Supporting Information

An in situ-activated and chemi-excited photooxygenation system based on G-poly(thioacetal) for $A\beta_{1-42}$ aggregates

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Experimental Procedures

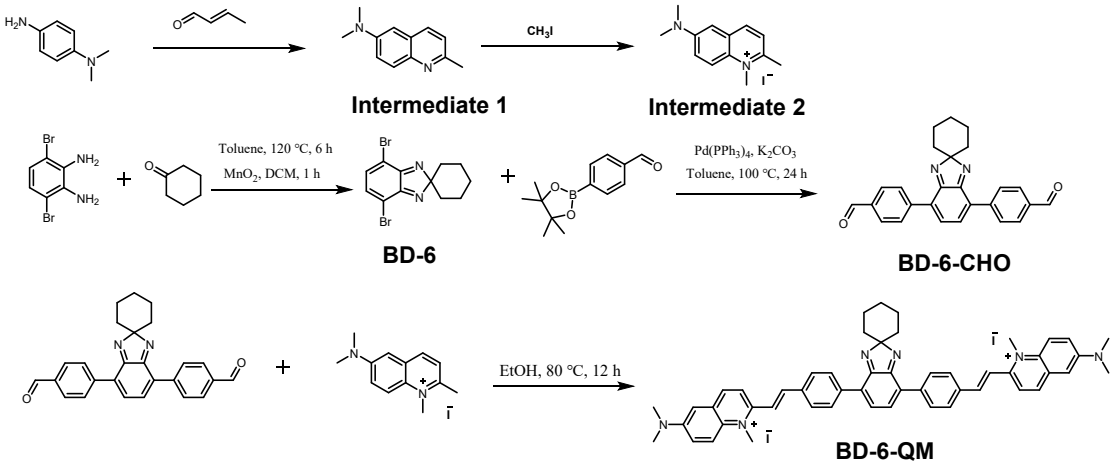
1. Materials

All compounds were from commercial sources and were not subject to purification before use. All working solutions were prepared by serial dilution of stock solutions with PBS (20 mM, pH 7.4). 3,6-dibromo-1,2-benzenediamine, 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl) benzaldehyde, cyclohexanone, cinnamic aldehyde (CA), 1,3-Dichloro-2-propanol, N, N'-Disuccinimidyl carbonate, acetic acid, 2,2'-Dithiodipyridine, sodium disulfide nonahydrate ($Na_2S{\cdot}9H_2O$) were purchased from Energy chemical Co. Ltd. Iodomethane (CH_3I), Methoxypolyethylene glycol amine were purchased from Innochem. β-D-Glucose (contains α-D-Glucose) were purchased from macklin. Tetrakis(triphenylphosphine)palladium, 2-amino-5-methylbenzoic acid were purchased from BiDe. Carbon disulfide (CS_2) was obtained from Aladdin. The synthetic trifluoroacetic acid salt forms of $A\beta_{1\text{-}42}$ peptides, human serum albumin (HSA), and bovine serum albumin (BSA) were obtained from Qiang Yao Biological Technology Co. Ltd. (China). TEM images were taken using 120kV field emission esports.

^1H and ^{13}C NMR spectra were recorded on a Bruker BioSpin GmbH spectrometer at 400 MHz and 100 MHz (150 MHz) taking TMS as the internal standard in MeOD, $CDCl_3$, or DMSO-d_6 at 25°C, respectively. Cells and tissue slices images were captured using confocal laser fluorescence microscope (TCS SP8, Leica, Germany). The UV-Vis

absorption spectra and fluorescence spectra were recorded on a UV-2600 spectrophotometer (Shimadzu, Japan) and an RF-6000 fluorescence spectrophotometer (Shimadzu, Japan). Circular dichroism spectroscopy (Applied Photophysics Ltd, Chirascan).

2. Synthesis of BD-6-QM.



Scheme S1 The Synthesis Steps of BD-6-QM.

Synthesis of 4,7-dibromospiro[benzo[d]imidazole-2,1'-cyclohexane].

3,6-Dibromo-1,2-phenylenediamine (413.4 mg, 1.56 mmol) and cyclohexanone (325 μL, 3.35 mmol) were completely dissolved in 75 mL solution of toluene. The mixture was then vacuum-sealed under inert gas protection and heated to 120°C for the reflux reaction of 6 hours. Upon completion of the reaction, crude product was obtained. After adding 85% active manganese dioxide (1.3 g, 15 mmol) and 8 mL of anhydrous dichloromethane to the crude product, the mixture was stirred at room temperature for 2 hours under an inert gas atmosphere. The reaction mixture was then filtered, and 40 mL of dichloromethane was added to the filtrate. Extracted

with 40 mL of water, dried with anhydrous sodium sulfate. Purified by column chromatography (SiO_2, eluent: petroleum ether: ethyl acetate = 15:1) to obtain the BD-6. Yield: 83.00%; ^{1}H NMR (400 MHz, $CDCl_3$-d) δ 7.21 (s, 2 H), 1.99 (d, J = 6.0 Hz, 2 H), 1.78 (s, 4 H), 1.74 (s, 4 H).

Synthesis of 4,4'-(spiro[benzo[d]imidazole-2,1'-cyclohexane]-4,7-diyl) dibenzaldehyde.

Added K_2CO_3 aqueous solution (5.2 mL, 2 M) dropwise to a solution of 4,7-dibromo-2H-benzo[b]thiophene-2-spiro-cyclohexane (549.8 mg, 1.6 mmol), 4-formylphenylboronic acid pinacol ester (1.5 mg, 6.4 mmol), and (Pd (PPh_3)$_4$) (96.6 mg, 0.084 mmol) in toluene (12 mL). Evacuated and replaced with an inert gas, then refluxed the reaction mixture at 78°C for 12 hours. After the reaction was completed, cooled to room temperature, evaporated the solvent under reduced pressure, and extracted the residue with dichloromethane and water, followed by drying over anhydrous sodium sulfate. Purified by column chromatography (silica gel, dichloromethane: petroleum ether = 10:3) to obtain BD-6-CHO. Yield: 83.00%; ^{1}H NMR (400 MHz, $CDCl_3$-d) δ 10.10 (s, 2 H), 8.16 (s, 4 H), 8.00 (d, J = 8.4 Hz, 4 H), 7.45 (s, 2 H), 1.91(m, 4 H), 1.69(m, 2 H), 1.64 (s, 4 H).

Synthesis of N, N, 2-trimethylquinolin-6-amine.

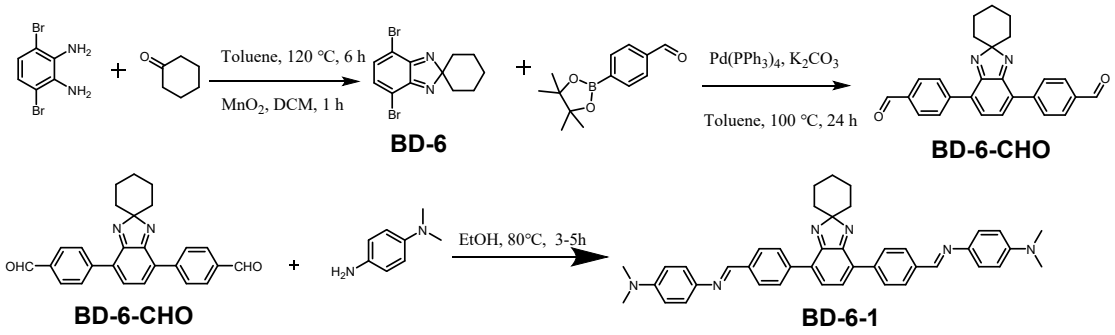
After fully dissolving N, N-Dimethyl-1,4-phenylenediamine (para-dimethylaminobenzene) (11.6 g, 85.2 mmol) in hydrochloric acid solution (6 M, 500 mL), crotonaldehyde (13 mL) was added. The mixture was then evacuated and filled with an inert gas for protection, followed by the addition of 80 mL of anhydrous toluene.

Heated the reaction mixture to reflux at 115 ± 5°C, monitored the reaction progress at intervals of 1 hour by thin-layer chromatography until the reaction was completed. After completion of the reaction, cooled to room temperature, removed toluene by extraction, adjusted the pH of the water to neutral in an ice bath, and then extracted and dried with dichloromethane. Purified by column chromatography (silica gel, petroleum ether: ethyl acetate = 20:1) to obtain the purified yellow solid. Yield: 35.00%; ^{1}H-NMR (400 MHz, Chloroform-d): δ=7.91 (dd, J = 14.3, 8.9 Hz, 2H), 7.36 (dd, J = 9.3, 2.8 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 2.9 Hz, 1H), 3.07 (s, 6H), 2.70 (s, 3H).

Synthesis of 6-(dimethylamino)-1,2-dimethylquinolin-1-ium.

The synthetic step involves dissolving N, N, 2-trimethylquinolin-6-amine (5.2 g, 27.92 mmol) in 80 mL of ethanol, then adding methyl iodide (9.72 g, 68.48 mmol) to the solution. Evacuated and replaced with an inert gas, heated to reflux at 80 ± 5°C for 10 hours. After completion of the reaction, cooled to room temperature and removed the solvent by rotary evaporation to obtain thecrude product. Purified the product by column chromatography (silica gel, dichloromethane: methanol = 40:1) to yield the orange solid.Yield: 26.08%; ^{1}H NMR (400 MHz, DMSO-d_6): δ=8.73 (d, *J* = 8.6 Hz, 1H), 8.35 (d, *J* = 9.7 Hz, 1H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.77 (dd, *J* = 9.9, 3.0 Hz, 1H), 7.27 (d, *J* = 3.0 Hz, 1H), 4.36 (s, 3H), 3.13 (d, *J* = 1.2 Hz, 6H), 2.95 (s, 3H).

