

Supporting Information

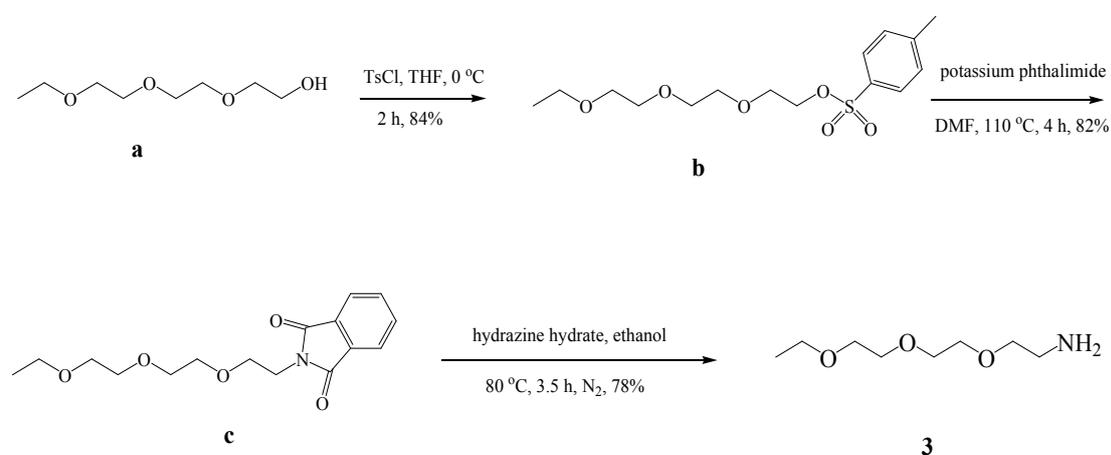
Small organic molecule-based nanoparticles with red/near-infrared aggregation-induced emission for bioimaging and PDT/PTT synergistic therapy

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Scheme S1. Synthetic routes of compound **3**

Synthesis of 2-[2-(2-ethoxyethoxy) ethoxy]ethyl p-tosylate (b)

Triethylene glycol monoethyl ether (a) (10 g, 56.11 mmol) was dissolved in THF (20 mL), and the solution was cooled to 0 °C in an ice bath, to which a solution of sodium hydroxide (4.6 g, 115 mmol) in water (18.4 mL) was added. Then a solution of toluenesulfonyl chloride (13.79 g, 72.38 mmol) in THF (20 mL) was added dropwise over 15 min. The reaction mixture was allowed to warm to ambient temperature and stirred for another 2 h. The organic solvent was then evaporated in vacuo, and 150 mL ice water was added. The resulting solution was extracted with dichloromethane and the organic layer was washed with water and dried over anhydrous Na₂SO₄. The solvent was evaporated in vacuo to give the product as a colorless oil (15.61 g, 84%), which was used in the next reaction without further purification. ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.78 (d, *J* = 8.4 Hz, 2H, ArH), 7.32 (d, *J* = 8.4 Hz, 2H, ArH), 4.14 (t, *J* = 4.8 Hz, 2H, CH₂SO₃), 3.66 (t, *J* = 4.8 Hz, 2H, OCH₂), 3.61–3.53 (m, 8H, OCH₂), 3.49 (quartet, *J* = 6.9 Hz, 2H, CH₂CH₃), 2.42 (s, 3H, ArCH₃), 1.18 (t, *J* = 7 Hz, 3H, CH₂CH₃).

Synthesis of 2-(2-(2-Ethoxyethoxy)ethoxy)isoindoline-1,3-dione (c)

[2-(2-ethoxyethoxy) ethoxy]ethyl p-tosylate (b) (15 g, 45.10 mmol) was dissolved in DMF (30 mL) under a nitrogen atmosphere, and to this solution was added potassium phthalimide (11.10 g, 59.95 mmol). The reaction mixture was heated to 110 °C and stirred for 4 h. To remove the solvents, DMF was first evaporated under reduced pressure on a rotary evaporator until approximately 25 mL was collected in the receiving flask. Ethyl acetate (250 mL) was added to the reaction mixture, which was then filtered to remove precipitated potassium tosylate. The filtrate was washed with water and dried over anhydrous Na₂SO₄. The solvent was evaporated in vacuo to give the product as a colorless oil (11.38 g, 82%), which was used in the next reaction without further purification. ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.73-7.77 (m, 2H, ArH), 7.63-7.66 (m, 2H, ArH), 3.80-3.83 (t, *J* = 6.0 Hz, 2H, NCH₂), 3.65-3.68 (t, *J* = 5.8 Hz, 2H, OCH₂), 3.49-3.59 (m, 6H, OCH₂), 3.38-3.45 (m, 4H, OCH₂), 1.08-1.11 (t, *J* = 7.0 Hz, 3H, CH₂CH₃).

