Electronic Supplementary Information

Dentin Hypersensitivity Treatment Using Highly Stable Photothermal Conversion Nanoparticles

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Experimental section

Materials.

1-Bromonaphthalene (J&K Chemical Scientific Ltd.), 4-methoxy-aniline (J&K Chemical Scientific Ltd.), 1,4-bromoiodobenzene (J&K Chemical Scientific Ltd.), 1,1'-Bis(diphenylphosphino)ferrocene (J&K Chemical Scientific Ltd.), palladium diacetate (J&K Chemical Scientific Ltd.), sodium t-butanolate (J&K Chemical Scientific Ltd.), sodium t-butanolate and potassium tert-butoxide (Energy Chemical Ltd.), (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride (J&K Chemical Scientific Ltd.), 4,5-bis(diphenylphos4,5-bis(diphenylphosphino)-9,9-dimethylxanthenephino)-9,9-dimethylxanthene (J&K Chemical Scientific Ltd.), potassium acetate (J&K Chemical Scientific Ltd.), bis(pinacol)diborane (J&K Chemical Scientific Ltd.), tetrakis(triphenylphosphine) palladium(0) (J&K Chemical Scientific Ltd.), n-butyllithium (J&K Chemical Scientific Ltd.), tributyltin chloride (J&K Chemical Scientific Ltd.), N,N-Dimethylformamide (DMF) (J&K Chemical Scientific Ltd.) were analytical reagents. All these materials were used without further purification. Tetrahydrofuran (THF) were purchased from Sinopharm Chemical Reagent Co. Ltd. and distilled before use. 1,4-dioxane, Dichloromethane (DCM) and petroleum ether (PE) were obtained from Sinopharm Chemical Reagent Co. Ltd. and used without further purification. The amphiphilic co-polymer MPEG2000-DSPE was purchased from Aladdin Reagent Ltd.

General method.

^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a 400 MHz Bruker AVANCE III NMR spectrometer and chemical shifts were reported in ppm relative to tetramethylsilane (TMS, $\delta = 0$ ppm). High-resolution mass spectra of synthetic small molecules were recorded on the Varian

7.0 T FTMS. UV-vis spectra were measured on a Shimadzu UV-2600. Photoluminescence spectra were determined with FLS1000 spectrometer. Photographs of the nanoparticle solution were taken by a digital camera (Canon EOS 70D, Japan). Transmission electron microscopy (TEM) images were acquired from a JEM-2010F transmission electron microscope with an accelerating voltage of 200 kV. Scanning electron microscope (SEM) images were acquired from a QUANTA-200 scanning electron microscope. Dynamic light scattering (DLS) was measured on a 90 plus particle size analyzer.

Computational method.

Density functional theory (DFT) calculations were performedon Gaussian 09 program (Revision D01). [S1] The ground state (S_0) geometries were optimizedwith B3LYP/6-31G (d) method.

Compound 1 and compound 3 were synthesized according to the literature. [S2, S3]

Synthesis of compound 2.

To the solutions of compound 1 (1 mmol, 404 mg), potassium acetate (3 mmol, 294 mg), (1,1'-bis (diphenylphosphino) ferrocene) palladium (II) dichloride (0.06 mmol, 44 mg) and bis(pinacol)diborane (1.5 mmol, 381 mg) in 10 mL toluene. The flask was evacuated under vacuum and flushed with dry nitrogen three times. Then the mixture was stirred overnight at 110°C. After cooling to room temperature, the mixture was quenched by water. Then the mixture was extracted with DCM, and dried with anhydrous Na_2SO_4. After filtration, the solvent was concentrated by evaporation under reduced pressure. The crude product was further purified on a silica-gel column using EtOAc/PE (1/10 ~ 1/5, v/v) as eluent. A whitish yellow solid was obtained in 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 8.1 Hz, 2H), 7.44 (t, J = 7.9 Hz, 2H), 7.38 – 7.27 (m, 2H), 7.12 (d, J = 8.6 Hz, 2H), 6.78 (t, J = 8.5 Hz, 4H), 3.76 (s, 3H), 1.30 (s, 10H).^{13}C NMR

(101 MHz, $CDCl_3$) δ 156.07, 151.90, 143.35, 140.81, 135.88, 135.28, 131.12, 128.44, 127.00, 126.51, 126.44, 126.38, 126.17, 126.10, 124.32, 117.93, 114.70, 83.42, 55.49, 24.89.