3. Synthesis of BD-6-1.

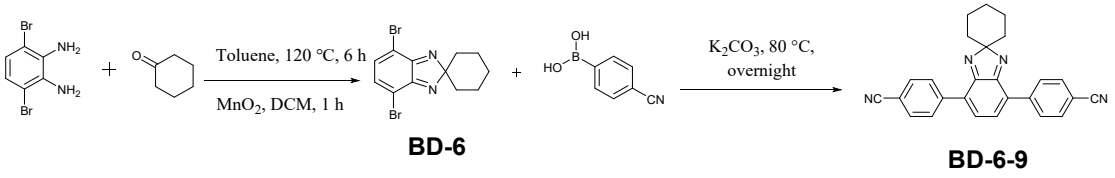


Scheme S2 The Synthesis Steps of BD-6-1.

Synthesis of 4,4'-(((1E,1'E) -(spiro[benzo[d]imidazole-2,1'-cyclohexane]-4,7-diylbis(4,1-phenylene))bis(methaneylylidene))bis(azaneylylidene))bis(N,N-dimethylaniline).

Placed BD-6-CHO (72 mg, 0.184 mmol) and (91.7 mg, 0.67 mmol) N,N-dimethylbenzene-1,4-diamine into a pressure-resistant tube, added 8 mL of anhydrous ethanol to mix them evenly, heated to 80°C, and reacted overnight. After the reaction, the dark red solid precipitates. Filtered it, washed and dried with anhydrous ethanol to obtain the product BD-6-1 (103 mg, 0.163 mmol). Yield: 88.58%; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.58 (s, 2H), 8.11 (d, J = 8.3 Hz, 4H), 8.01 (d, J = 8.3 Hz, 4H), 7.41 (s, 2H), 7.35 (d, J = 8.5 Hz, 4H), 6.83 (d, J = 8.4 Hz, 4H), 3.03 (s, 12H), 2.03 (d, J = 6.0 Hz, 4H), 1.79 (d, J = 17.6 Hz, 6H).

4. Synthesis of BD-6-9.

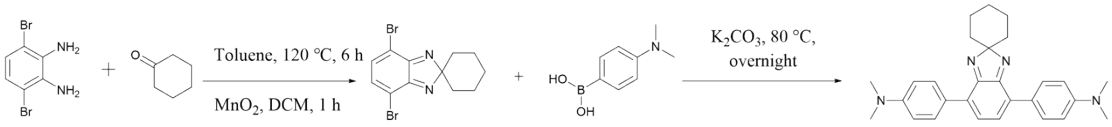


Scheme S3 The Synthesis Steps of BD-6-9.

Synthesis of 4,4'-(spiro[benzo[d]imidazole-2,1'-cyclohexane]-4,7-diyl) dibenzonitrile.

Added BD-6 (68 mg, 0.2 mmol) and 4-cyanophenylboronic acid (72.8 mg, 0.5 mmol) to a two-necked reaction flask, followed by potassium carbonate. Under argon protection, added a solvent mixture of toluene and methanol (1:1), placed the flask in an oil bath (80°C), and stirred overnight for 12 hours. After completion, cooled to room temperature, performed vacuum distillation, silica gel column chromatography purification, to yield final product BD-6-9 (47.8 mg, 0.12 mmol). Yield: 60%; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 – 7.99 (m, 4H), 7.86 – 7.62 (m, 4H), 7.41 (s, 2H), 2.02 (p, *J* = 6.1 Hz, 4H), 1.59 (s, 6H).

5. Synthesis of BD-6-8.



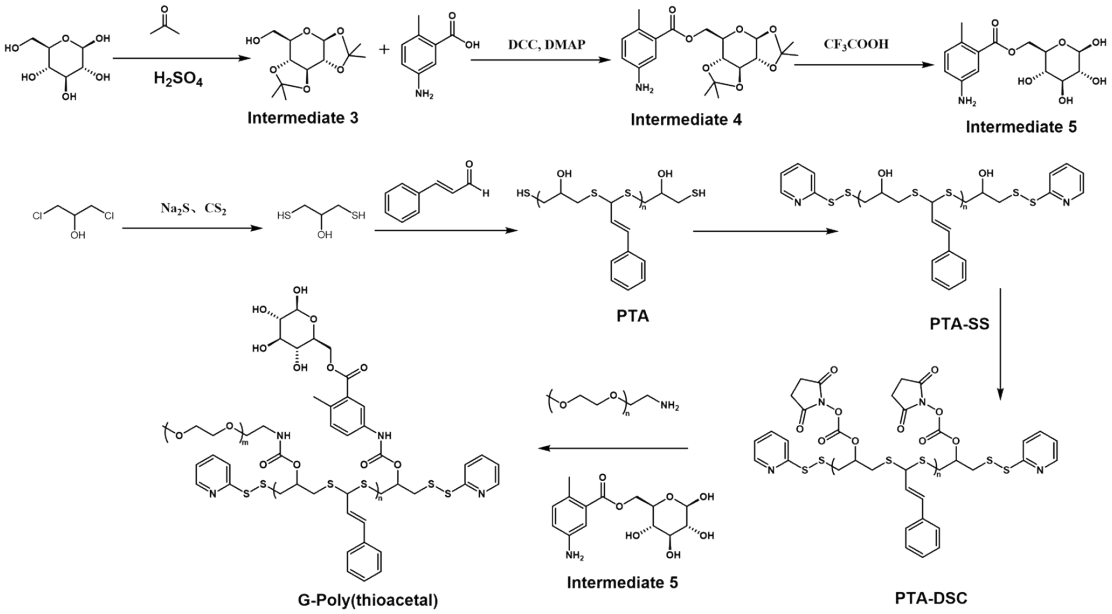
Scheme S4 The Synthesis Steps of BD-6-8.

Synthesis of 4,4'-(spiro[benzo[d]imidazole-2,1'-cyclohexane]-4,7-diyl) bis (N, N-dimethylaniline).

Placed BD-6 (80.6 mg, 0.24 mmol) and 4-N, N-dimethylphenylboronic (96.6 mg, 0.59 mmol) acid into a two-necked reaction flask, added palladium chloride catalyst, 50 mg Na_2CO_3, and a solvent mixture of toluene and methanol (3 mL, 1:1), stirred to

mix evenly. Put the flask into an oil bath and heated to 80°C, letting it react overnight. After the reaction, the reaction mixture was subjected to vacuum concentration and column chromatography purification to obtain the product BD-6-8 (15 mg, 0.035 mmol). Yield: 14.6%; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 (d, *J* = 8.9 Hz, 4H), 7.17 (s, 2H), 6.83 (d, *J* = 8.5 Hz, 4H), 3.03 (s, 12H), 2.03 (p, *J* = 5.9 Hz, 4H), 1.44 – 1.12 (m, 6H).

6. Synthesis of G-Poly(thioacetal).



Scheme S5 The Synthesis Steps of G-Poly(thioacetal).

Synthesis of ((3aS,5R,5aR,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis ([1,3] dioxolo) [4,5-b:4',5'-d] pyran-5-yl) methanol.

Added D-glucose (90 mg, 0.5 mmol) and 3.3 mL acetone to a round-bottom flask. Slowly added concentrated sulfuric acid (0.1 mL) using a syringe in an ice bath, and stirred the reaction at room temperature for 4 hours. Adjusted the pH of the reaction mixture to neutral in an ice bath, then extracted with ethyl acetate and water, retaining the organic phase. Concentrated under reduced pressure to obtain intermediate 3. Yield: 95.30%. ^{1}H NMR (δ [ppm], 400 MHz, $CDCl_3$): 1.33 (s, 6H, 2 × CH_3), 1.47 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 2.35 (br s, 1H, OH), 3.83–3.89 (m, 3H, CH_2 + CH), 4.26 (dd, J = 7.9 Hz, J = 1.7 Hz, 1H, CH), 4.33(dd, J = 5.0 Hz, J = 2.4 Hz, 1H, CH), 4.60 (dd, J = 7.9 Hz, 2.4 Hz, 1H, CH), 5.60 (d, J = 5.0 Hz, 1H, anomeric CH).

Synthesis of ((3aS,5R,5aR,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis ([1,3]

dioxolo) [4,5-b:4',5'-d] pyran-5-yl) methyl5-amino-2-methylbenzoate.

Added intermediate 3 (0.05 g, 0.2 mmol) and 5-amino-2-methylbenzoic acid (0.061 g, 0.4 mmol) into a round-bottom flask. Added diisopropyl carbodiimide (0.041 g, 0.2 mmol), 4-dimethylaminopyridine (0.004 g, 0.04 mol), dissolving in 0.8 mL DCM and 0.8 mL DMF. Stirred the reaction at room temperature for 12 hours. After completion of the reaction, concentrated the reaction mixture to obtain solid. Purified by column chromatography using petroleum ether: ethyl acetate = 1:8. The purified product was intermediate 4. colourless liquid; Yield:43.80%**;** ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.09 (d, J = 2.5 Hz, 1H), 6.98 (d, J = 8.2 Hz, 1H), 6.71 (dd, J = 8.1, 2.6 Hz, 1H), 5.95 (d, J = 3.8 Hz, 1H), 5.22 (d, J = 3.0 Hz, 1H), 5.18 (s, 2H), 4.67 (d, J = 3.7 Hz, 1H), 4.33 (dt, J = 7.7, 5.5 Hz, 1H), 4.20 (dd, J = 7.7, 3.0 Hz, 1H), 4.05 (dd, J = 8.5, 6.1 Hz, 1H), 3.92 (dd, J = 8.5, 5.1 Hz, 1H), 2.34 (s, 3H), 1.47 (s, 3H), 1.35 (s, 3H), 1.28 (s, 3H), 1.24 (s, 3H).

Synthesis of ((2R,3S,4S,5R,6R)-3,4,5,6-tetrahydroxytetrahydro-2H-pyran-2-yl) methyl 5-amino-2-methylbenzoate.

Intermediate 4 was added to the solution of trifluoroacetic acid (trifluoroacetic acid: water = 1:1) and stirred for 2 hours. The reaction liquid was extracted with dichloromethane, and the organic phase was concentrated and dried to obtain the intermediate 5. Oily yellow; Yield:40.3%.

Synthesis of 1,3-dimercaptopropan-2-ol

After dissolving carbon disulfide (CS_2) (13.2 mL, 220 mmol) and $Na_2S•9H_2O$ (48 g, 200 mmol) in water (48 mL), the mixture was heated to 40°C and stirred for 5 hours.