Synthesis of 2-(2-(2-Ethoxyethoxy)ethoxy)ethylamine (3)

The phthalimide (c) (2.00 g, 6.27 mmol), hydrazine hydrate (0.63 mL of 64 wt% solution, 12.5 mmol), and ethanol (30 mL) were combined in a round-bottom flask. The reaction mixture

was refluxed for 3.5 h, during which a white solid was formed in the reaction mixture. Ethanol was removed from the reaction mixture in vacuo until the precipitate was nearly dry. Cold diethyl ether (75 mL) was then added into the round-bottom flask, and the amine was extracted from the fluffy solid by stirring the mixture over a magnetic stir plate. The solution was filtered and the residual solid was washed using cold diethyl ether (50 mL). The combined filtrate and washings were evaporated under reduced pressure to obtain 4 (866 mg) in 78% yield. ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 3.66–3.47 (m, 12H, OCH₂), 2.84 (t, *J* = 5 Hz, 2H, CH₂NH₂), 1.59 (s, broad, 2H, CH₂NH₂), 1.19 (t, *J* = 7.1 Hz, 3H, CH₂CH₃).

Synthesis of 4-(trimethylsilyl)ethynyl triar- ylamine (1)

4-Bromotriphenylamine (520.0 mg, 1.6 mmol) was dissolved in toluene (24 mL). The reaction mixture was degassed for 10 minutes. PdCl₂(PPh₃)₂ (56 mg, 0.08 mmol) and CuI (15 mg, 0.08 mmol) were added, The reaction mixture was stirred at room temperature for 30 minutes, followed by addition of 1,8-diazabicycloundec-7-ene (DBU; 490 mg, 3.5 mmol) and trimethylsilylacetylene (230 mg, 2.3mmol). The reaction mixture was heated to 70°C and stirred for 5 h under N₂ . The reaction mixture was then concentrated under reduced pressure and purified by column chromatography over silica with hexane/DCM to afford 4-(trimethylsilyl)ethynyl triarylamine (284.2mg, 52%) as a viscous brown liquid.

Synthesis of 4-ethynyl triarylamine (2)

K₂CO₃ (445.0 mg, 3.2 mmol) was added to the 4-(trimethylsilyl)ethynyl triar- ylamine (621.8 mg, 0.83 mmol) in dichloromethane: methanol solution = 1: 1 (30 mL), and the mixture was stirred at room temperature. Under a N₂ atmosphere for 12 hours. The solvent was evaporated under reduced pressure, and the mixture was extracted with CH₂Cl₂ and water. The organic layer was dried, and the crude product was purified by column chromatography (silica gel, DCM/hexane ether = 1: 3, v / v). A yellow solid was obtained; yield 166.0 mg, 0.45 mmol, 76.2%. ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.32 (d, *J* = 8.8 Hz, 2H, ArH), 7.27 (t, *J* = 8.4 Hz, 4H, ArH), 7.04-7.11 (m, 6H, ArH), 6.95 (d, *J* = 8.4 Hz, 2H, ArH), 3.01 (s, 1H, CH) .

Synthesis of PEG-4-Bromo-NI (4)

To a stirred solution of 4-bromo-1,8-naphthalic anhydride (1.0 g, 3.6 mmol) in ethanol (20

mL), compound **3** (363 μ L, 3.6 mmol) was added at 80 °C. After refluxing for 4 h, the reaction mixture was cooled to room temperature. The solvent was evaporated in vacuo, and the residue was dissolved with ethyl acetate. The mixture was washed with water and brine, respectively. The organic extract was collected and then dried over anhydrous sodium sulphate. The solvent was evaporated in vacuo and the obtained residue was purified by silica gel column chromatography to give product **2** as pale yellow solid (1.26 g, 80%). ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 8.60 (d, J = 7.2 Hz, 1H, ArH), 8.51 (d, J = 7.9 Hz, 1H, ArH), 8.35 (d, J = 7.8 Hz, 1H, ArH), 7.99 (d, J = 7.8 Hz, 1H, ArH), 7.80 (t, J = 7.9 Hz, 1H, ArH), 4.40 (t, J = 5.8 Hz, 2H, NCH₂), 3.91-3.29 (m, 12H, OCH₂), 1.14 (t, J = 7.0 Hz, 3H, CH₃).

