Supporting Information

A dual-functional benzobisthiadiazole derivative as an effective theranostic agent for near-infrared photoacoustic imaging and photothermal therapy

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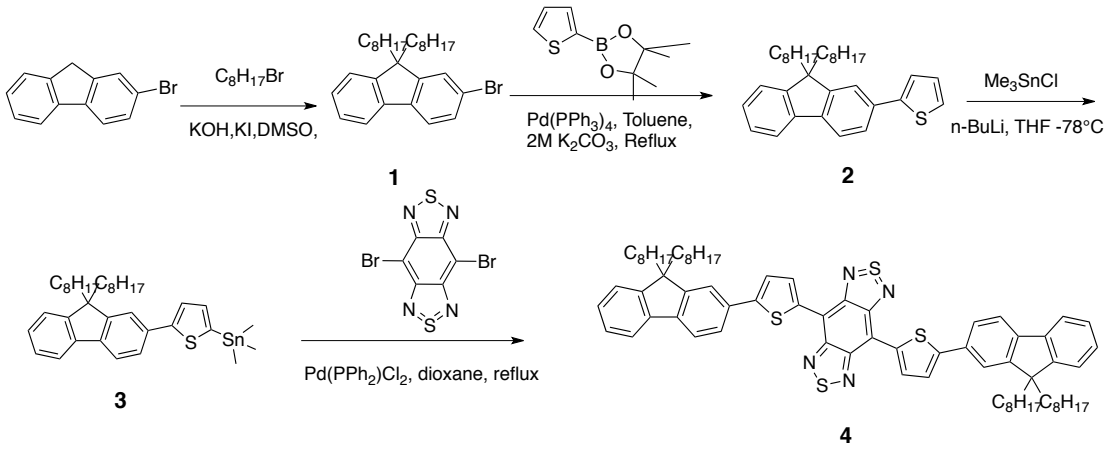
Supplementary Methods



Scheme 1. Synthetic route to BBT-2FT molecule.

2-Bromo-9, 9-dioctylfluorene (1).

1-Bromooctane (8.5 g, 44.0 mmol) was added by using a syringe to a mixture of 2-bromofluorene (4.5 g, 20.0 mmol), potassium iodide (330 mg, 2 mmol) and KOH (11.2 g, 200.0 mmol) in DMSO (20 mL). The solution was stirred at 60^{o}C overnight.

The mixture was poured into water (200 mL), and then was extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous MgSO4. The solvent was removed under reduced pressure. The crude product was purified by column chromatography by using hexane as eluent to yield oil (8.3 g, 89 %). ^{1}H-NMR (300 MHz, $CDCl_3$): d = 7.65 (m, 1H), 7.54 (m, 1H), 7.44 (m, 2H), 7.31 (m, 3H), 1.92 (m, 4H), 0.97–1.24 (m, 20H), 0.81 (t, J=7.2 Hz, 6H), 0.58 ppm (m, 4H).

2-(9,9-dioctyl-9H-fluoren-2-yl) thiophene (2)

2-bromo-9,9-dioctylfluorene (1 mmol) and the Thiophene-2-boronic acid bis(pinacol) ester (1.2 mmol) in the presence of 3 mol% $Pd(PPh_3)_4$ in an aqueous mixture of toluene (12 mL) / K_2CO_3(2 M, 3 mL). The solution was stirred and refluxed for 12 h under an inert atmosphere. The mixture was poured into water and extracted with diethyl ether. The organic extracts were washed with brine and dried over magnesium sulfate. The solvent was removed, and the residue was purified by column chromatography using hexanes as the eluent. The yield was 69%.

(5-(9,9-dioctyl-9H-fluoren-2-yl)thiophen-2-yl)trimethylstannane (3)

To a solution of 2-(9,9-dioctyl-9*H*-fluoren-2-yl)thiophene (1.77 g, 4.1 mmol) in 30 mL of THF at -78 °C was added *n*-BuLi (1.6 M in hexane, 2.82 mL, 4.5 mmol) dropwise. After the mixture was stirred for 1 h at -78 °C, then return to 0 °C for 1h, and then at -78 °C trimethylstannyl chloride (4.5 mL, 4.5 mmol) was added to the mixture. Then it was slowly warmed to room temperature and stirred for another 12 h.