Synthesis of compound 4.

To the solutions of compound 2 (1 mmol, 451 mg), compound 3 (1 mmol, 275 mg),Potassium carbonate (4 mmol, 552 mg), tetrakis(triphenylphosphine) palladium (0.02 mmol, 23 mg) and Tetrabutylammonium bromide (0.1 mmol, 32 mg) in 10 mL toluene and 2 mL water. The flask was evacuated under vacuum and flushed with dry nitrogen three times. Then the mixture was stirred overnight at 110°C. After cooling to room temperature, the mixture was quenched by water. Then the mixture was extracted with DCM, and dried with anhydrous Na_2SO_4. After filtration, the solvent was concentrated by evaporation under reduced pressure. The crude product was further purified on a silica-gel column using EtOAc/PE (1/10 ~ 1/8, v/v) as eluent. A yellow oil was obtained in 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.93 (m, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.40 – 7.35 (m, 2H), 7.33 – 7.27 (m, 2H), 7.21 – 7.08 (m, 3H), 6.92 – 6.79 (m, 5H), 3.78 (s, 3H), 2.60 – 2.43 (m, 2H), 1.38 – 1.25 (m, 6H), 1.24 – 1.11 (m, 3H), 0.91 – 0.84 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.90, 148.90, 143.67, 142.16, 138.69, 137.91, 135.32, 132.39, 131.04, 130.23, 128.49, 126.90, 126.81, 126.44, 126.39, 126.30, 126.21, 126.17, 125.71, 125.61, 125.50, 125.41, 124.27, 123.04, 119.57, 119.27, 114.73, 114.69, 107.24, 55.52, 40.01, 32.54, 28.85, 26.98, 25.72, 23.10, 14.18, 10.89.

Synthesis of compound NDTB.

To the solutions of compound 4 (1 mmol, 520 mg) in 10 mL tetrahydrofuran. The flask was evacuated under vacuum and flushed with dry nitrogen three times. Then the mixture was cooled down to -80 °C for 10 min. The 0.5 mL n-butyllithium (2.4 M in THF solution) was added in the mixture solution by drops. Then the tributyltin chloride (1 mmol, 325 mg) was added after

stirring for 30 min. The mixture solution was warmed to room temperature and stirred for 2 h. After that the mixture was concentrated by evaporation under reduced pressure. Then the (1,1'-bis (diphenylphosphino) ferrocene) palladium (II) dichloride (0.1 mmol, 70 mg) and 10 mL toluene was added in the reaction system. Then the mixture was stirred overnight at 110°C. After cooling to room temperature, the mixture was quenched by water. Then the mixture was extracted with DCM, and dried with anhydrous Na_2SO_4. After filtration, the solvent was concentrated by evaporation under reduced pressure. The crude product was further purified on a silica-gel column using DCM/PE (1/5 ~ 1/2, v/v) as eluent. A green solid was obtained in 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.0 Hz, 2H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.52 – 7.47 (m, 4H), 7.44 (d, *J* = 8.4 Hz, 4H), 7.39 (d, *J* = 8.4 Hz, 4H), 7.19 (d, *J* = 8.4 Hz, 4H), 6.93 (d, *J* = 8.4 Hz, 4H), 6.86 (d, *J* = 8.4 Hz, 4H), 3.81 (s, 6H), 2.82 –2.75 (m, 4H), 1.70 – 1.53 (m, 6H), 1.37 – 1.22 (m, 12H), 0.95 – 0.81 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.98, 154.53, 150.69, 149.17, 147.43, 143.46, 141.01, 138.89, 137.98, 135.35, 134.91, 131.08, 129.99, 128.49, 126.91, 126.45, 126.41, 126.22, 125.79, 124.36, 119.09, 114.76, 55.53, 40.53, 32.91, 31.97, 29.74, 27.11, 22.74, 13.68, 10.92. MALDI-TOF, *m/z*: $[M]^+$ calcd. 1228.46, found 1228.70.