Synthesis of PEG-NI-benzaldehyde (**5**)

4-Formylbenzeneboronic acid (500 mg, 3.3 mmol), compound **2** (1.14 g, 2.6 mmol), potassium carbonate (1.11 g, 11.2 mmol) and Pd(PPh₃)₄ (125 mg, 0.1 mmol) were added to a 250 mL round-bottomed flask with 180 mL THF and 30 mL H₂O. Under a N₂ atmosphere, the solution was heated to 70 °C and stirred for 12 h. After the completion of reaction, the solvent was evaporated under reduced pressure. The crude product was purified using silica gel column chromatography (85 % DCM:15 % ethyl acetate (v/v)) to yield a yellow sticky solid (890 mg, 74 %). ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 10.12 (s, 1H, CHO), 8.60 (t, J = 7.2 Hz, 2H, ArH), 8.16 (t, J = 9.1 Hz, 1H, ArH), 8.05 (d, J = 7.5 Hz, 2H, ArH), 7.68 (t, J = 6.4 Hz, 4H, ArH), 4.42 (d, J = 5.3 Hz, 2H, NCH₂), 3.86-3.38 (m, 12H, OCH₂), 1.14 (t, J = 6.0 Hz, 3H, CH₃).

UV-vis absorption and fluorescence spectra

The UV-vis absorption and fluorescence spectra of T-BDP molecules was measured in Ethanol solution, while the nanoparticles was measured in deionized water. The fluorescence spectra were recorded at room temperature using a 1 cm path length rectangular quartz cuvette. The emission and excitation slit widths are 2 nm. The fluorescence quantum yield (ϕ_f) were determined in ethanol solution using rhodamine B (ϕ_f = 0.73) and ICG (ϕ_f = 0.078) as the reference. The fluorescence quantum yield (ϕ_f) of an unknown sample is calculated using Eq. (S1)^[1]

$$\varphi_f = \varphi_f^R \frac{I_f}{I_f^R} \left(\frac{n}{n^R} \right)^2 \quad \text{----- equation (S1)}$$

Where, φ_f^R is the known fluorescence quantum yield of the reference sample (referred by the superscript 'R'); I_f and I_f^R are the integrated fluorescence intensities of the unknown sample and reference sample, respectively; n and n^R are the refractive indices of the solvents for the unknown sample and reference sample, respectively. The fluorescence quantum yield of the samples are measured at room temperature.

Calculation of the photothermal conversion efficiency

The photothermal conversion efficiencies (η) were measured according to a previously described method^[2]:

$$\eta = \frac{hs(T_{Max} - T_{Surr}) - Q_{Dis}}{I(1 - 10^{-A_{635}})} \quad \text{----- equation (S2)}$$

h is the heat transfer coefficient, s is the surface area of the container, and the value of hs is determined from the equation (3). Q_{Dis} represents heat dissipated from the laser mediated by the solvent and container. I is the laser power and A is the absorbance at 635 nm.

$$\tau_s = \frac{mC}{hs} \quad \text{----- equation (S3)}$$

m is the mass of the solution containing the photoactive material, C is the specific heat capacity of the solution, and τ_s is the associated time constant, which can be determined from equation (S4).

$$t = -\tau_s \ln(\theta) \quad \text{----- equation (S4)}$$

θ is a dimensionless parameter, known as the driving force temperature, as calculated using equation (S5).

$$\theta = \frac{T - T_{Surr}}{T_{Max} - T_{Surr}} \quad \text{----- equation (S5)}$$

T_{Max} and T_{Surr} are the maximum steady state temperature and the environmental temperature, respectively.