The mixture was poured into water and extracted with dichloromethane. The organic extracts were dried over MgSO4. Upon evaporation of the solvent, the crude product was obtained for the next step without further purification.

BBT-2FT (4)

In a two-neck 100 ml round-bottom flask, to the mixture of 4,8-dibromo-BBT (0.14 g, 0.40 mmol), of $Pd(PPh_3)_2Cl_2$ (28 mg 10 mol %) in 8 mL of anhydrous dioxane was added trimethyl(4-(2-octyldodecyl)thiophen-2-yl)stannane (80% purity) (0.909 g, 1.0 mmol). The mixture was bubbled with Argon for 10 min and refluxed for 20 hours. Then the solvent was removed under reduced pressure, and the crude product was purified by column chromatography, by using hexane as the eluent to remove the unreacted tin compound, using DCM/hexane = 1/9 to isolate the BBT-2FT as a dark green solid (400 mg, 88%).

Synthesis of PEG-*b*-PCL:

β-capeolactone (5 g) and MePEG (2.5 g) were dissolved in 5 mL of anhydrous toluene in 100-mL dried Schlenk tube. The equipment was degassed and filled nitrogen three times. Then stannous 2-ethylhexanoate (1 droplet) was added into the solution. The refluxing mixture was stirred at 110 °C for 24 h. After cooling to room temperature, the mixtures were precipitated in ethyl ether three times to obtain white powder. The molecule weight was measured by GPC (Figure S3, THF as the eluent) and the chemical structure was characterized by ^{1}H-NMR (Figure S4).

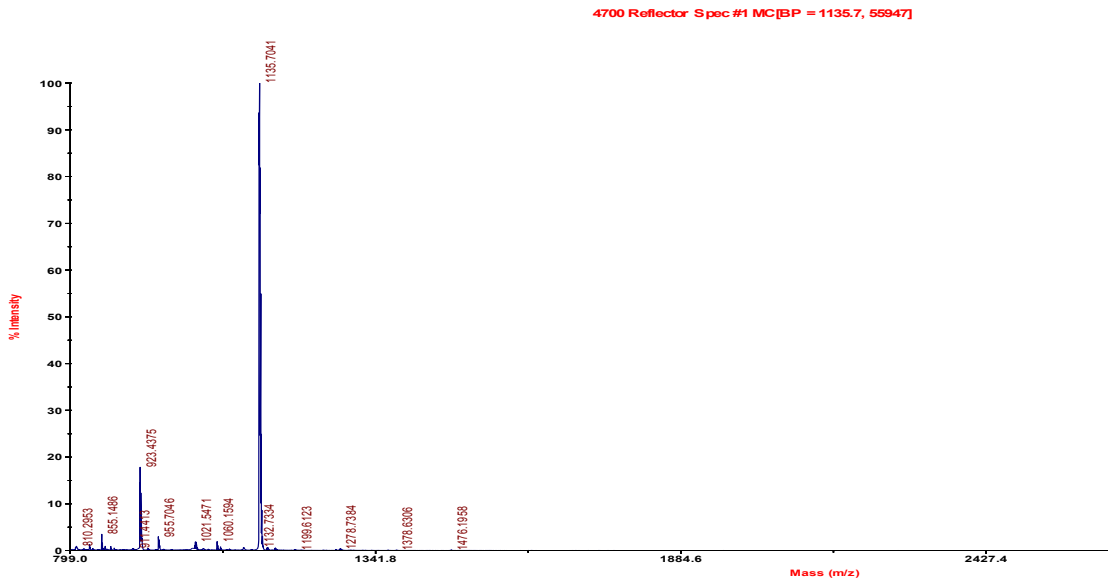


Figure S1. MADLI-TOF mass spectrum of BBT-2FT.

