resulting solution was stirred at room temperature for 7 h. The solution was then removed and the crude product was re-dissolved in ethylacetate (100 mL), and then washed with 1 M HCl (30 mL) to remove pyridine. This process was repeated for three times. The ethyl acetate was removed under vacuum to get the crude product. The product was purified *via* silica gel column chromatography, eluted with DCM:Methanol (99:1, v/v) (yield 49.2%).

Preparation of pro-gelator: 0.15 mmol of peptide and 48.3 mg of Curcumin

Glutaric acid N-Hydroxysuccinimide (NHS) active ester (0.1 mmol) were dissolved in 3 mL of DMF, 41.25 μL of diisopropylethylamine (DIPEA, 0.25 mmol) was then added. The resulting reaction mixture was stirred at room temperature overnight. The progelators were obtained by HPLC (yields of 30-40%).

Characterization of the conjugates: ^{1}H NMR (400 MHz, DMSO) δ 8.19 (d, *J* = 7.8 Hz, 2H), 8.14-7.94 (m, 9H), 7.63 – 7.56 (m, 3H), 7.49 (t, *J* = 3.9 Hz, 1H), 7.34 (s, 4H), 7.27 – 7.14 (m, 17H), 7.09 (s, 3H), 6.86 – 6.80 (m, 2H), 6.14 (s, 1H), 4.58-4.50 m, 4H), 4.28 – 4.20 (m, 4H), 3.83 (d, *J* = 8.0 Hz, 6H), 2.89 (s, 2H), 2.79 – 2.71 (m, 7H), 2.67 (s, 2H), 2.61 (dd, *J* = 8.6, 2.5 Hz, 2H), 2.40 – 2.31 (m, 8H), 2.28 – 2.20 (m, 5H), 2.16 – 2.10 (m, 3H), 1.31 – 1.23 (m, 3H). MS: calc. M^+ =1596.5789, obsvd. $(M+H)^+$ =1597.5849.