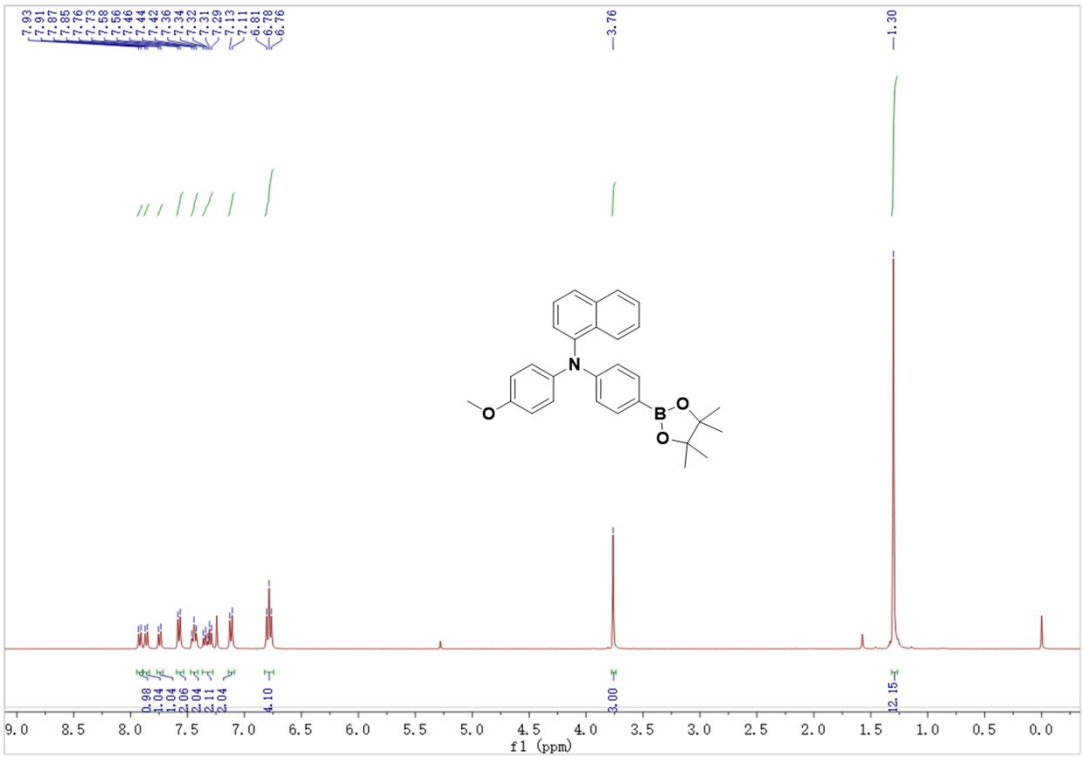

Fig. S1 ^{1}H NMR spectrum of compound 2.