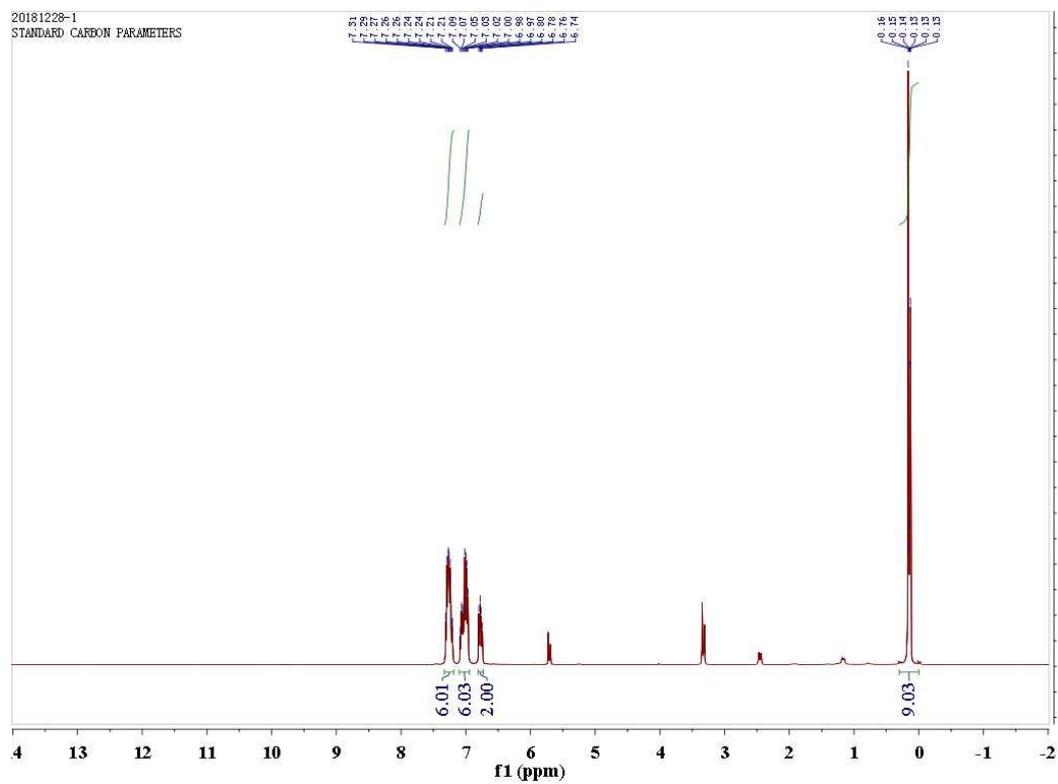


Fig. S1 ¹H-NMR of 4-ethynyl triarylamine (2)

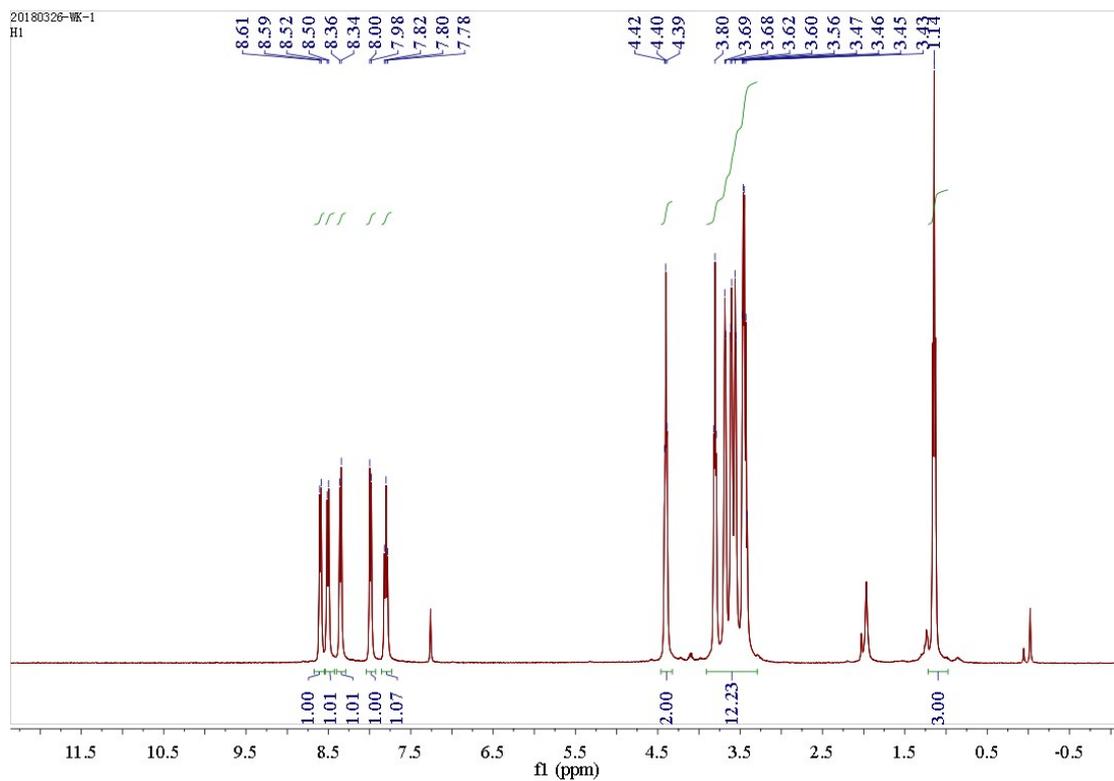


Fig. S2 $^1\text{H-NMR}$ of PEG-4-Bromo-NI (4)