Removed excess carbon disulfide by vacuum concentration, then added 70 mL water to obtain a 33% solution of sodium trithiocarbonate. Then, 1,3-dichloropropanol (6.72 mL, 70 mmol) was added in an ice bath, followed by heating to 60°C and stirring for 5 hours. After the reaction was completed, the reaction mixture was cooled to room temperature, washed with ethyl acetate (5 × 100 mL), and the aqueous phase was collected. It was then slowly acidified with concentrated sulfuric acid in an ice bath, followed by extraction of the aqueous phase with ether. The organic phase was collected until it became colorless. Concentrated and dried to obtain the crude product as a light brown oil. Further purified by vacuum distillation, heated to 160℃, and collected the pale yellow liquid as the obtained product 1,3-dimercaptopropan-2-ol. Light yellow liquid; Yield: 30.46%; ^{1}H NMR (400 MHz, Chloroform-d): δ 3.72 (tq, J = 7.5, 4.3 Hz, 1H), 2.85 – 2.63 (m, 5H), 1.55 – 1.42 (m, 2H).

Synthesis of the PTA-SS

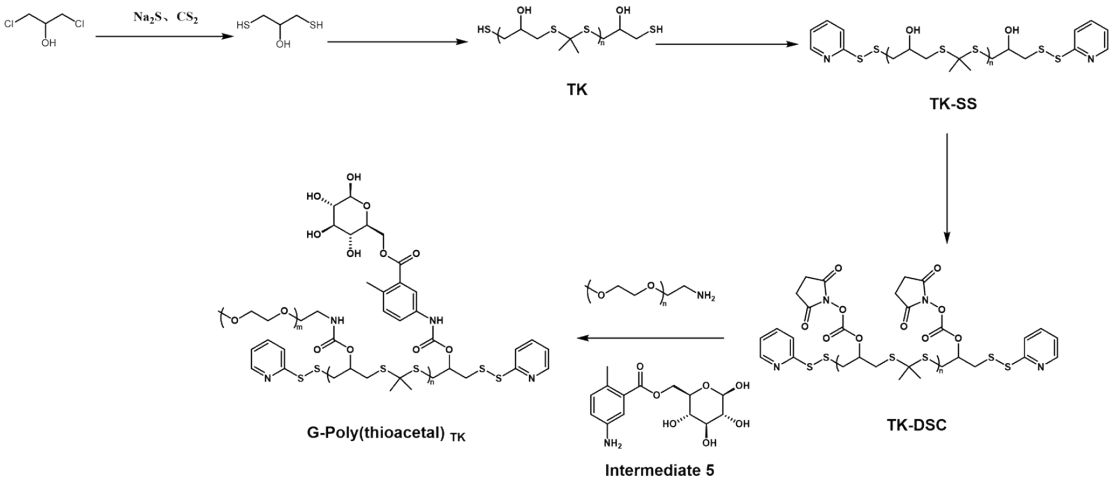
Added 1,3-dimercaptopropan-2-ol (0.26 g, 2.09 mmol), cinnamaldehyde (0.26 g, 2 mmol) and 8 μL of hydrochloric acid to a round-bottom flask, evacuated and filled with inert gas, stirred at room temperature for 30 min. Washed the sticky solution with water to remove most of the hydrochloric acid, dissolved in 2 mL of tetrahydrofuran, and precipitated in excess cold n-hexane. Removed the n-hexane and dissolved the precipitate in a minimal amount of tetrahydrofuran, purified using a gel column with the molecular weight range of 600-14000, eluting with tetrahydrofuran to obtain PTA (0.2 g, 38.36%). Added PTA (0.4 g, 0.09 mmol) and 2,2-dithiobispyridine (0.39 g, 0.18 mmol) to a round-bottom flask, evacuated and

filled with inert gas, dissolved in anhydrous tetrahydrofuran, and slowly added 100 μL of ice-cold acetic acid. Stirred at room temperature for 24 hours. After concentration under vacuum, the product was purified using a gel column with a molecular weight range of 600-14000, and eluted with tetrahydrofuran to obtain PTA-SS (0.18 g, 22.78%).

Synthesis of the G-Poly(thioacetal).

Added PTA-SS (0.18 g, 0.04 mmol) and N, N-disuccinimidyl carbonate (DSC) (0.19 g, 1.2 mmol) to 5 mL DMF, evacuated and filled with inert gas, stirred for 24 hours. Subsequently, the reaction solution was concentrated under vacuum and purified using 1% cross-linked gel column with a molecular weight range of 600-14000. The elution with N, N-Dimethylformamide yielded PTA-DSC (0.2 g, 54.05%). Dissolved PTA-DSC (0.2 g, 0.033 mmol), intermediate 5 (0.04 g, 0.12 mmol), and methoxy polyethylene glycol amine (0.09 g, 0.04 mmol) in DMF (5 mL), evacuated and filled with inert gas, stirred for 24 hours. After the reaction, vacuumed concentrate the reaction mixture, purified using gels with 1% cross-linking: separation molecular weight of 600-14000 hydrophobic polymer, eluting with N, N-dimethylformamide. Purified to obtain the final product G-PTA (0.1 g, 30.30%).

7. Synthesis of G-Poly(thioacetal)-$_{TK}$.



Scheme S6. Synthetic procedures of G-Poly(thioacetal)-$_{TK}$.

Synthesis of TK.

TK was synthesized by a similar procedure with PTA by changing the CA into acetone and obtained as a crude product and directly used for the next reaction without further purification.

Synthesis of TK-SS.

TK-SS was synthesized using a method similar to that of PTA-SS by converting PTA into TK, resulting in the yellow viscous liquid and a light yellow waxy solid (Yield: 89%).

Synthesis of TK-DSC.

TK-DSC was synthesized using a method similar to that of PTA-DSC by converting PTA-SS into TK-SS, resulting in the yellow solid (Yield: 92%).

Synthesis of G-Poly(thioacetal)-$_{TK}$.

G-Poly(thioacetal) $_{TK}$ was synthesized using a method similar to that of G-Poly(thioacetal) by converting PTA-DSC into TK-DSC, resulting in the yellow solid (Yield: 43%).

8. UV absorption spectrum of BD-6-QM and BD-6-QM/NPs.

Dissolved photosensitizers (10 μm) and BD-6-QM/NPs (10 μm) in different solvents and tested their ultraviolet absorption using a UV spectrophotometer.

9. Fluorescence spectrum of photosensitizers and BD-6-QM/NPs.

Dissolved photosensitizers (10 μm) and BD-6-QM/NPs (10 μm) in various solvents and analyzed their fluorescence spectra using a fluorescence spectrophotometer.

10. Preparation of $A\beta_{1-42}$ Oligomer, $A\beta_{1-42}$Monomer, $A\beta_{1-42}$ Aggregates.

$A\beta_{1-42}$ powder was dissolved in hexafluoroisopropanol, freeze-dried to obtain $A\beta_{1-42}$ monomer powder and stored at -80℃. The $A\beta_{1-42}$ monomer powder was dissolved in PBS to create the $A\beta_{1-42}$ monomer solution (100 μM), which is kept on ice when not in active use. The $A\beta_{1-42}$ monomer powder was dissolved in PBS and incubated at 37℃ for 24 hours to obtain $A\beta_{1-42}$ oligomers (100 μM). The $A\beta_{1-42}$ aggregates powder was dissolved in PBS and incubated at 37℃ for 7 days to obtain $A\beta_{1-42}$ aggregates (100 μM).

11. Fluorescence spectrum of photosensitizers and BD-6-QM/NPs in the presence of $A\beta_{1-42}$ aggregates.

Photosensitizers (1 μM)/ BD-6-QM/NPs (1 μM), $A\beta_{1-42}$ aggregates (10 μM), $A\beta_{1-42}$ monomers (10 μM), $A\beta_{1-42}$ oligomers (10 μM), other amino acids (10 μM), and various ions (10 μM) were incubated in PBS for 10 minutes. Afterward, the fluorescence spectra were measured using a fluorescence spectrophotometer.

12. Molecular docking.

Using PyMOL (open-source), removed water molecules and ions from the protein structure. Added hydrogen atoms to the protein, calculated the charges, and converted the protein structure to a PDBQT file. After energy minimization of the compound, converted it to a MOL file, and then to a PDBQT file. Used the prepared PDBQT files to perform molecular docking simulations of the protein and compound.

13. Viscosity response of BD-6-QM.

First, BD-6-QM was prepared in different viscosity systems (ratios ranging from 1: 1 to 99: 1). BD-6-QM (1 μM) was tested in water/glycerol systems with varying viscosities using a fluorescence spectrophotometer to examine the fluorescence spectra in different systems.

14. Singlet Oxygen detection of photosensitizers and BD-6-QM/NPs.

9,10-Anthracenediyl-bis(methylene) dimalonic acid (ABDA) is a reactive oxygen species indicator, which exhibits a gradual decrease in ultraviolet absorption at 378 nm under the oxidative action of singlet oxygen ($^1O_2$). 1,3-Diphenylisobenzofuran (DPBF) is a highly specific $^1O_2$ indicator that forms an endoperoxide, which decomposes into 1,2-diphenylethane, resulting in a rapid decrease in ultraviolet-visible absorption at 410 nm. Under dark conditions, the photosensitizer BD-6-QM and RB were at a concentration of 10 μM, ABDA indicator concentration was 100 μM, and the solvent was PBS. Subsequently, using the multifunctional microplate reader Biotek Cytation 5, the UV absorption intensity of ABDA activated by white light was measured over time under different conditions. Under dark conditions, BD-Se-QM/NPs concentration was 10 μM, DPBF indicator concentration was 100 μM, H_2O_2

concentration was 500 μM, and the solvent was PBS. The UV absorption intensity of DPBF activated by H_2O_2 was then measured over time using the multifunctional microplate reader Biotek Cytation 5 under different conditions.

15. Calculation of $^1O_2$ yield.

The Φ value represents the yield of $^1O_2$ and is given as the best-fit values ± Std. Error. The Φ_{sam} value is calculated using linear regression with Graphpad Prism 8.0 software. The calculation formula for Φ_{sam} is as follows:

$$\Phi_{sam} = \Phi_{std} \left(\frac{K_{sam}}{k_{std}}\right) \cdot \left(\frac{S_{std}}{S_{sam}}\right)$$

Φ_{std} represents the $^1O_2$ yield of the standard reference material RB in methanol. K_{sam} and K_{std} are the slopes of the UV absorption changes before and after illumination for the sample and RB, respectively. F=1-10^(-OD).