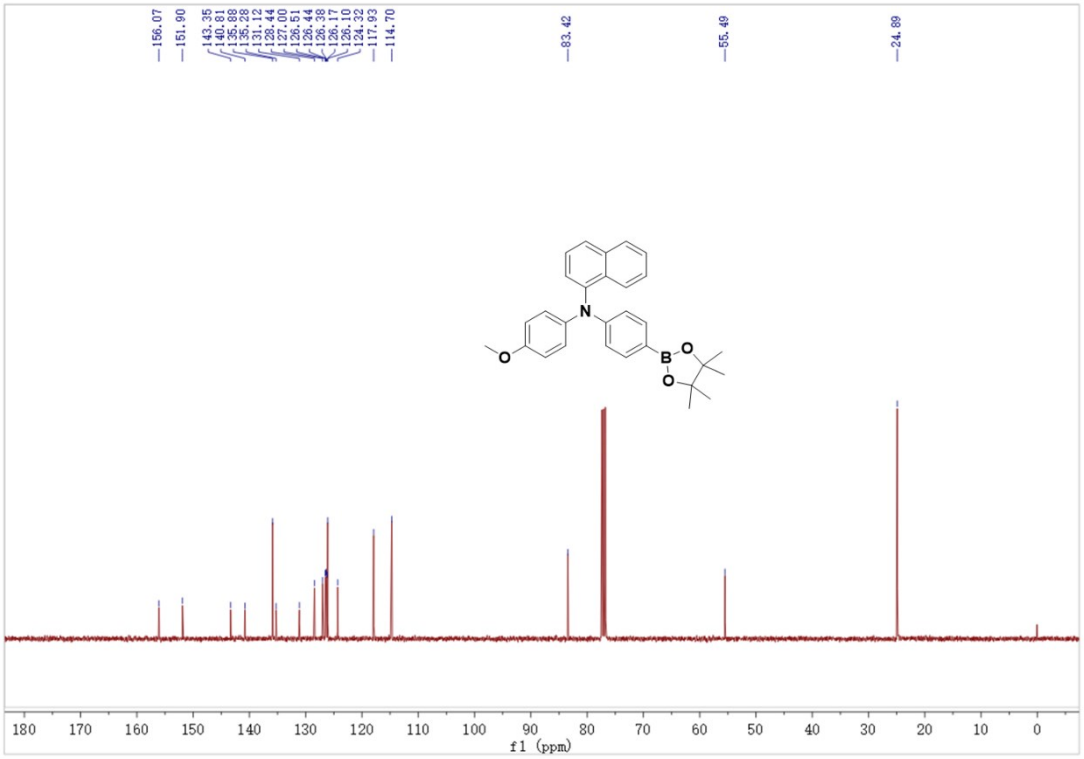

Fig. S2^{13}C NMR spectrum of compound 2.

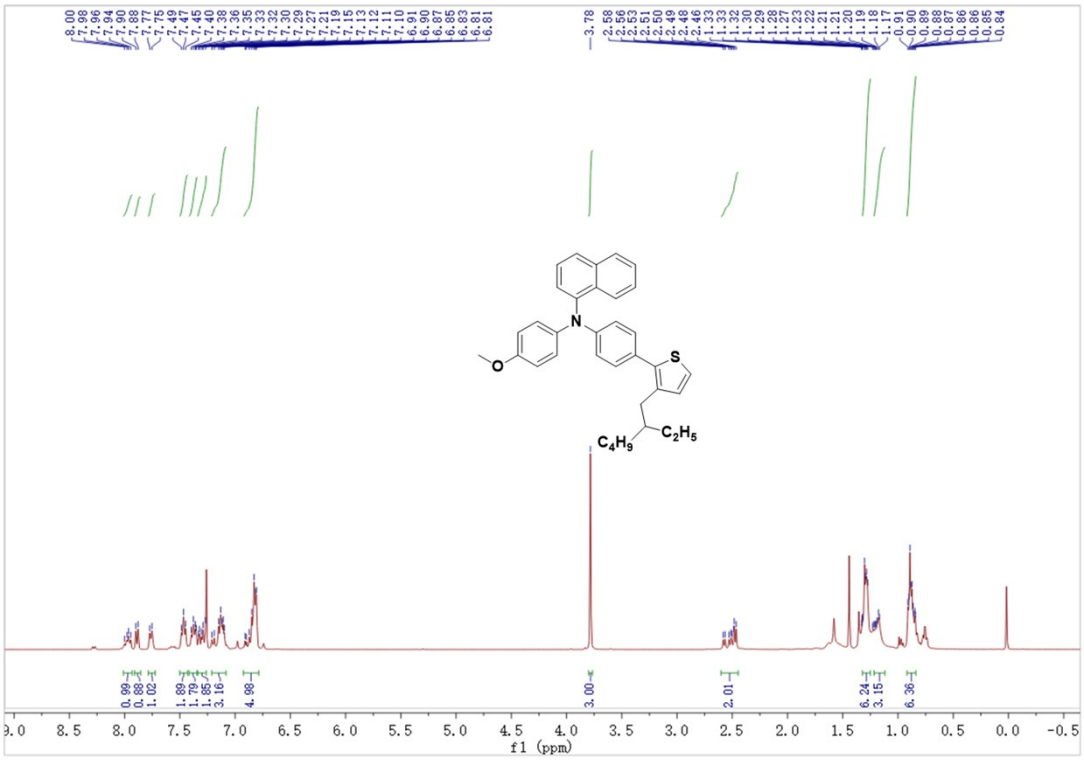

Fig. S3[1]H NMR spectrum of compound 4.