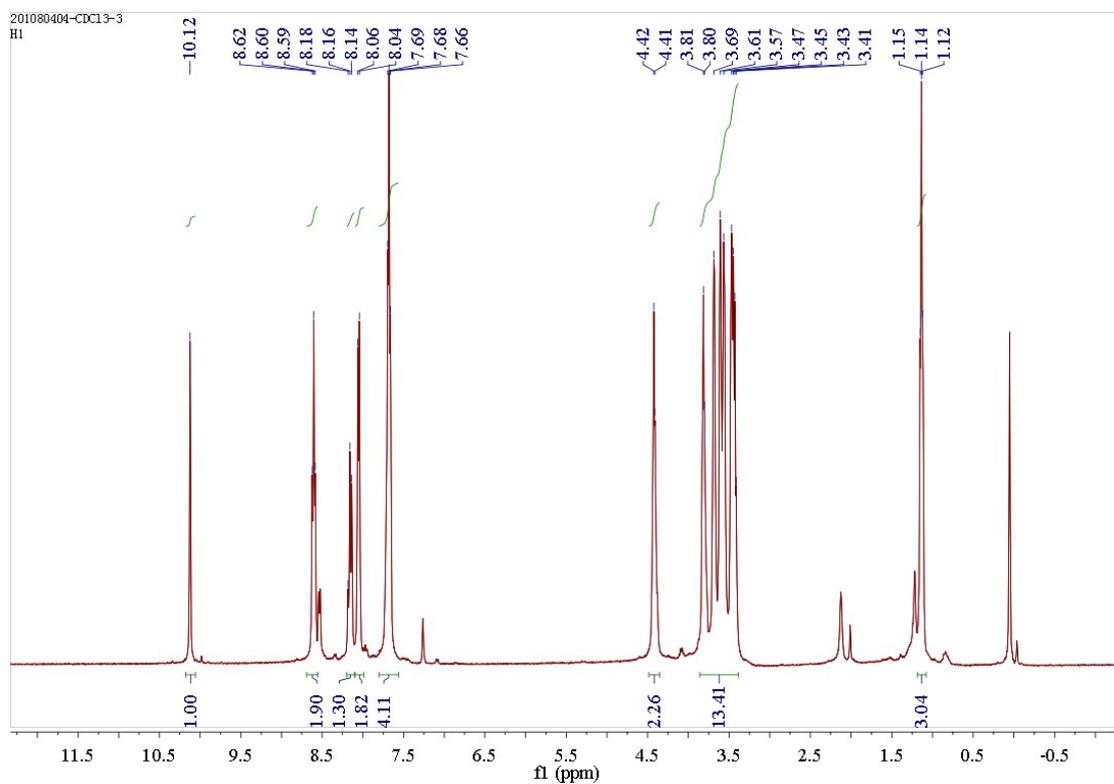


Fig. S3 $^1\text{H-NMR}$ of PEG-NI-benzaldehyde (5)