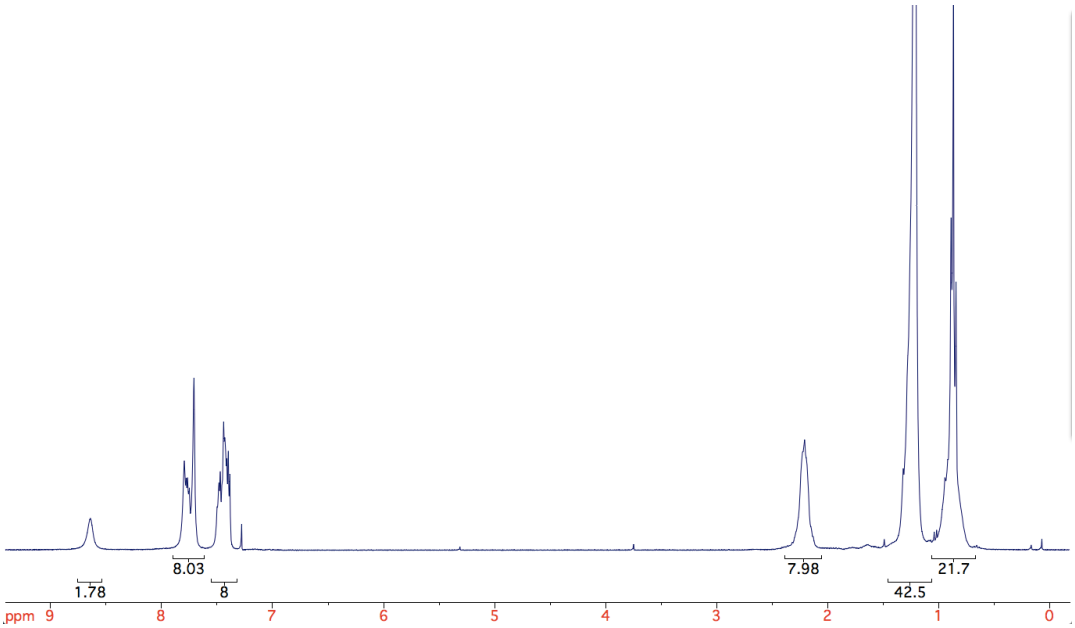


Figure S2. ^{1}H-NMR (300 MHz, $CDCl_3$) spectrum of BBT-2FT.

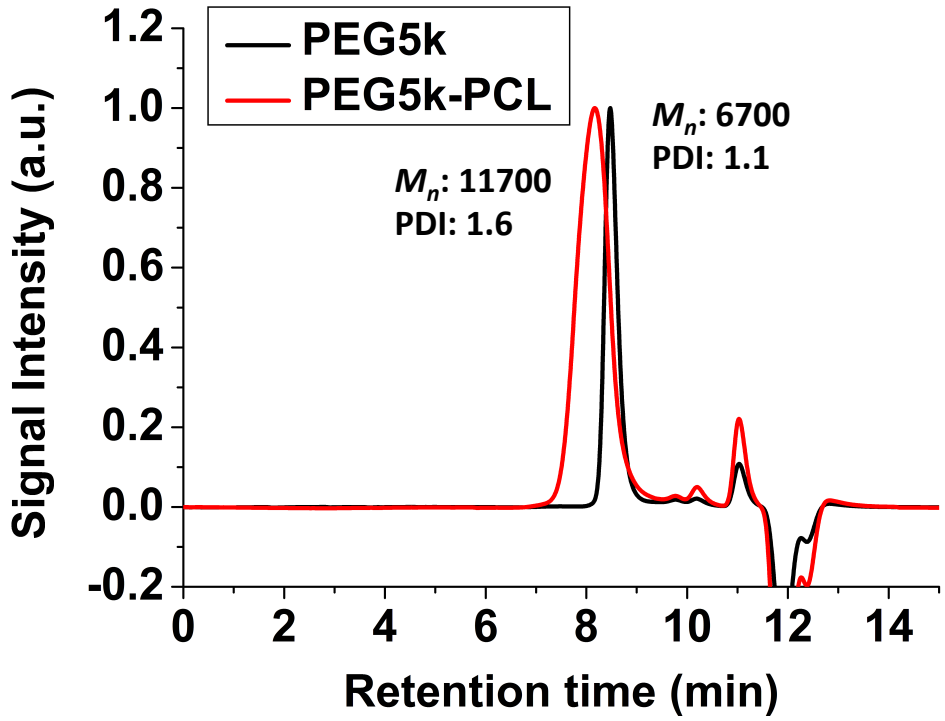


Figure S3. GPC traces of PEG-*b*-PCL vs. PEG-5K.