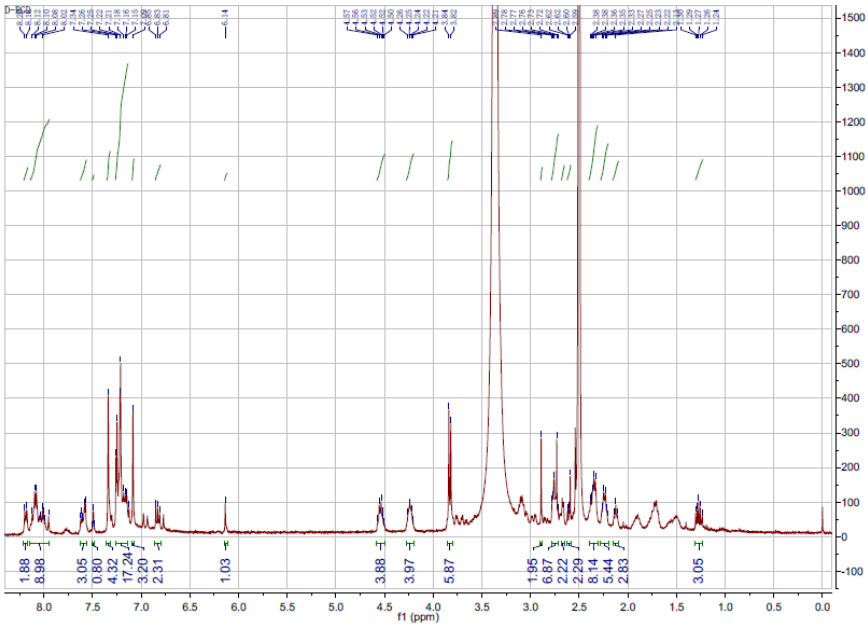

Fig. S-1. ^{1}H NMR of Cur-FFEssERGD

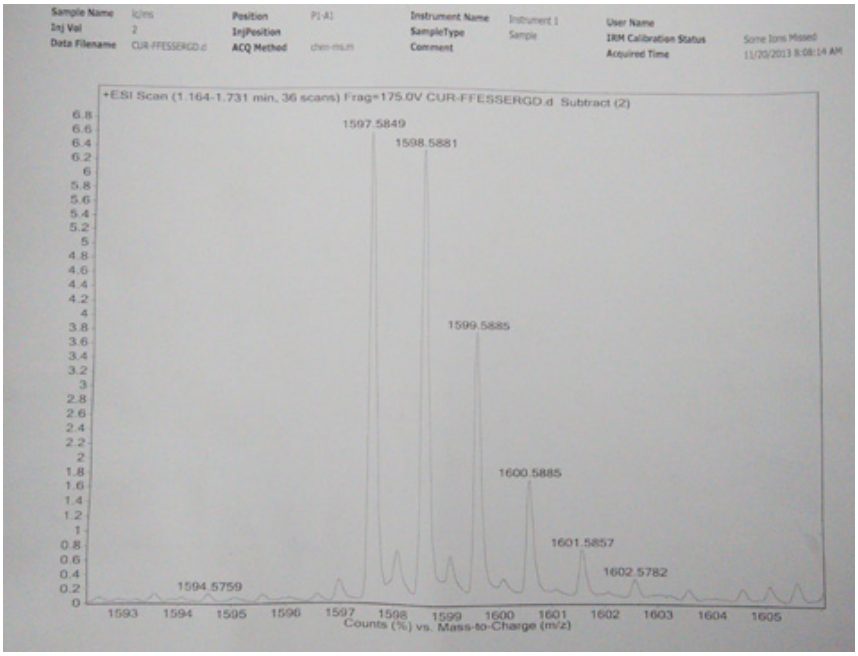

Fig. S-2. HR-MS of Cur-FFEssERGD

Formation of hydrogel: 1 mg of compond was dissolved in 0.1 mL of PBS buffer solution containing 7 equiv. of Na_2CO_3 (3 equiv. of Na_2CO_3 were used to neutralize the compounds and the additional 4 equiv. of Na_2CO_3 were used to neutralize GSH to make the final pH value to 7.4). And then 0.1 mL of PBS buffer solution containing 4 equiv. of GSH was added. Gels would form after being kept at 37℃ for 1.5h.

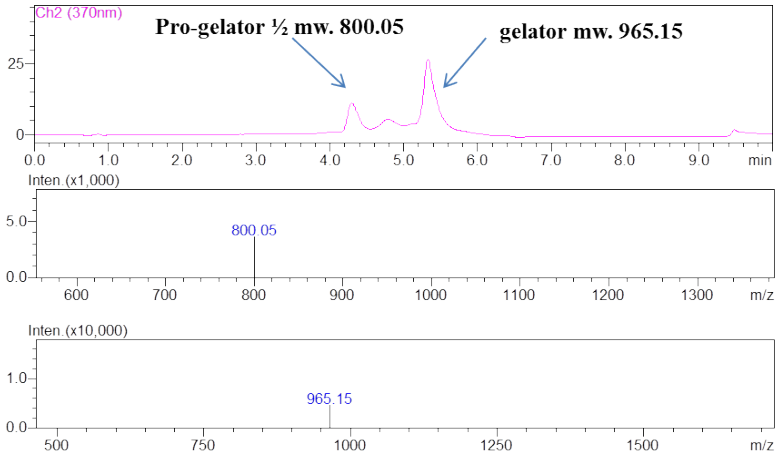

Fig. S-3. The LC-MS of component at the time point of hydrogel formation

Drug release: A hydrogel was formed from PBS (PH=7.4) solutions containing 0.5 wt% of progelator in EP tube at 37^0C. 0.25 mL of PBS was added on the surface of the hydrogels, we took out 0.2 mL solution at the desired time point and 0.2 mL PBS

was added back. For the following time points, 0.2 mL of PBS was taken out and 0.2 mL of PBS was added back at each point. After 24 h, We then monitored the release profile from the gel formed at 24 h at 37 ^{0}C by a LCMS-20AD (Shimadzu) system.

Rheology: Rheology test was carried out on an AR 2000ex (TA instrument) system, 40 mm parallel plates was used during the experiment at the gap of 500μm. For the dynamic time sweep, the solution of compounds were directly transferred to the rheometer and it was conducted at the frequency of 1 rad/s and the strain of 1% immediately. The gels were also characterized by the mode of dynamic frequency sweep in the region of 0.1-100 rad/s at the strain of 1%. A dynamic strain sweep at the frequency of 1 rad s^{-1} was conducted finally.