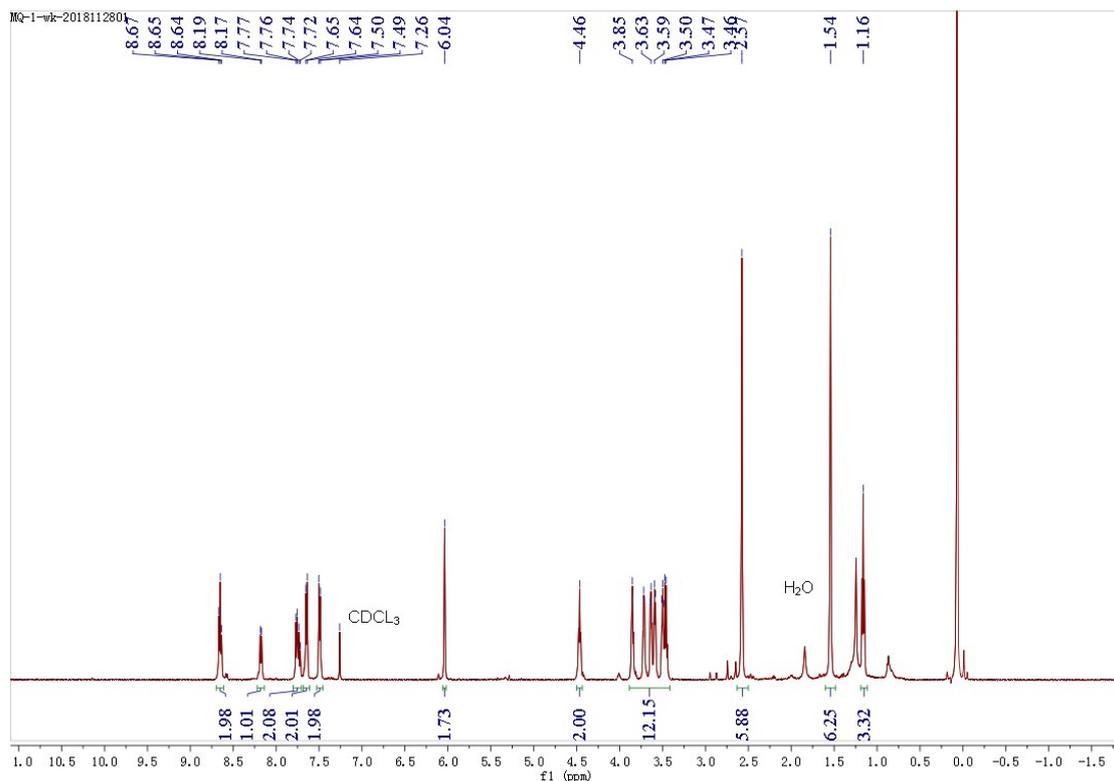
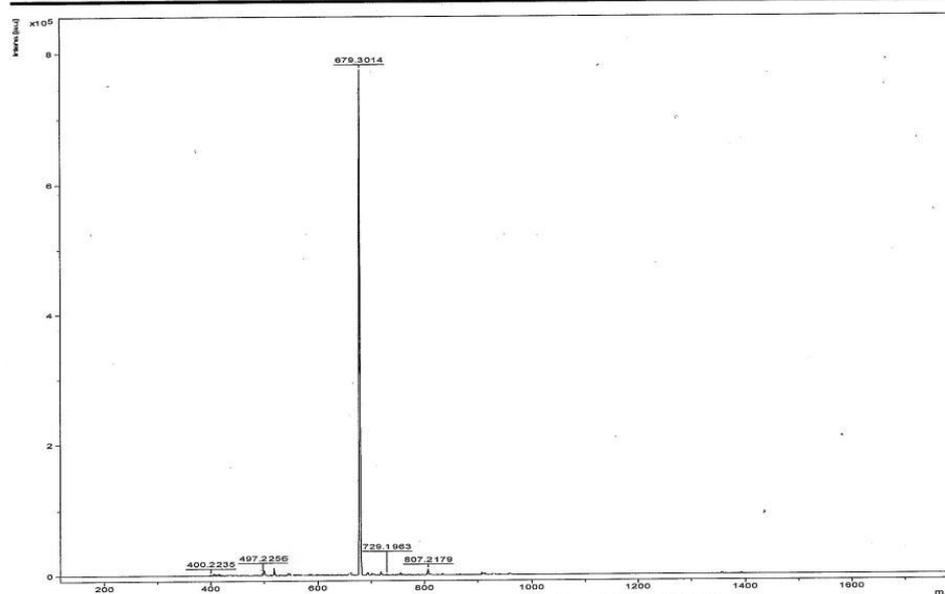