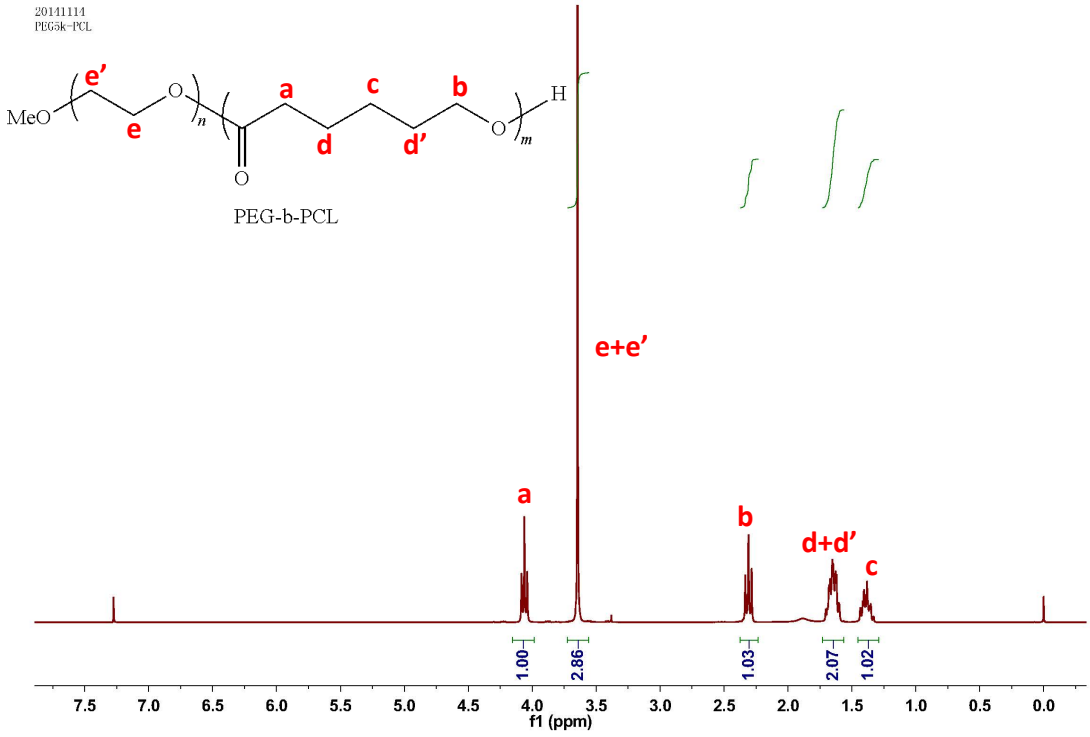


Figure S4. ^{1}H-NMR (300 MHz, $CDCl_3$) spectrum of PEG-*b*-PCL.