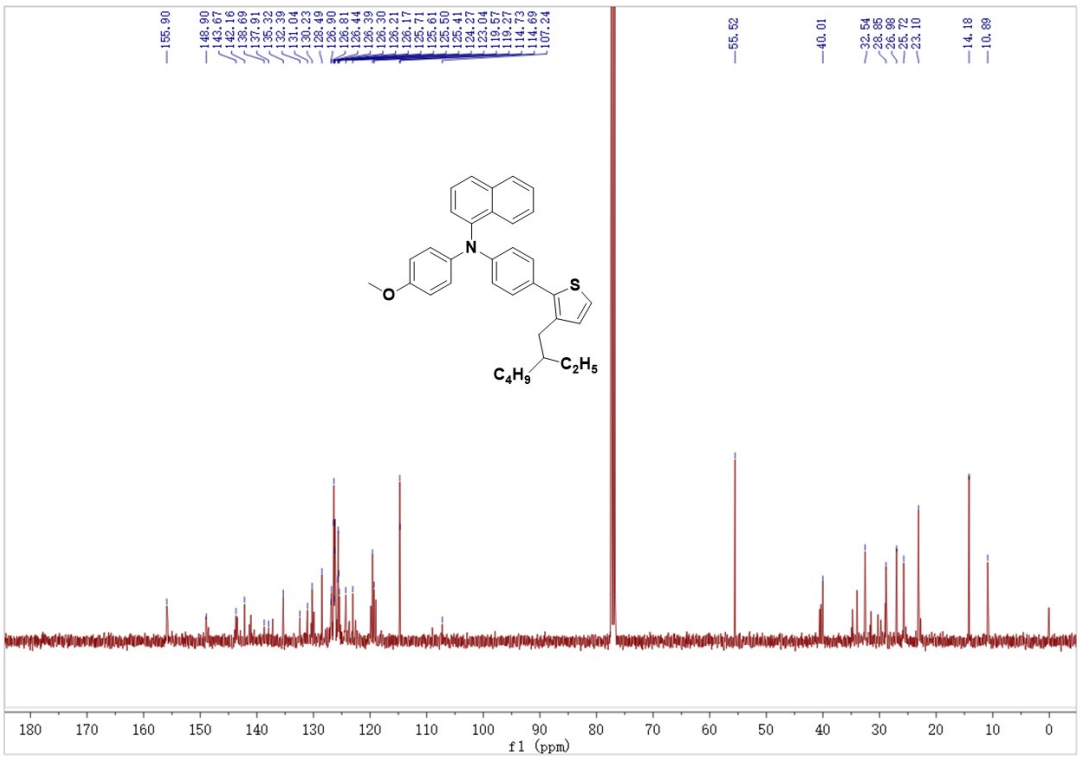

Fig. S4[13]C NMR spectrum of compound 4.

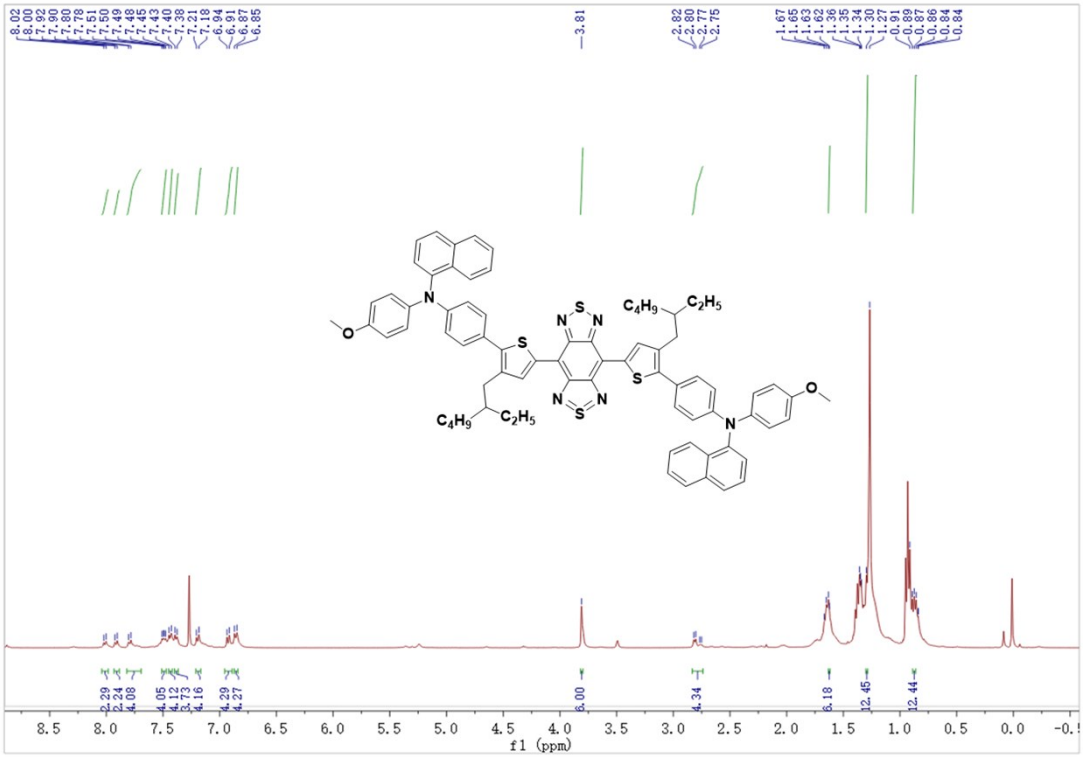

Fig. S5[1]H NMR spectrum of compound NDTB.