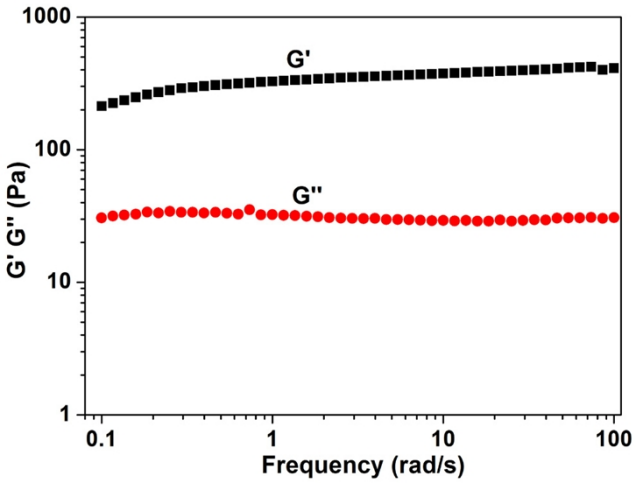

Fig. S-4. Dynamic frequency sweep at the strain of 1% at 37℃

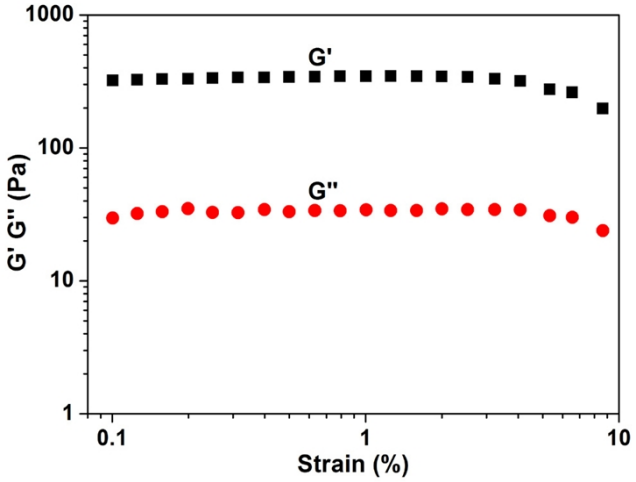

Fig. S-5. strain at the frequency of 1 rad/s at 37℃

Determination of IC_{50} values of the compounds: The IC_{50} values of curcumin,

prodrug, formed nanofibers were evaluated by the MTT assay. The HepG2, MCF-7 and Hela cells were seeded in 96-well plates at a density of 2,000 cells per well with a total medium volume of 200 μL and incubated for 24 hours. Then removed the media and 200 μL of the solutions containing a serial of concentrations of the above four compounds were added into the cells. 72 hours later, we replaced the medium with fresh medium supplemented with 5 μL MTT reagent (5 mg/mL). After 4 hours, the medium containing MTT was removed and DMSO (100 μL/well) was added to dissolve the formazan crystals. Using a microplate reader (Bio-RAD iMarkTM, America) to measure the optical density of the solution at 597 nm. Cells without any treatment were used as the control. The cell viability percent was calculated according to the following formula:

The cell viability percent (%) = ODsample/ODcontrol *100%

The concentrations of the compounds when 50% of cell viability was recorded.