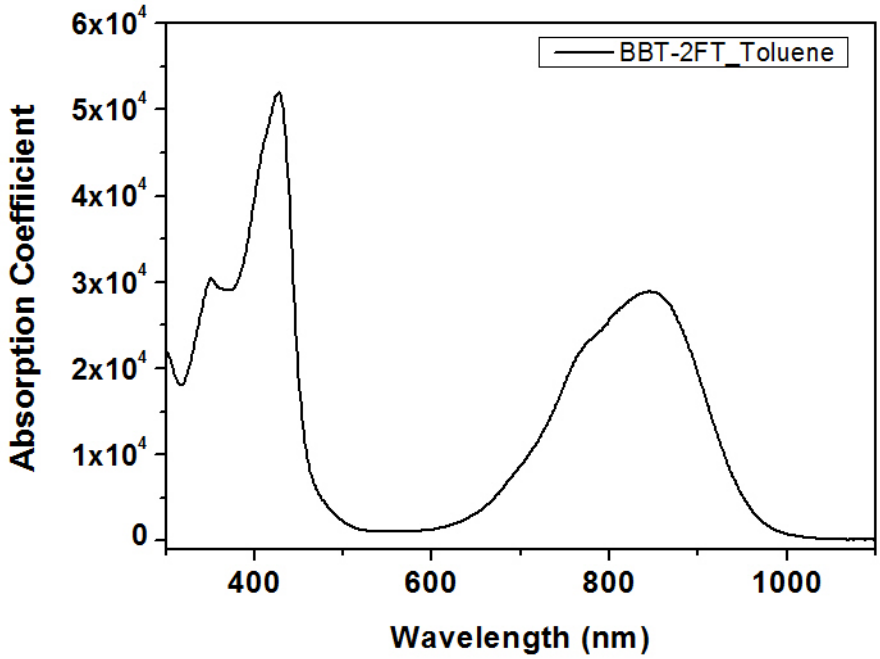


Figure S5. Molar absorption coefficient of BBT-2FT in toluene.

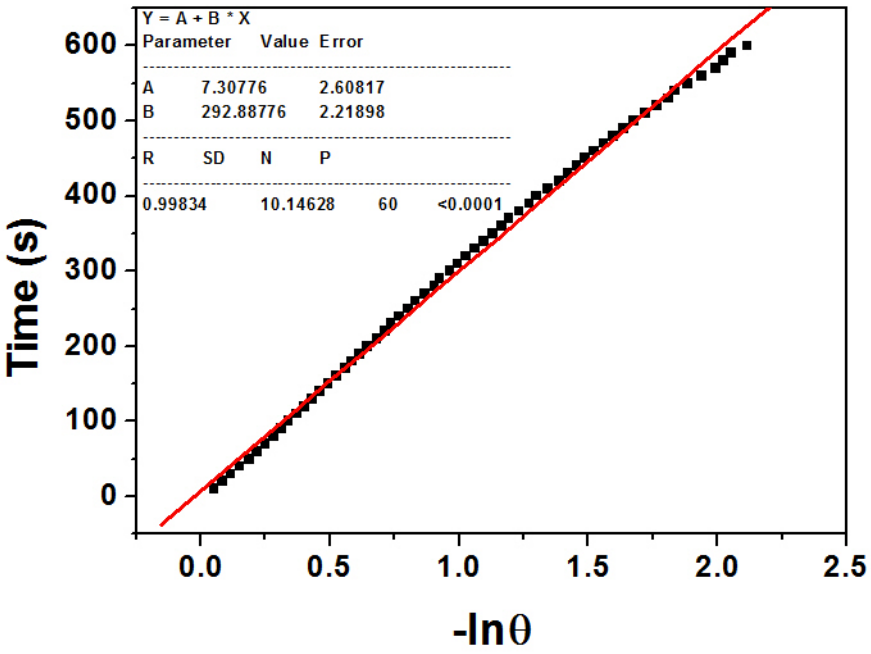


Figure S6. Linear time versus –lnθ obtained from the cooling period.

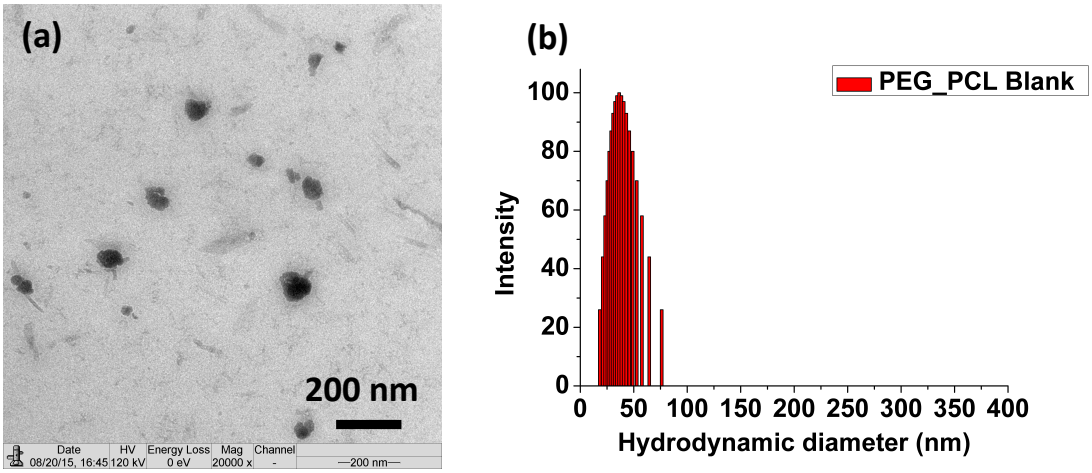


Figure S7. TEM image (a) and DLS result (b) of blank PEG-*b*-PCL micelles prepared by Method A, showing an average diameter of 42 ± 14 nm and 40 nm (PDI = 0.27), respectively.