Fig. S4 ¹H-NMR of NI-BDP (6)



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 Target serial number 1002444
 Position 017

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 Laser beam focus 35
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 Number of shots 1000

Spectrometer
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 PIE delay 150 ns
 Ion source voltage 1 19 kV
 Ion source voltage 2 16.85 kV
 Lens voltage 8.6 kV
 Linear detector voltage 2.95 kV
 Deflection on
 Deflection mass

Reflector voltage 1 21 kV
 Reflector voltage 2 9.6 kV
 Reflector detector volt. 1.667 kV

Instrument
 Instrument type autoflex
 Instrument serial 1857351.00824
 Name of computer FLEX-PC
 Operator ID or name admin
 flexControl version flexControl 3.4.168.0
 flexAnalysis version

RESULT
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 Experimental Mass = [M]⁺ = 679.3014
 Error = -2.3553ppm

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Bruker Daltonics

Fig. S5 Maldi-TOF MS of NI-BDP (6)

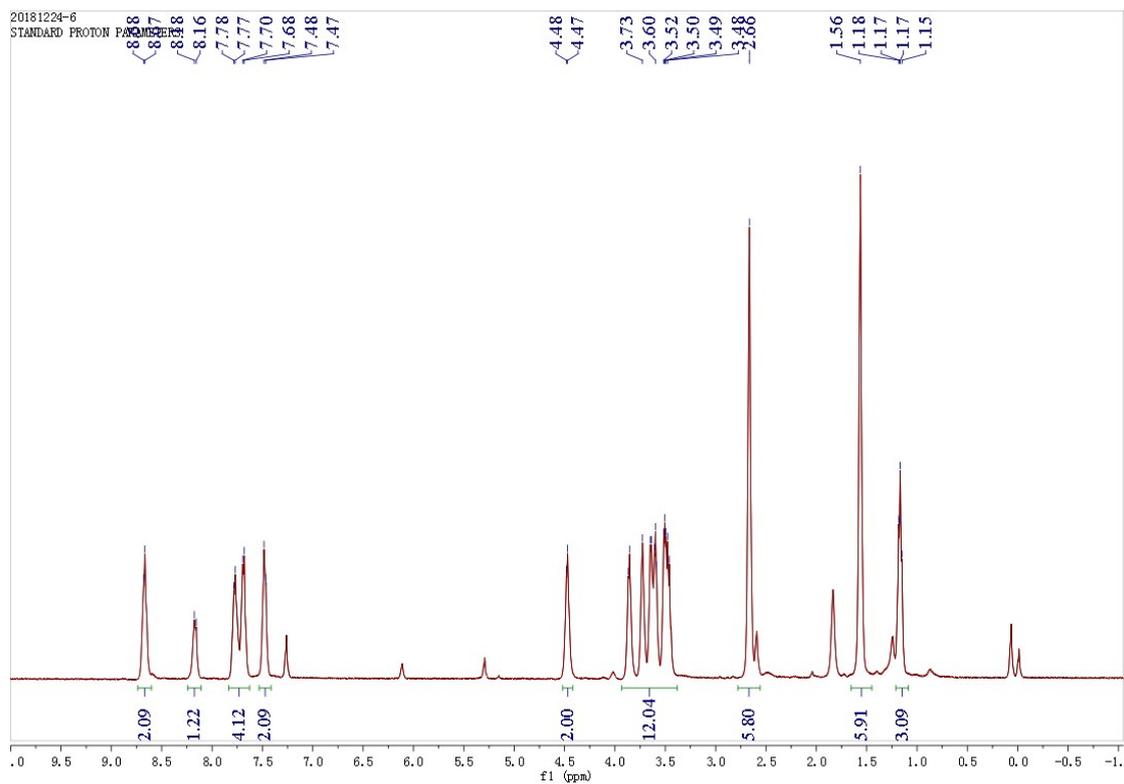


Fig. S6 $^1\text{H-NMR}$ of I-BDP (7)

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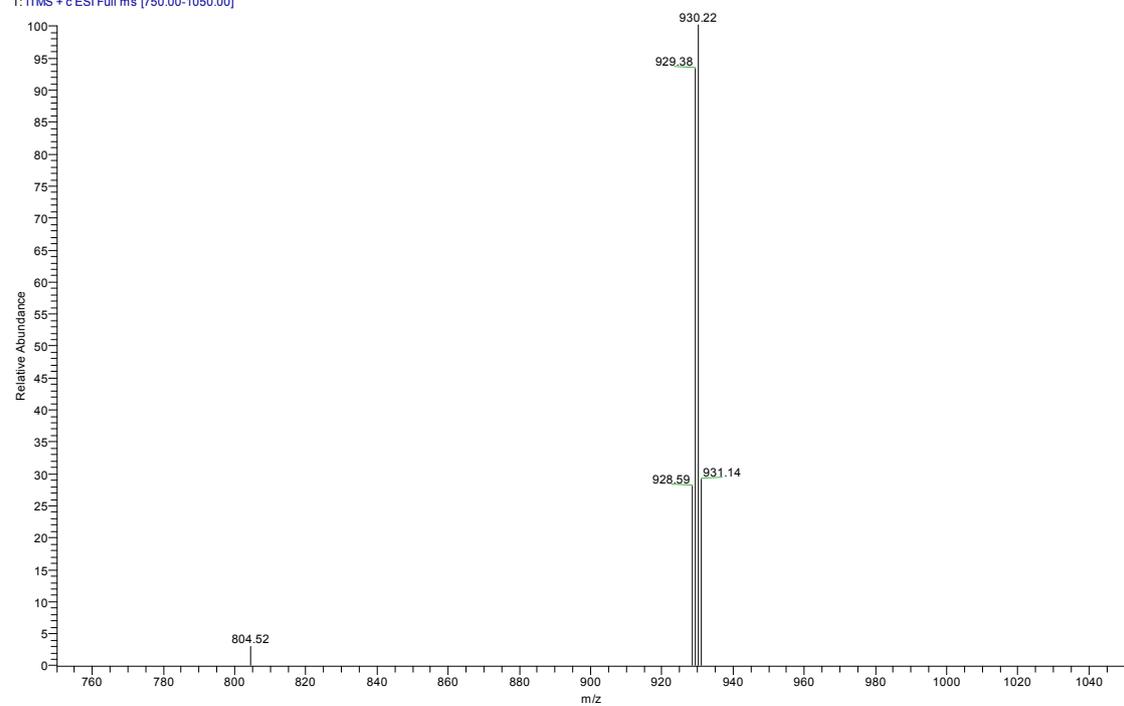


Fig. S7 ESI-MS of I-BDP (7)