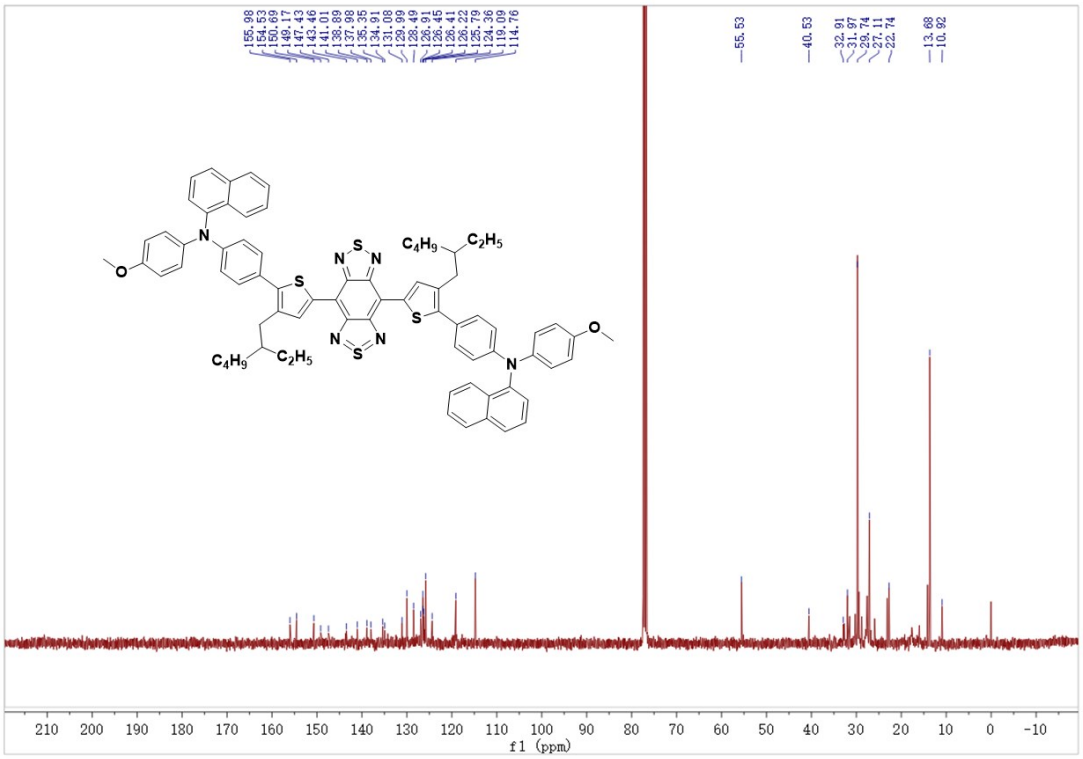

Fig. S6[13]C NMR spectrum of compound NDTB.