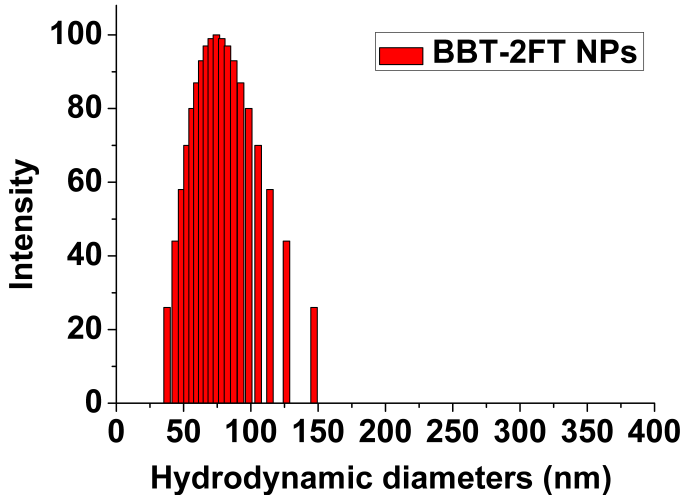


Figure S8. Dynamic light scattering analysis of BBT-2FT NPs, showing an average diameter of 68 nm (PDI = 0.28).

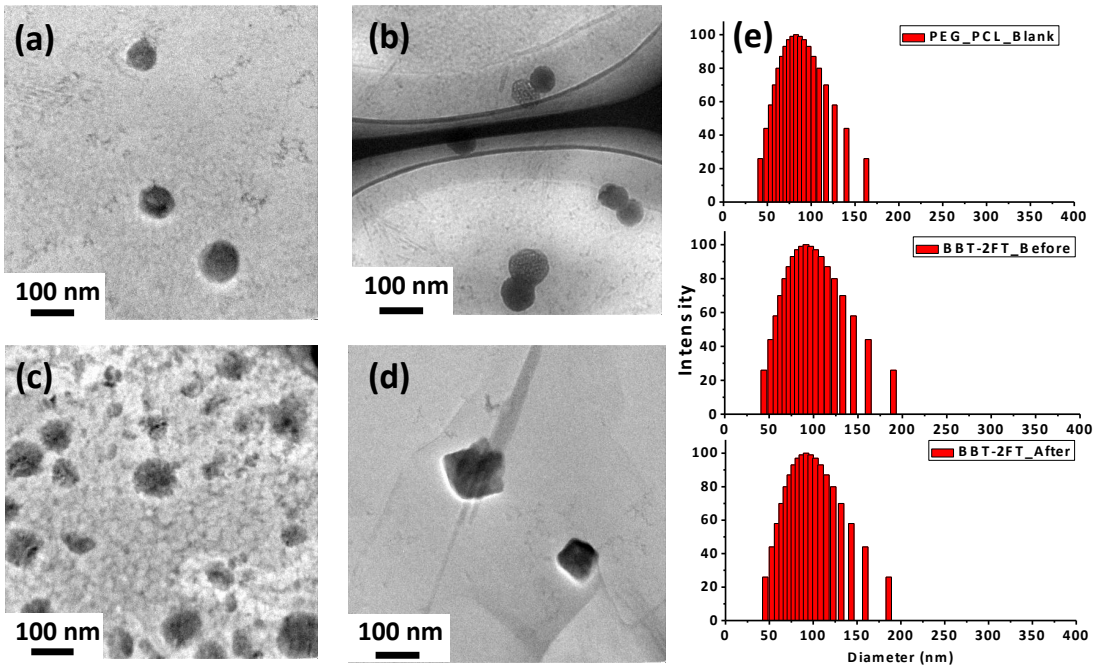


Figure S9. TEM (a-d) and the dynamic light scattering (DLS) (e) characterization of PEG-PCL blank micelles (a), BBT-2FT-loaded PEG-PCL micelles before (b) and after (c,d) 6 cycles of laser irradiation. The PDI of DLS from top to bottom are 0.26, 0.29 and 0.29, respectively. All samples presented here were prepared by Method B.