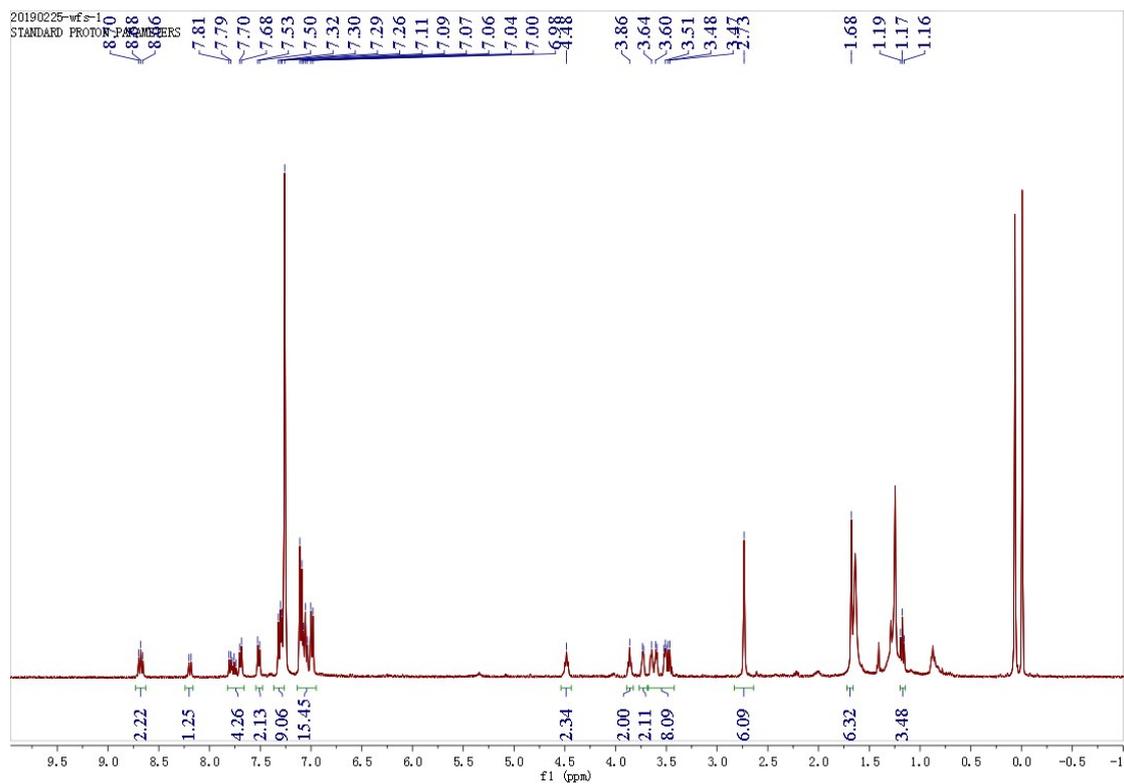


Fig. S8 ¹H-NMR of T-BDP (8)

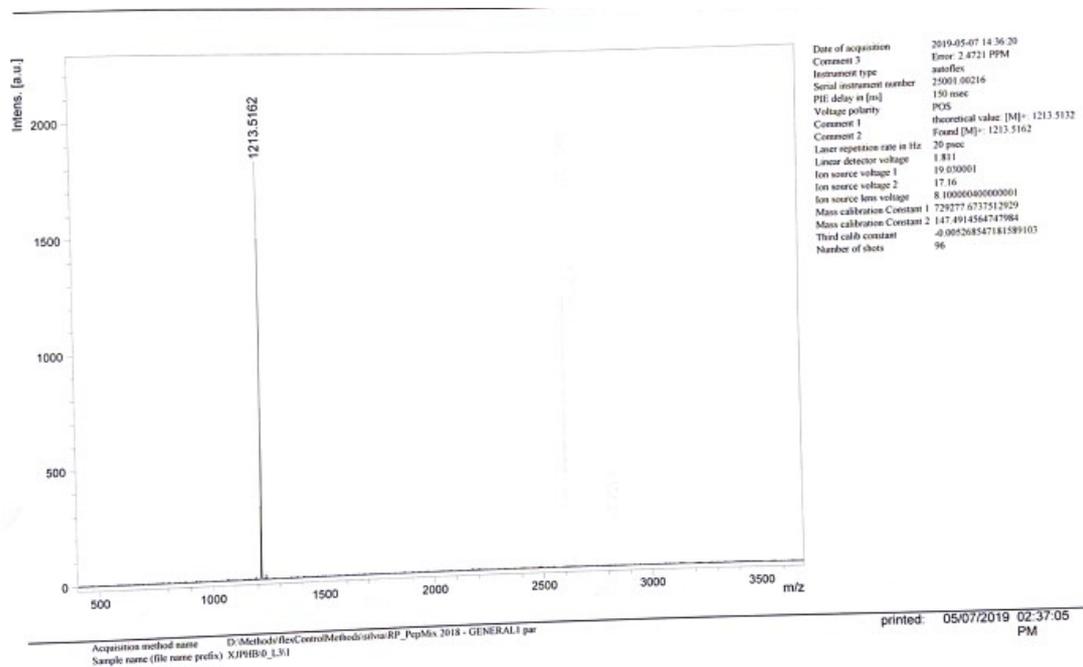


Fig. S9 Maldi-TOF MS of T-BDP (8)

Reference

- [1] Jung, H. S.; Lee, J. H.; Kim, K. et al. A Mitochondria-targeted Cryptocyanine-Based Photothermogenic Photosensitizer. *J. Am. Chem. Soc.* 2017, 139, 9972-9978
- [2] Ghosh, M.; Mora, A. K.; Nath, S.; Chandra, A. K.; Hajra, A.; Sinha, S., Photophysics of Soret-excited free base tetraphenylporphyrin and its zinc analog in solution. *Spectrochim. Acta. A.* **2013**, 116, 466-72.