16. Monitoring the generation of $^1O_2$ within cells.

The ability of photosensitizers to produce $^1O_2$ within cells was measured using the $^1O_2$ detection agent 2',7'-dichlorofluorescin diacetate (DCFH-DA). This agent is oxidized by reactive oxygen species into dichlorofluorescein (DCF), which emits green fluorescence. SH-SY5Y cells were incubated with the photosensitizers (1 μM) or BD-6-QM/NPs, BD-6-QM/NPs$_{-TK}$ (1 μM) in the presence of $A\beta_{1-42}$ for 2 hours. After washing with PBS, DCFH-DA (10 μM) was added and incubated for 30 minutes. Following 10 minutes of light exposure or darkness, the cells were washed three more times and then imaged using laser confocal microscopy. The excitation wavelength (λex) for DCFH-DA was 488 nm, and the emission wavelength (λem) was 500-560 nm.

17. Particle Size Measurement.

Took 3 mL of BD-6-QM/NPs solution and used the Litesizer 500 Nanoparticle Size Analyzer for dynamic light scattering (DLS) measurements of the nanoparticle size at room temperature. Additionally, performed DLS recovery tests and observed the morphology of nanoparticles under a Talos L120c transmission electron microscope at an acceleration voltage of 120KV to obtain the actual particle size of the nanoparticles.

18. The drug release of BD-6-QM/NPs.

BD-6-QM/NPs was dissolved in PBS or H_2O_2 (500 μM), mixed thoroughly in a water bath at 37°C, and centrifuged to collect the supernatant at intervals of 30 min within 0 to 6 hours. The UV absorption intensity of the supernatant at different time points was measured using a UV-visible spectrophotometer.

19. Data analysis.

Data are presented as mean ± standard deviation. One-way analysis of variance (t-test) was used to determine the significance of differences. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ are considered statistically significant.

20.Result and discussion

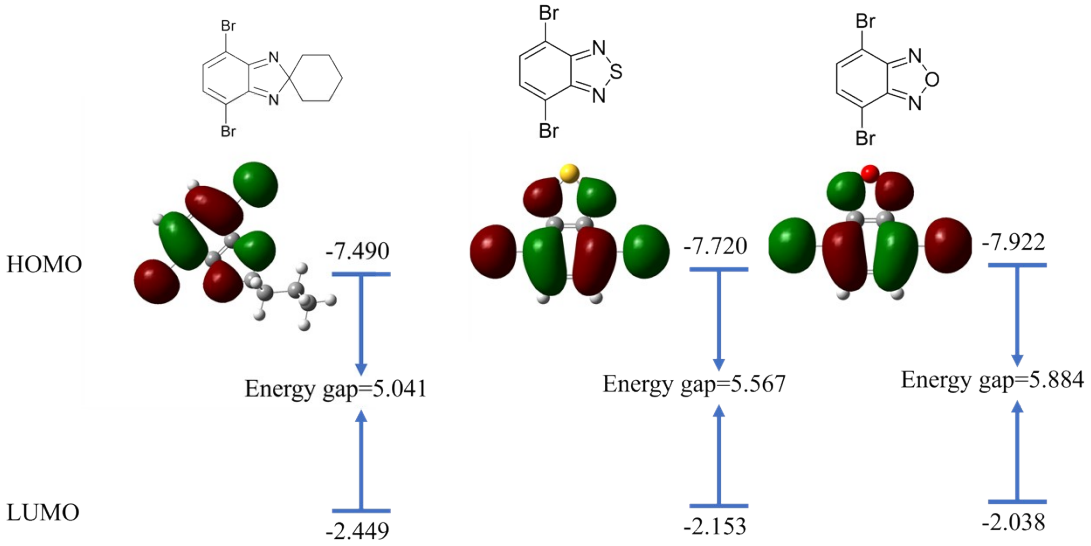


Fig.S1 The HOMO-LUMO electron cloud distribution and energy level gap of benzodiazoles substituted at the 2-position with C, S, and O atoms.

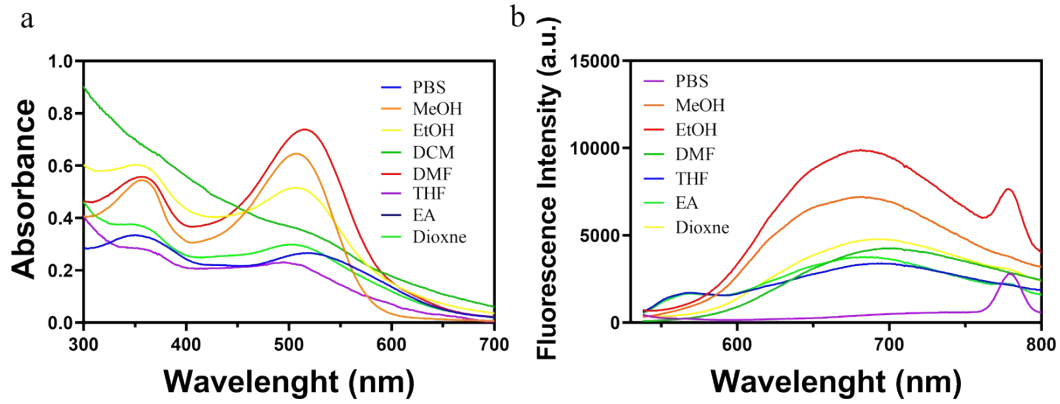


Fig.S2 Spectral properties of BD-6-QM.

(a) Uv spectra of BD-6-QM in different solvents.

(b) Fluorescence spectra of BD-6-QM in different solvents.

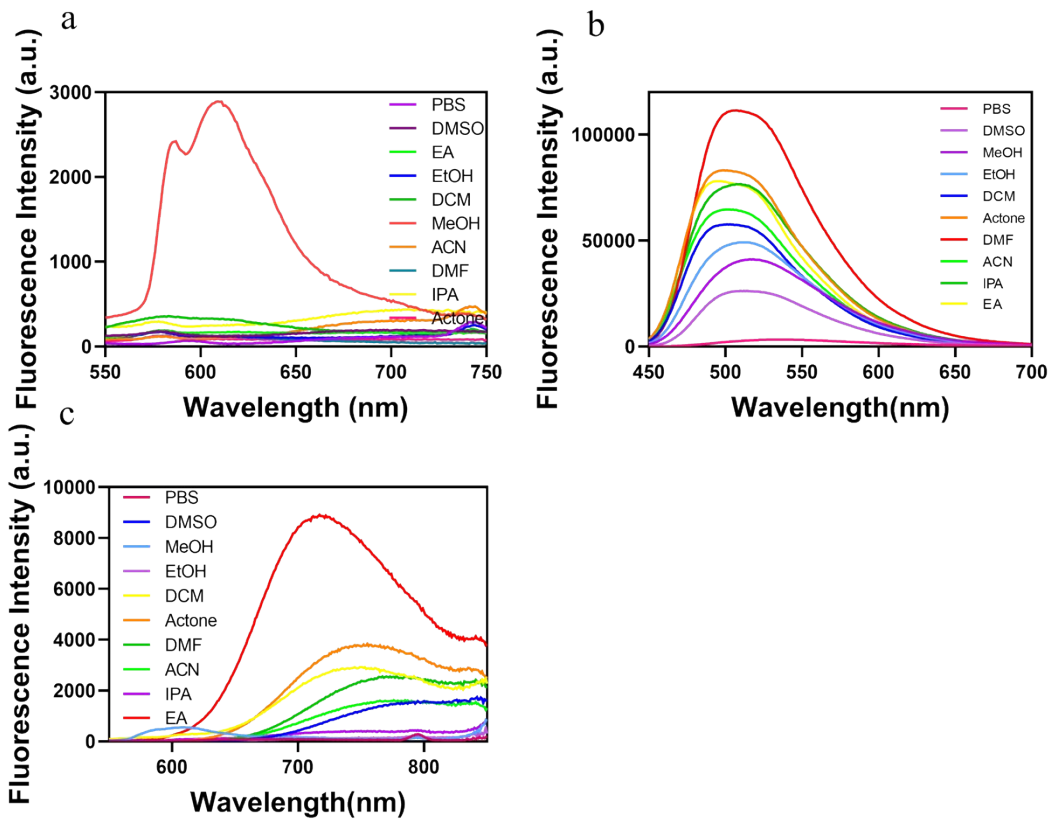


Fig.S3 Spectral properties of BD-6-1, BD-6-9, BD-6-8.

(a) Fluorescence spectra of BD-6-1 in different solvents.

(b) Fluorescence spectra of BD-6-9 in different solvents.

(c) Fluorescence spectra of BD-6-8 in different solvents.

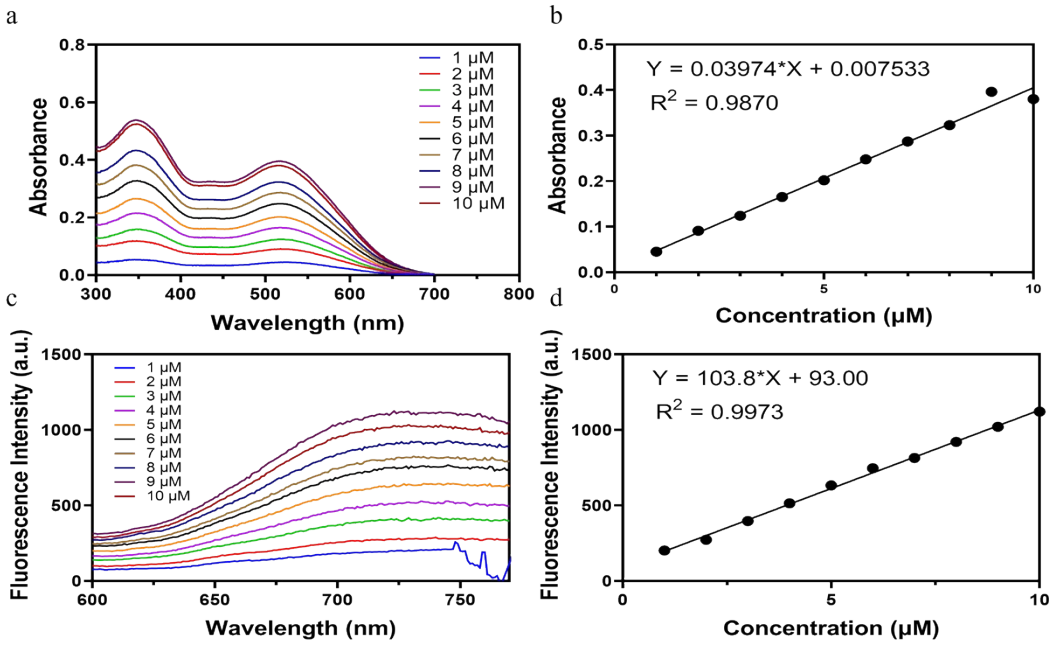


Fig.S4 Titration spectra of BD-6-QM.