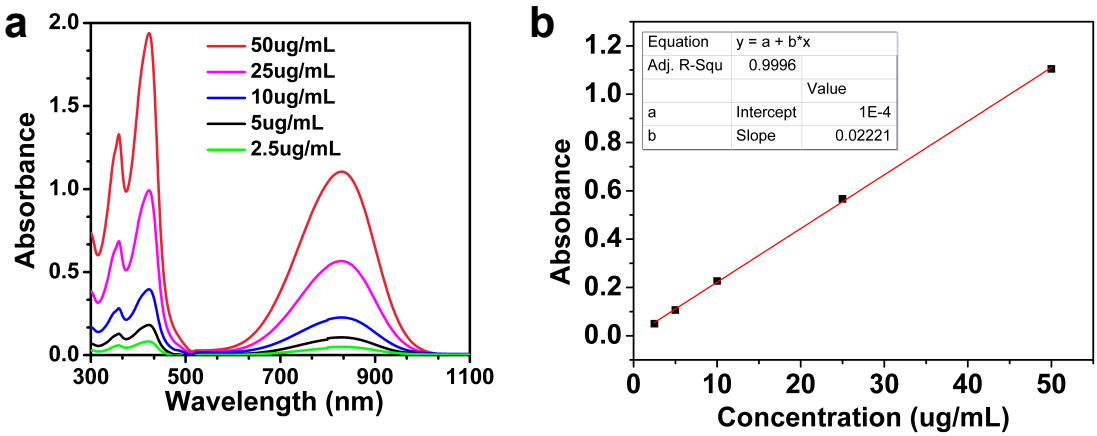


Figure S10. (a) The absorption spectra of BBT-2FT at various concentrations in THF. (b) The calibration curve of BBT-2FT's absorbance at 830 nm vs. concentration in THF.

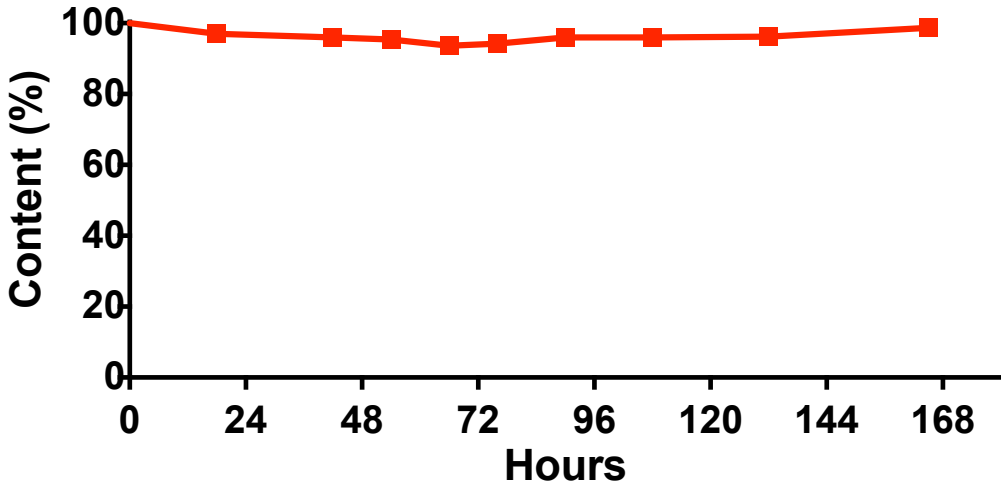


Figure S11. The release profile of BBT-2FT colloidal NPs in PBS at 37 ℃. The Y axis shows the remaining content of BBT-2FT NPs in the dialysis membrane and the X axis shows the incubation time of BBT-2FT NPs in PBS.