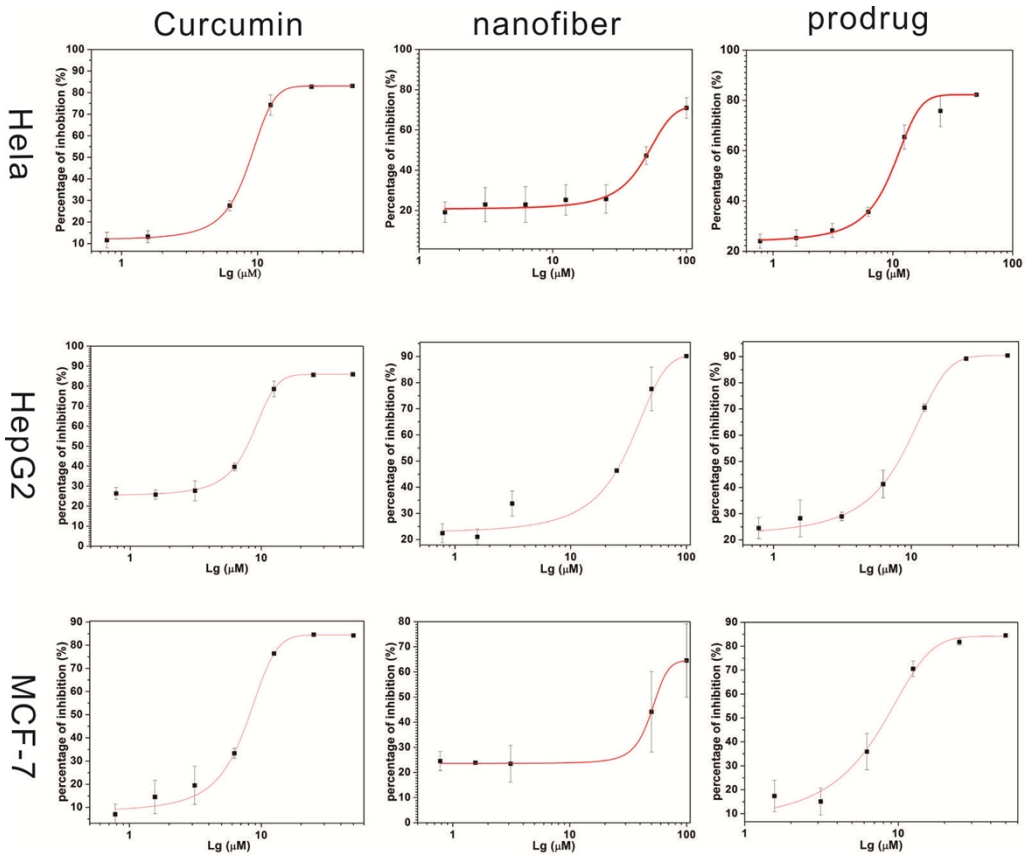

Fig. S-6. IC_{50} of compounds

Laser Scanning Confocal Microscopy for Imaging: After being incubated for 24 h in 24-well plates at a density of 10000 cells per well, MCF-7 cells was treated with 1 mL of DMEM solution containing 25 μM of curcumin contained prodrug and formed nanofibers. The medium was removed and washed three times with fresh PBS ahead of being recored. The images were recorded under the same detected conditions (excitation wavelength = 488 nm) after incubating for 4h. And then the samples were dyed with Dapi for 3 min. This part of the experiment was carried out by using a laser

scanning confocal microscope (OLYMPUS FV1000S-IX81).

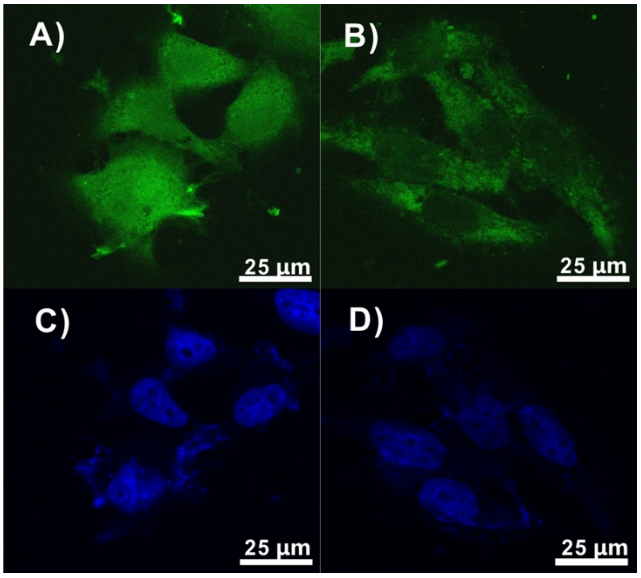

Fig. S-7. Confocal fluorescence microscopy images of MCF-7 cells treated with A) the pro-gelator and B) the formed nanofiber at 4 h time point containing 25 µM curcumin (excitation wavelength = 488 nm), C) and D) 1 µg/mL Dapi at 3min time point (excitation wavelength = 405 nm)

Determination of Peptide Concentration in Hela, HepG2 and MCF-7 Cells by LC−MS: Hela, HepG2 and MCF-7 cells were incubated in 24-well plates at a density of 1×10^6 cells per well for 24 h. The different solution containing 25 µM of Curcumin contained prodrug and the formed nanofibers were prepared in DMEM with 10% FBS respectively. And then 1mL of the solution were added to cells and the cells were then incubated at 37°C for 4h. The DMEM containing drugs was removed and cells were washed 3 times with fresh PBS. 500 µL of DMSO was added to each well to dissolve compounds in cells. The solutions were collected and centrifuged at 1570g for 15 min after treated with sonication for 15 min. The amount of compounds in the cells was determined by LC−MS.