(a) Uv titration spectra of BD-6-QM (1-10 μM), the UV absorption of BD-6-QM is at 518 nm.

(b) Linear fitting of ultraviolet titration for BD-6-QM.

(c) Fluorescence titration spectra of BD-6-QM (1-10 μM), the fluorescence emission of BD-6-QM is at 715 nm.

(d) Linear fitting of fluorescence titration for BD-6-QM.

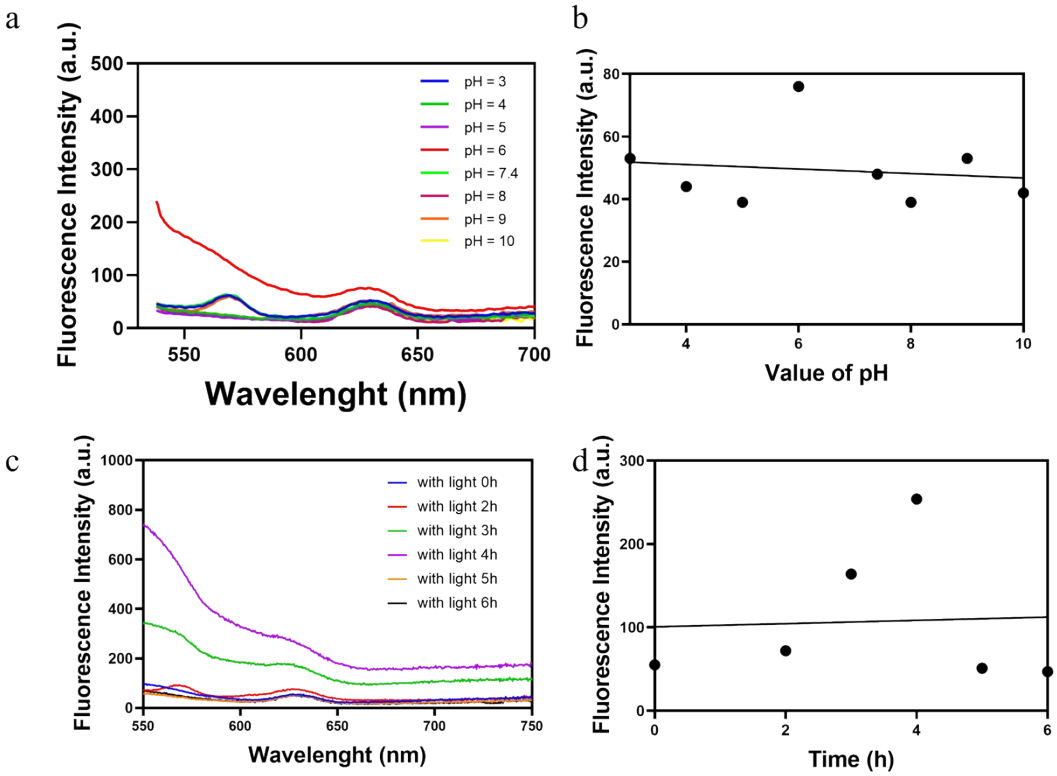


Fig. S5 The fluorescence properties of BD-6-QM.

(a) Fluorescence spectra of BD-6-QM at different PH.

(b) Fluorescence emission of BD-6-QM at different pH levels.

(c) Fluorescence spectra of BD-6-QM at different time under white lamp irradiation.

(d) Fluorescence emission of BD-6-QM at different times under white light irradiation.

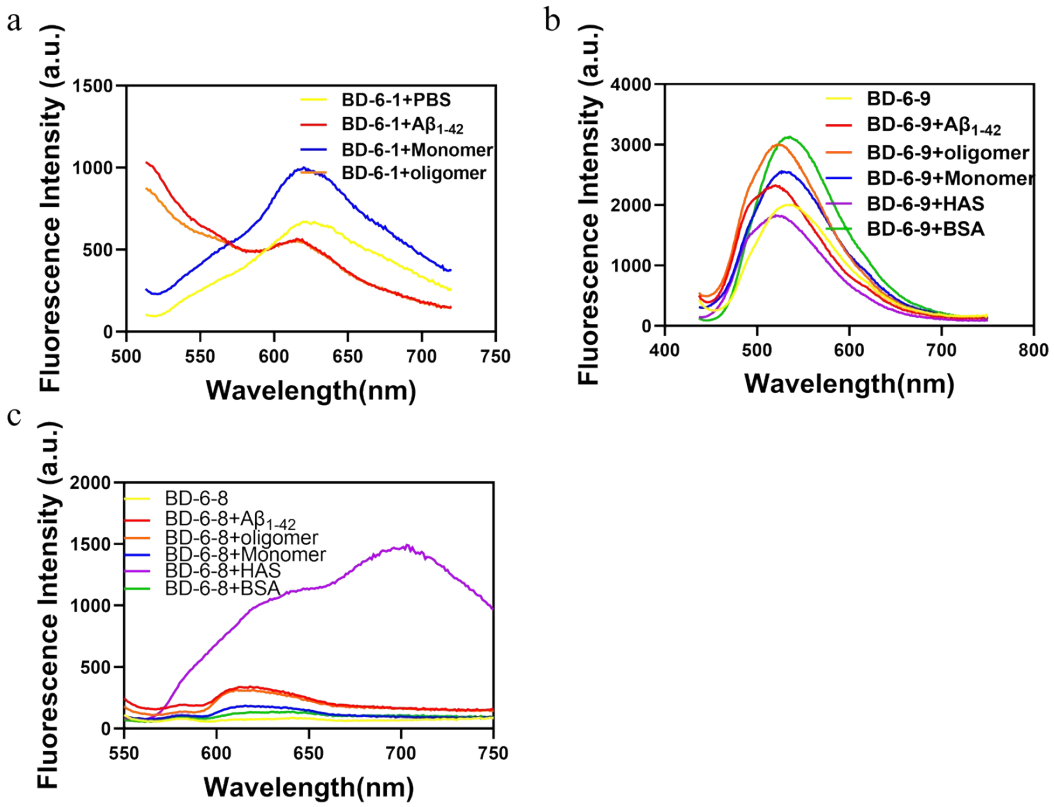


Fig.S6 Fluorescence spectra of BD-6-1, BD-6-9, BD-6-8 binding to different proteins.

(a) Fluorescence spectra of BD-6-1 binding to different proteins.

(b) Fluorescence spectra of BD-6-9 binding to different proteins.

(c) Fluorescence spectra of BD-6-8 binding to different proteins.

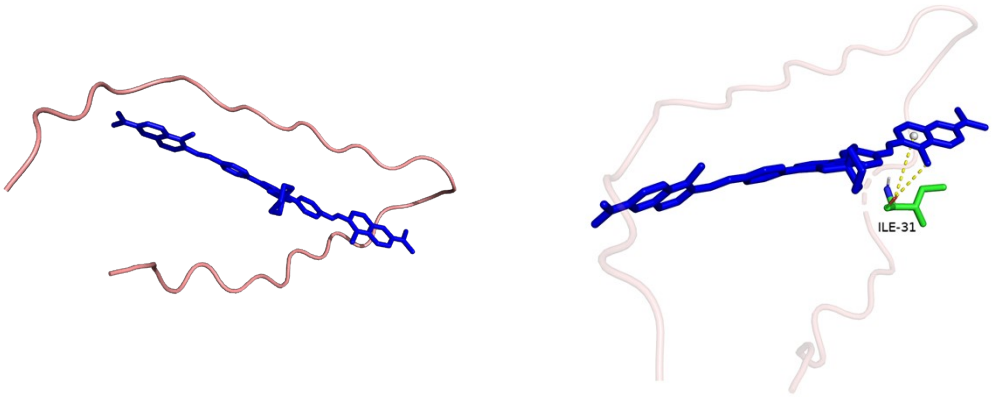


Fig.S7 Molecular docking of BD-6-QM with the Aβ protein (5KK3).