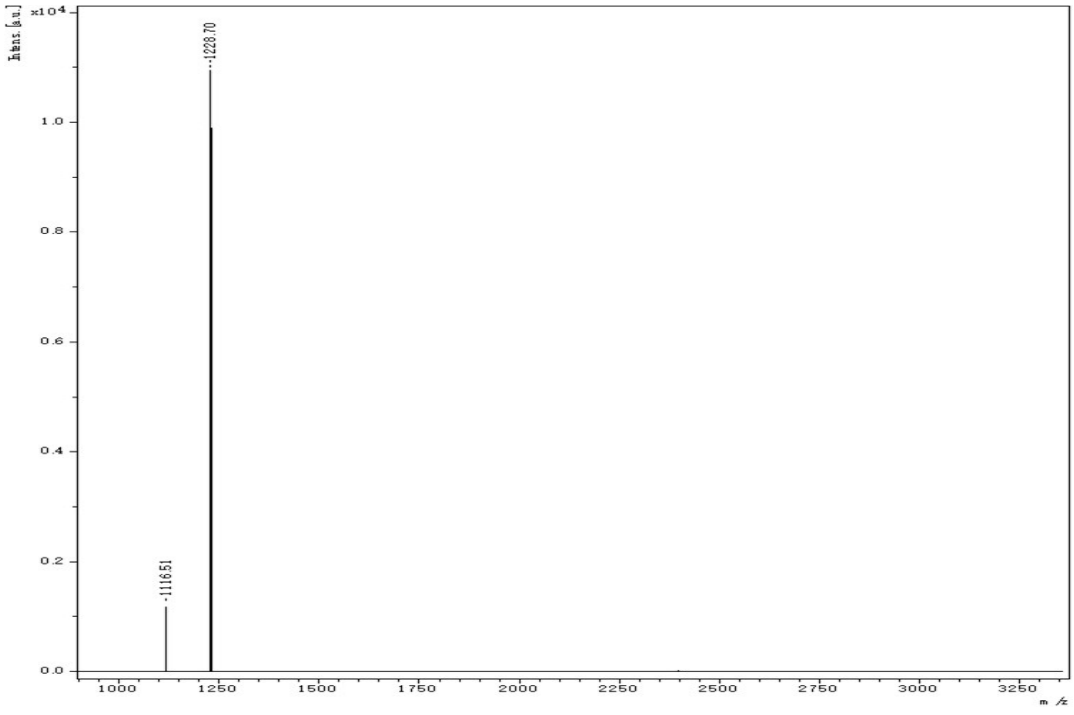

Fig. S7MALDI-TOF spectrum of compound NDTB.

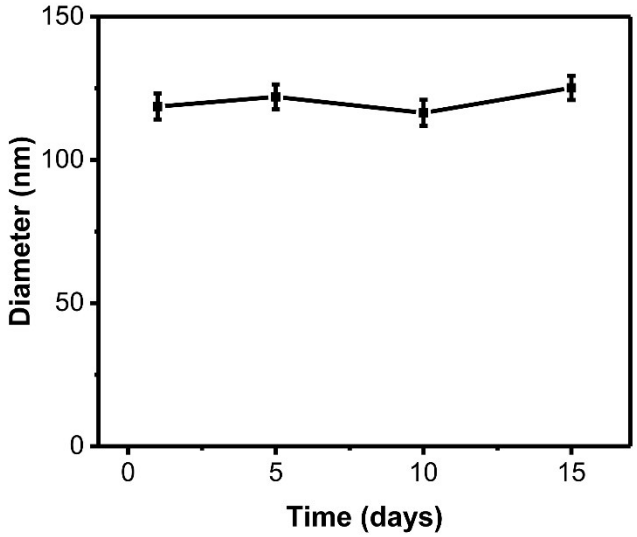

Fig. S8 The diameter of NDTB NPs after storage at 4 °C in dark for 1, 5, 10 and 15 days, respectively.

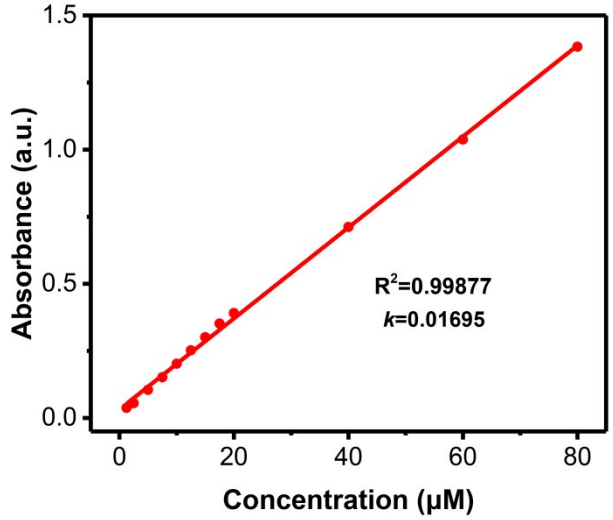

Fig. S9 Correlation of NDTB NPs concentration with absorbance.