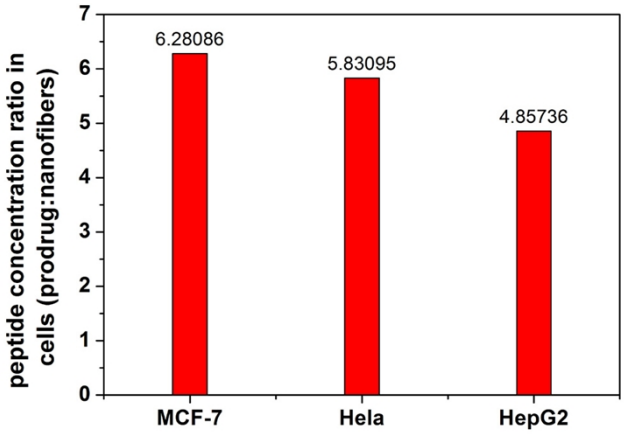

Fig. S-8. peptide concentration ratio in cells

Tumor inhibition assay: Aiming to build breast tumor model, we inoculated Female Balb/c mice with 1×10^5 4T1-luciferase cells in the mammary fat pad. The tumor growth was monitored every other day. Tumor volume was recieved through calculating by the formula: length × width × (Length + Width)/2. When tumors size reached ~13 mm^3, mice were randomly divided into different treatment groups. The day of giving drugs was designated as day 0. Mice weight was also monitored after receiving treatment.

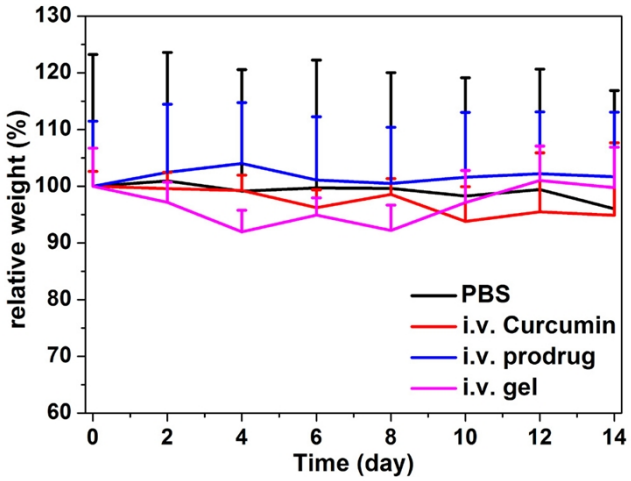

Fig. S-9. In vivo toxicity performance of our hydrogels at different dosages compared with PBS and curcumin

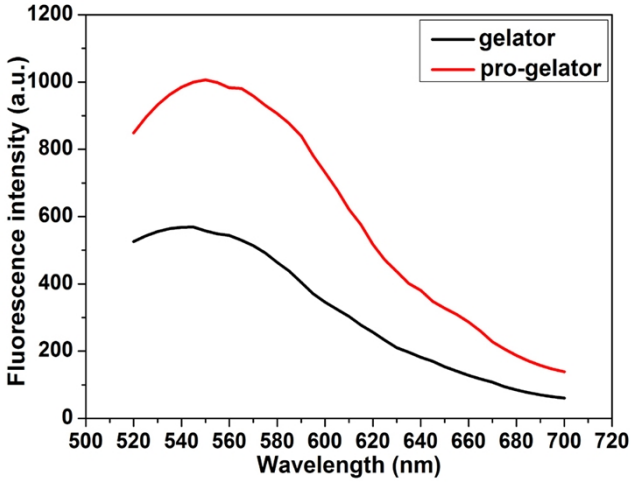

Fig. S-10. Emission spectra of solutions of pro-gelator and gelator at 25 μM excited at 488 nm (the result indicated the phenomenon of aggregation caused quenching)