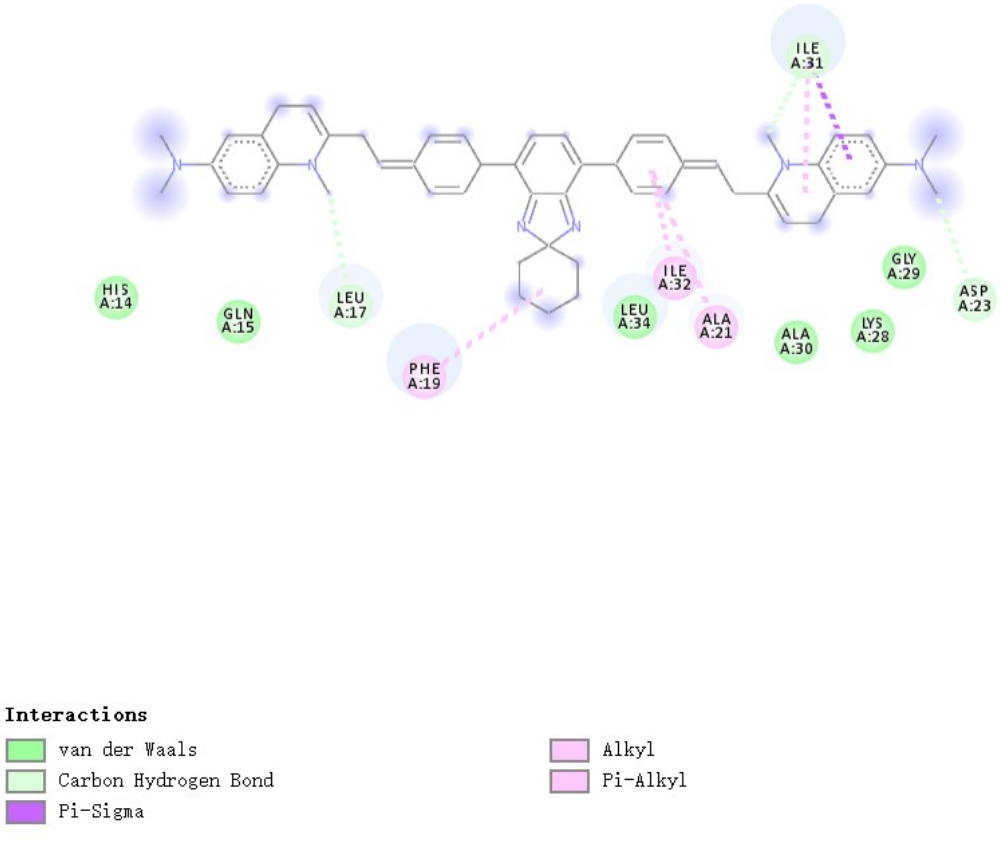


Fig.S8 Docking site of BD-6-QM with Aβ protein (5KK3).

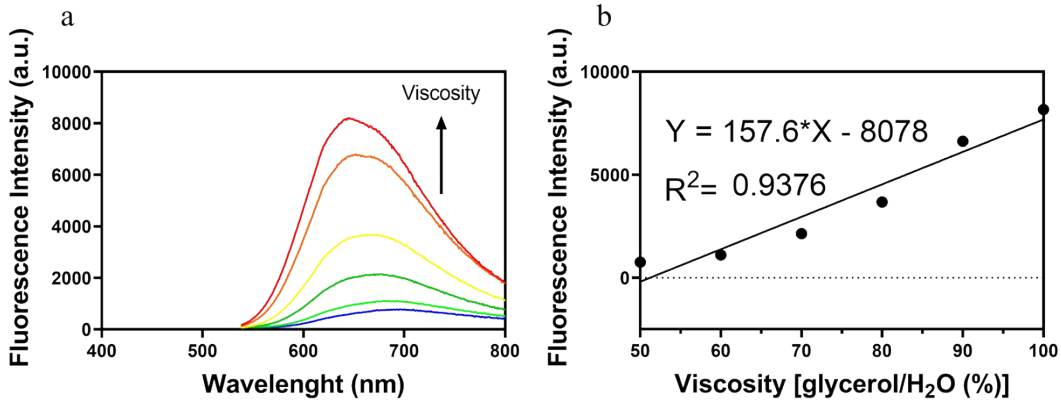


Fig.S9 Response of BD-6-QM to viscosity.

(a) Fluorescence spectra of BD-6-QM at different viscosities.

(b) Linear curve of BD-6-QM relating viscosity to fluorescence.

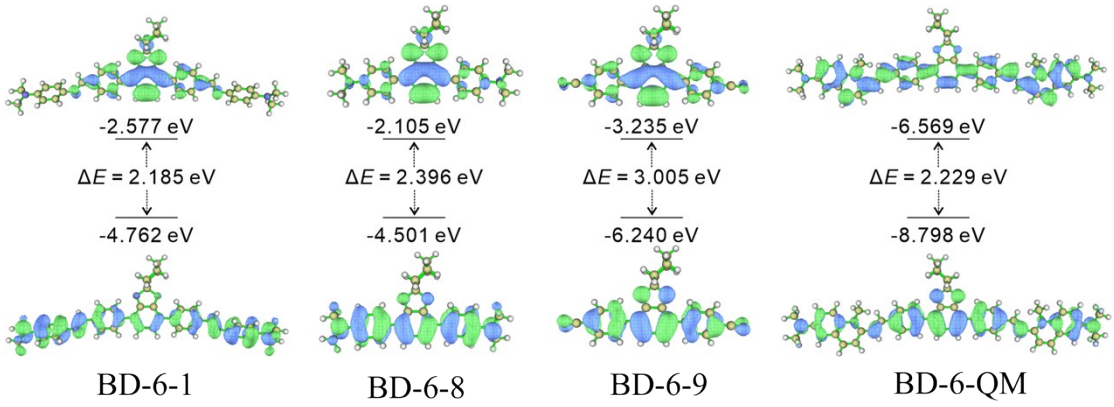


Fig.S10 The distributions and energy levels of HOMO and LUMO in BD-6-1, BD-6-8, BD-6-9, and BD-6-QM at B3LYP/6-31G* level.

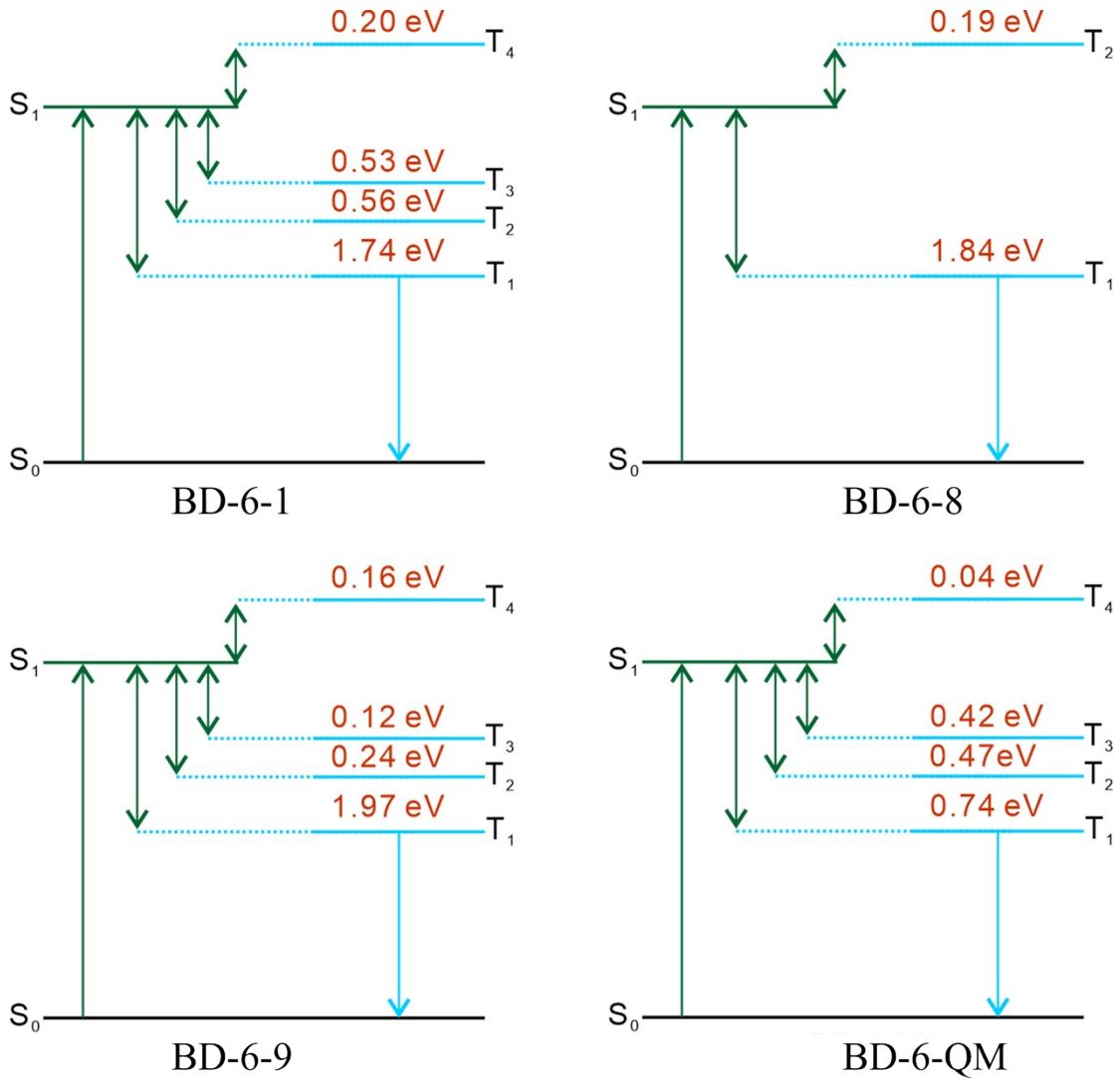


Figure 11. The calculated energy gap of singlet and triplet excited states in BD-6-1, BD-6-8, BD-6-9, and BD-6-QM at CAM-B3LTP/6-31G* level.