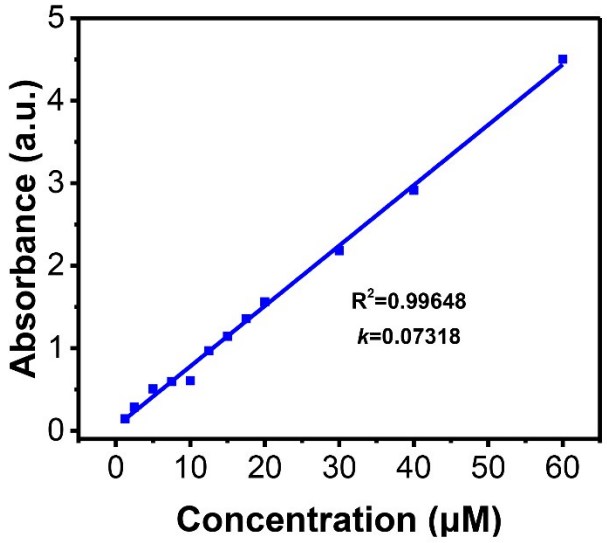

Fig. S10 Correlation of ICG concentration with absorbance.

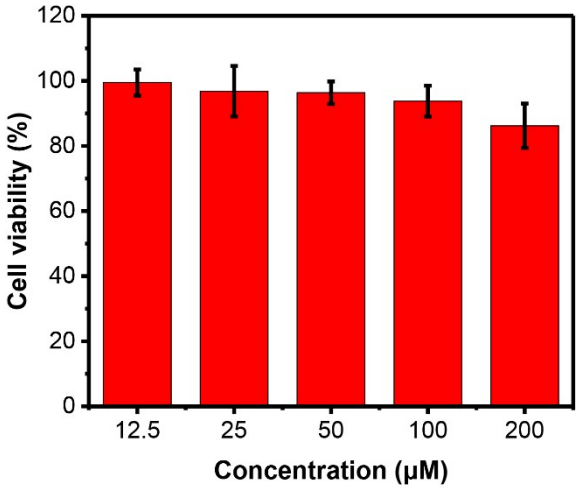

Fig. S11 Cell viability ofHPDLFcells after incubation with different concentrations of NDTB NPs for 24 h (n = 6).

Preparation of NDTB nanoparticles.

1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy-(polyethylene glycol)-2000 (DSPE-PEG_{2000}) (3.0 mg) and NDTB (1.2 mg) were dissolved in THF solution(1 mL), which was then poured into water (9 mL). Followed by sonication with a microtip probesonicator (XL2000, Misonix Incorporated, NY) for 3 min. The residueTHF solvent was evaporated by violent stirring the suspension in fumehood overnight, and colloidal solution was obtained and used directly.

Photothermal performance.

The PBS solutions (pH 7.4) ofNDTB NPs, and ICG were continuously exposed toan 808 nm NIR laser (660 mW/cm^2) for 3 min. The temperature wasmeasured every 10 s and stopped until the temperature nearly reachedto a plateau. The corresponding IR thermal images of the sample tubeswere also recorded.

Analysis of vertical dentin slices samples

Five fileds of the vertical section sample of dentin tubules in each group was randomly selected and the image was imported into Image-pro plus 6.0 analysis software. The sealing depth of all dentin tubules in the visual field was measured starting from the surface of the occlusion and ending from the occlusions. In order to ensure the same sample size for statistical analysis, the visual field with the least number of the tubules was taken as the benchmark, and the other four visual fields were compared with same number of closed depths.

Temperature measurement of dentin slice.

An infrared (IR) thermometer, Model FLIR E5 (FLIR Systems, Wilsonville, USA) sensitive from 7.5– 13 μm with a resolution of 120 × 90 pixels, a thermal sensitivity of 0.1 ℃ and auto focus was used to record temperature changes during the laser irradiation process. Near-infrared thermal imager was used to record the starting and ending temperatures of each irradiation, and repeat the irradiation and record one after an interval of 5 seconds after irradiation on the surface of dentin slice and on the opposite side. 5 samples were randomly selected from each group, one measurement were made to each side of the dentin disc. Differences between the initial and the highest temperature readings were taken, and the 5 calculated temperature changes were averaged to determine the value of the temperature increase.

Statistical analyses

The statistical analysis of normal hypothesis for the occlusion rate of dentin tubule in each group were conducted using SPSS 21.0 statistical software (Lead Technologies, Chicago, USA). The occlusive rate and depth of dentinal tubules in each group were expressed as mean ± standard deviation (SD). The differences between the groups were analyzed using a one-way analysis of variance (ANOVA), followed by Tukey's multiple comparisons test. A difference with a significance level of $p < 0.05$.

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