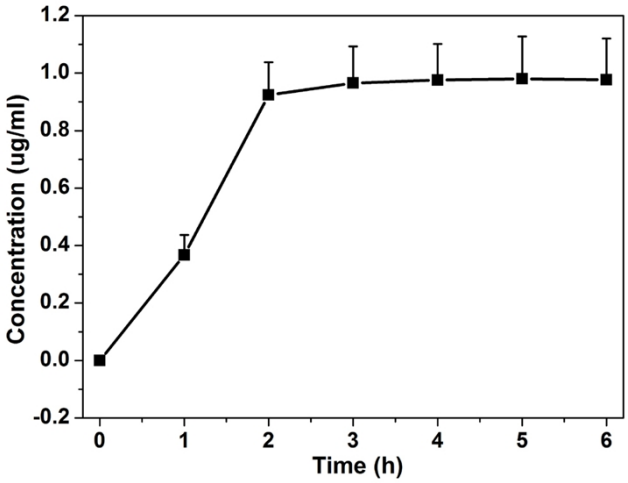

Fig. S-11. Accumulating release amount of Cur from the gel formed from PBS buffer containing 0.5 wt % of pro-gelator and 4 equiv. of GSH (A 0.25 mL of PBS was added on top of 0.25 mL of gel and the concentration of Cur in the upper 0.25 mL PBS was determined at different time points)

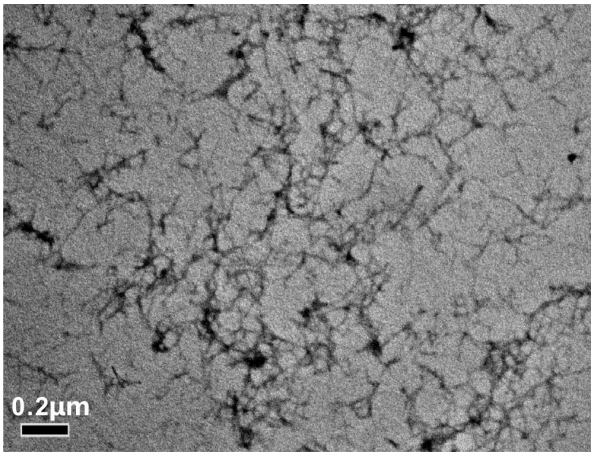

Fig. S-12. A TEM image of the solution containing 25 μM of gelator (the result indicated the presence of nanofiber at this concentration)

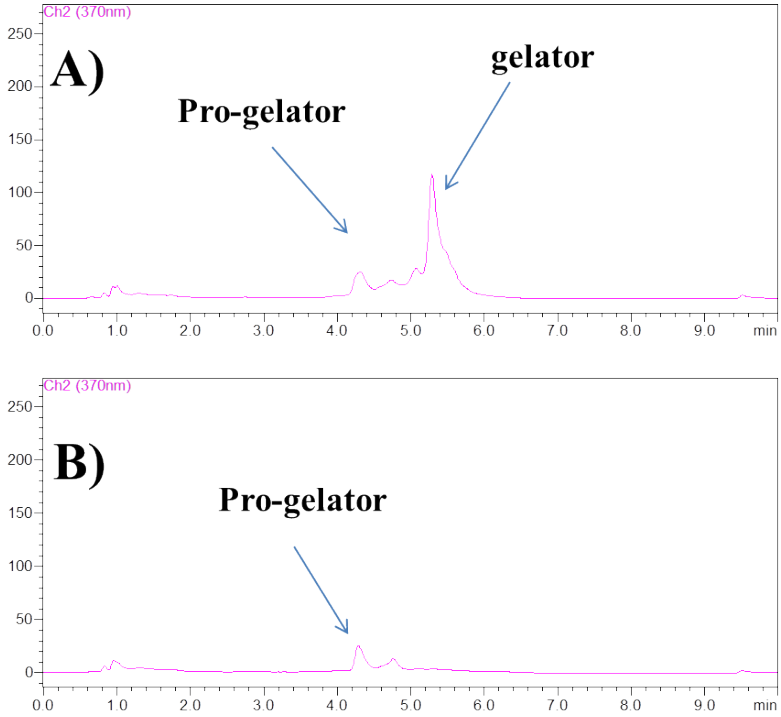

Fig. S-13. The LC-MS traces of cellular drug derivatives when treated with A) the formed nanofibers and B) pro-gelator