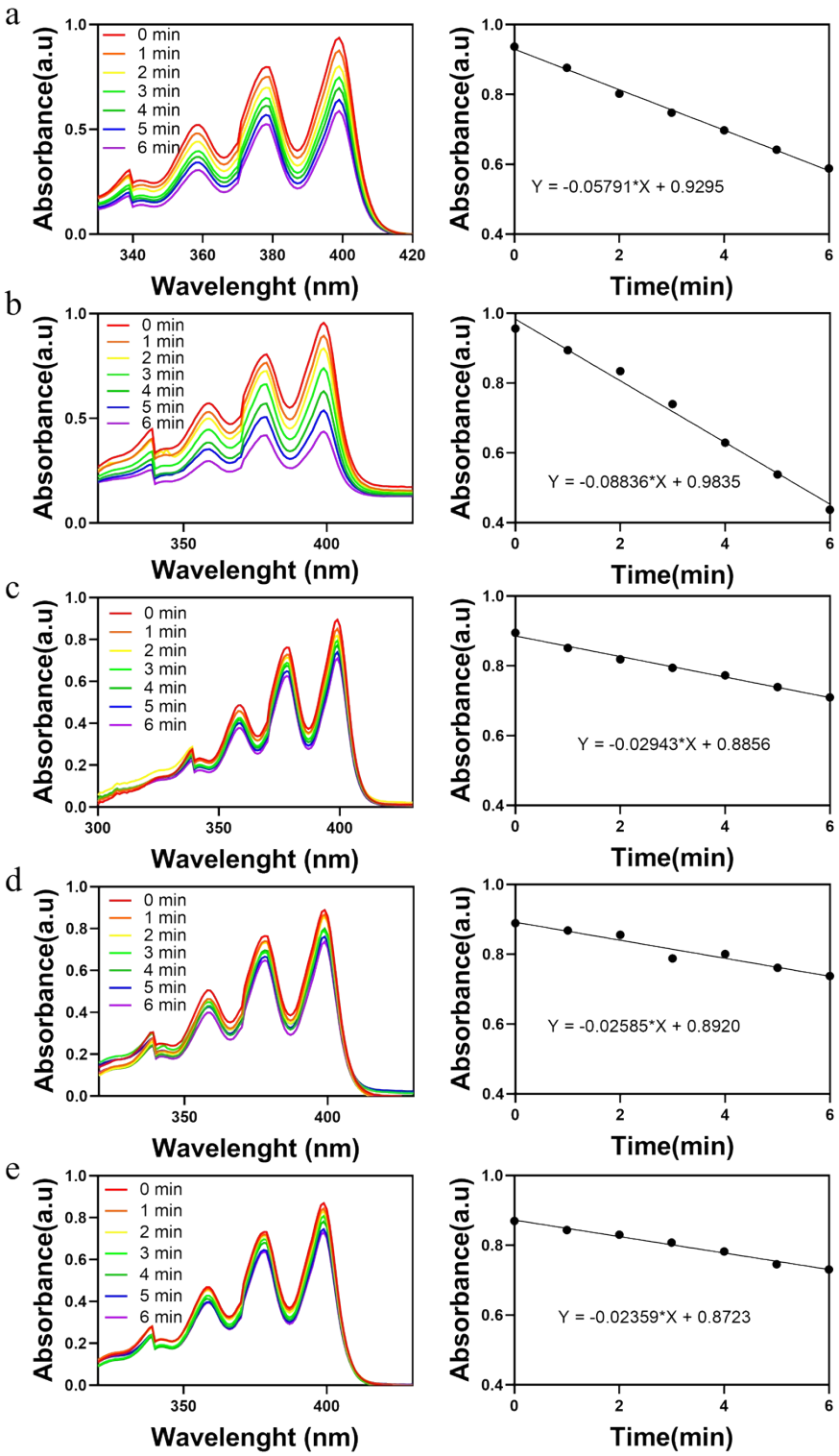


Fig.S12 Comparison of $^1O_2$ generation by photosensitizers.

(a) The UV spectrum of ABDA after white light irradiation of RB changes over time and shows a linear relationship.

(b) The UV spectrum of ABDA after white light irradiation of BD-6-QM changes over time and shows a linear relationship.

(c) The UV spectrum of ABDA after white light irradiation of BD-6-9 changes over time and shows a linear relationship.

(d) The UV spectrum of ABDA after white light irradiation of BD-6-8 changes over time and shows a linear relationship.

(e) The UV spectrum of ABDA after white light irradiation of BD-6-1 changes over time and shows a linear relationship.

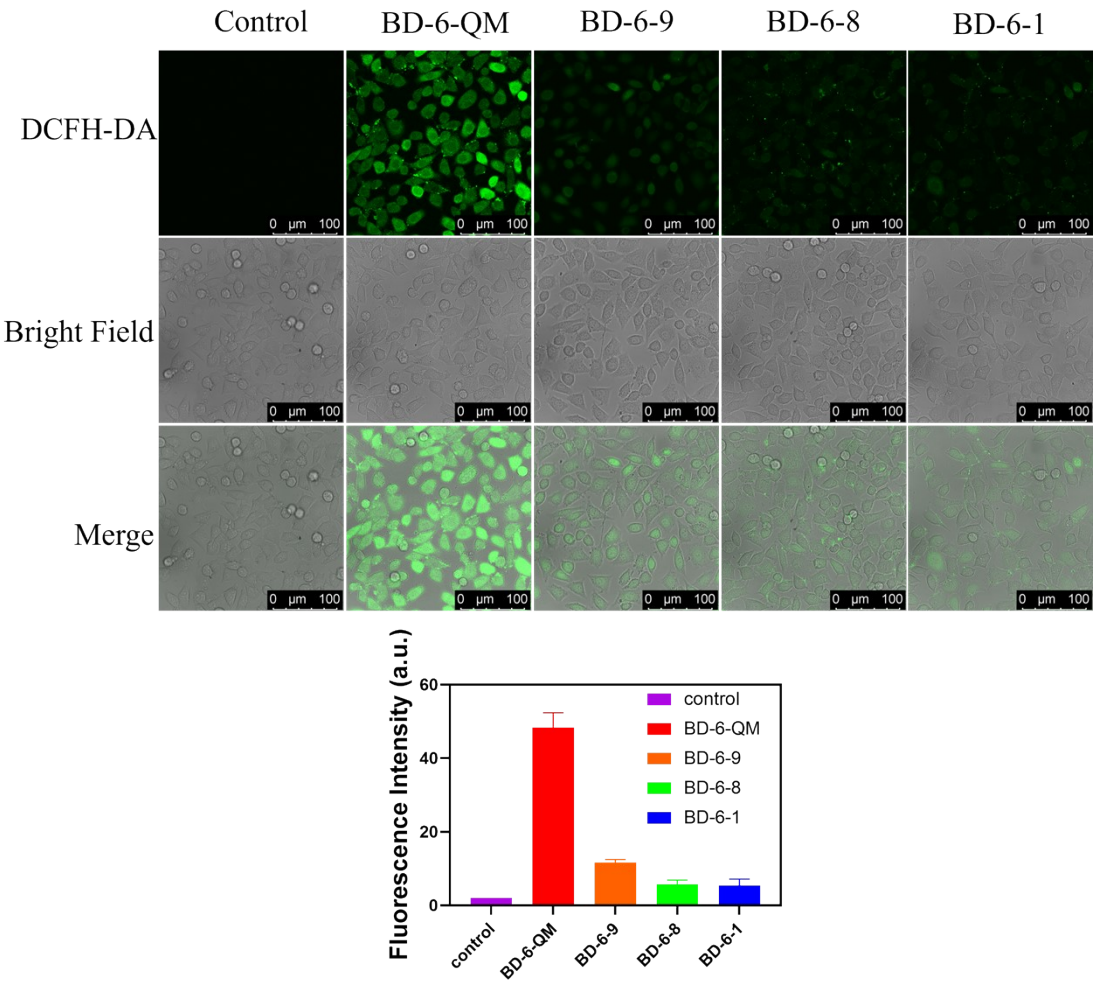


Fig.S13 Comparison of singlet oxygen generation by different photosensitizers within cells.

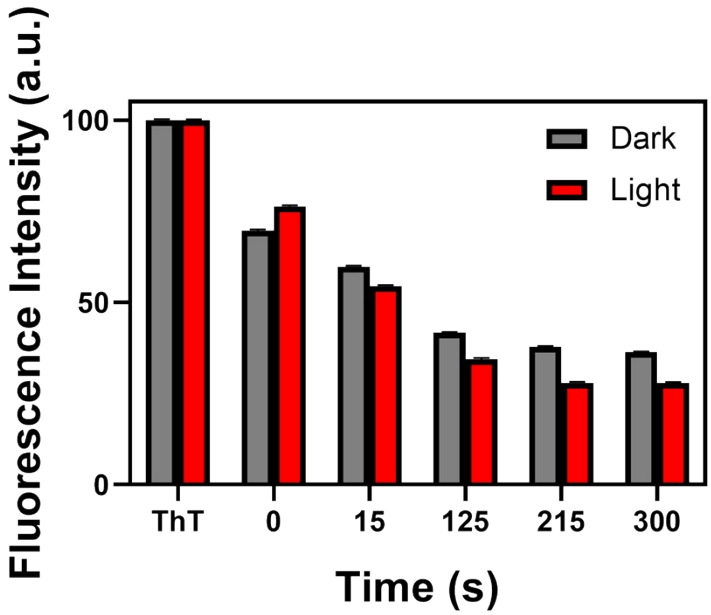


Fig.S14 Under dark or light conditions, the effect of BD-6-QM on $A\beta_{1-42}$ aggregation was detected by ThT.

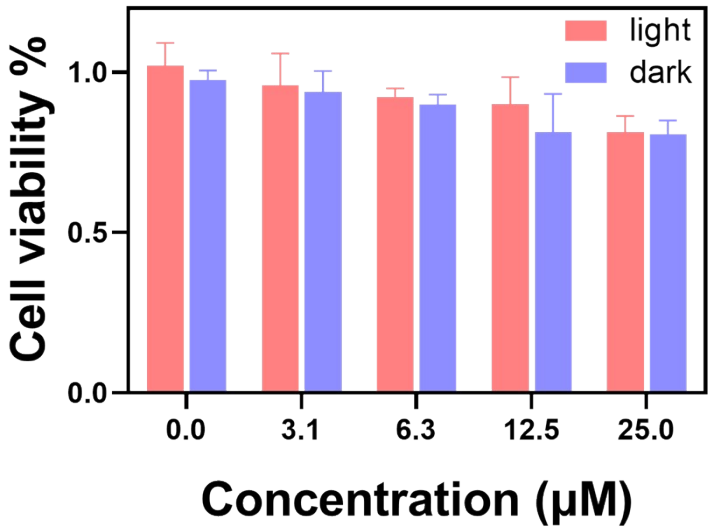


Fig.S15 Survival rate of SH-SY5Y cells with different concentrations of BD-6-QM under dark or light conditions.

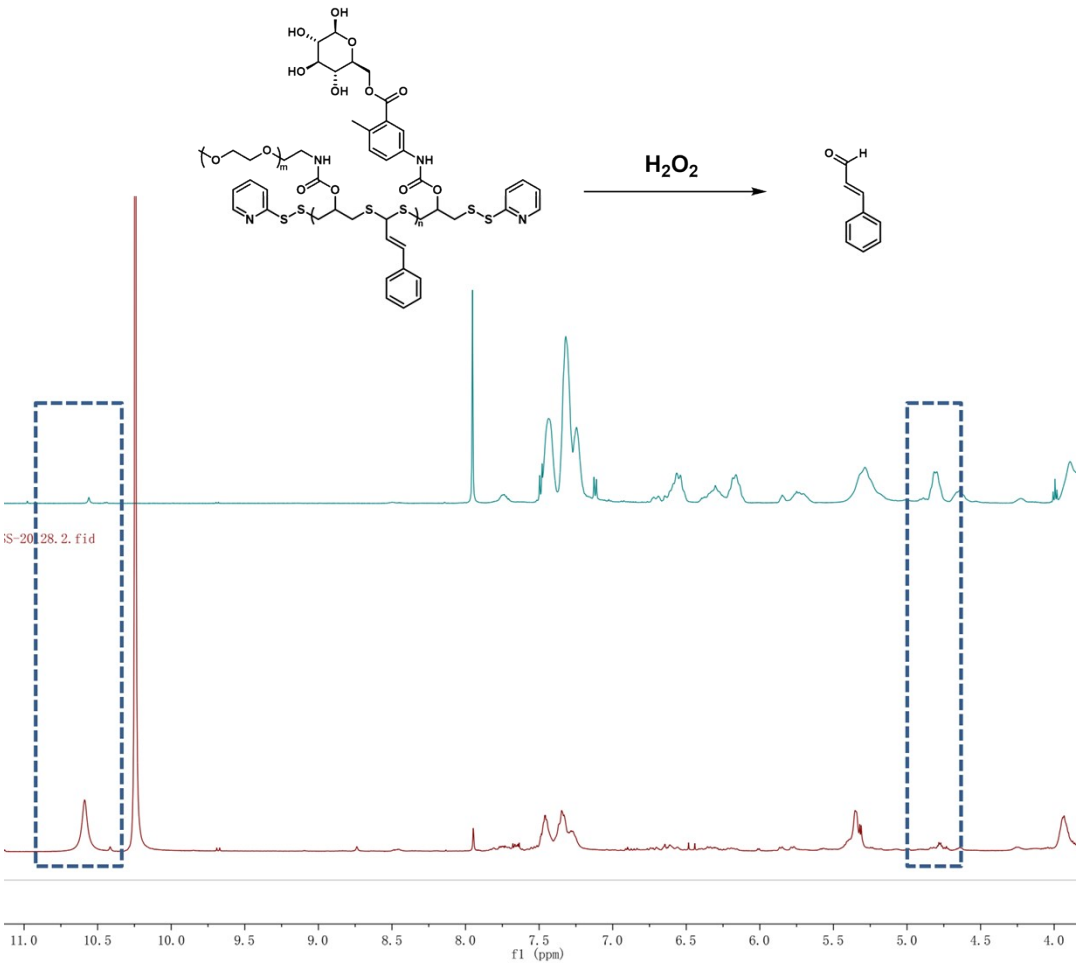


Fig.S16 ^{1}H NMR spectra of G-poly(thioacetal) after incubation with H_2O_2.

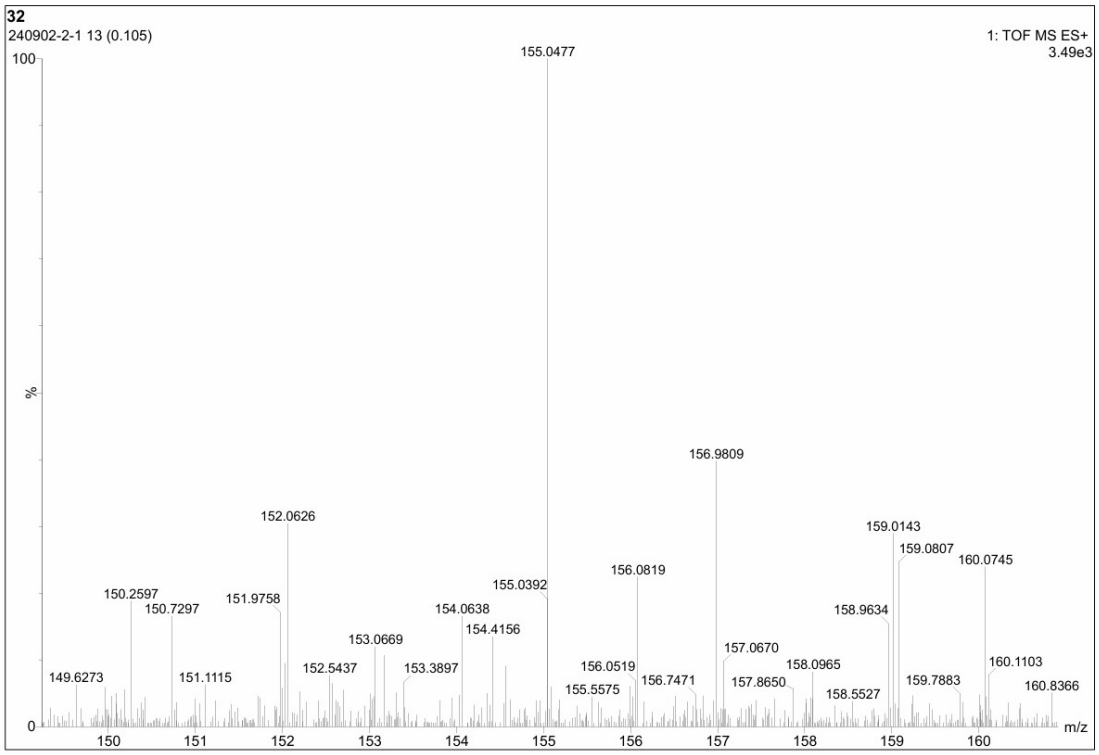


Fig.S17 Mass spectra of G-poly(thioacetal) after incubation with H_2O_2. Calc. Mass for $[C_9H_8ONa]$ 155.0473; found 155.0477.

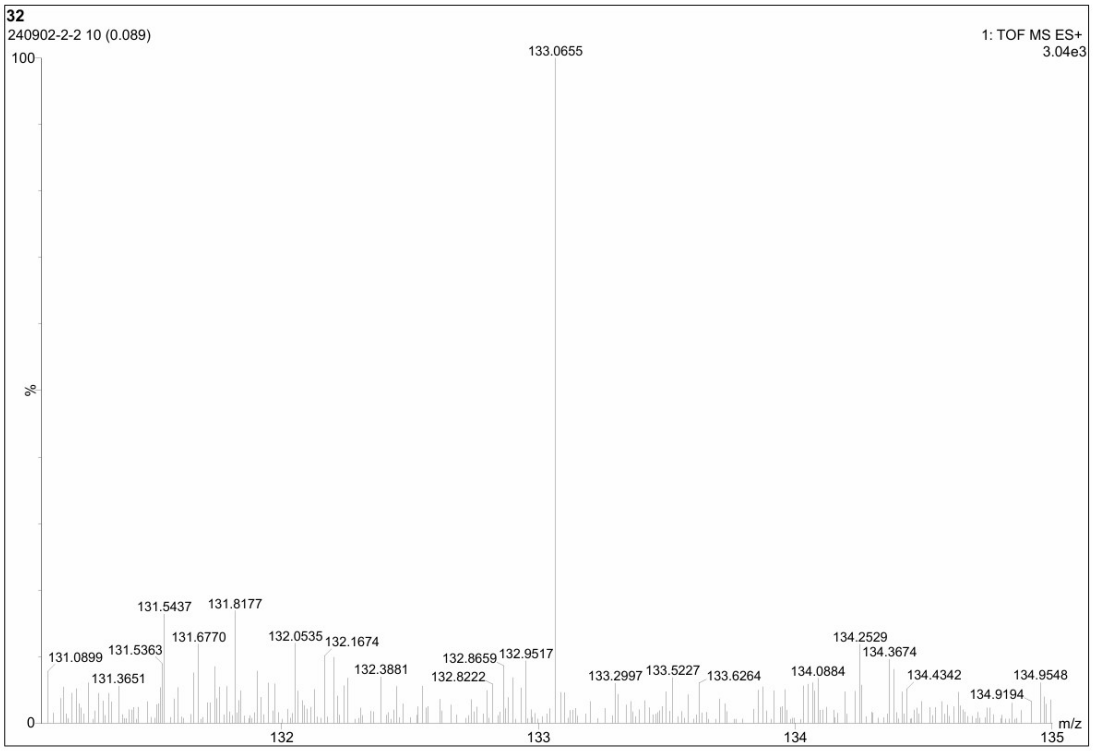


Fig.S18 Mass spectra of cinnamaldehyde. Calc. Mass for $[C_9H_8O+H]^+$ 133.0653; found

133.0655.

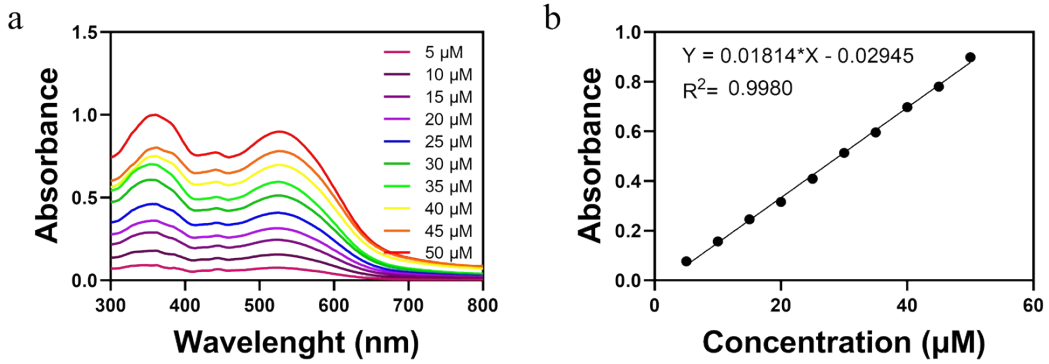


Fig.S19 Ultraviolet absorption spectrum of BD-6-QM.

(a) Uv titration curve of BD-6-QM.

(b) Standard curve for BD-6-QM.

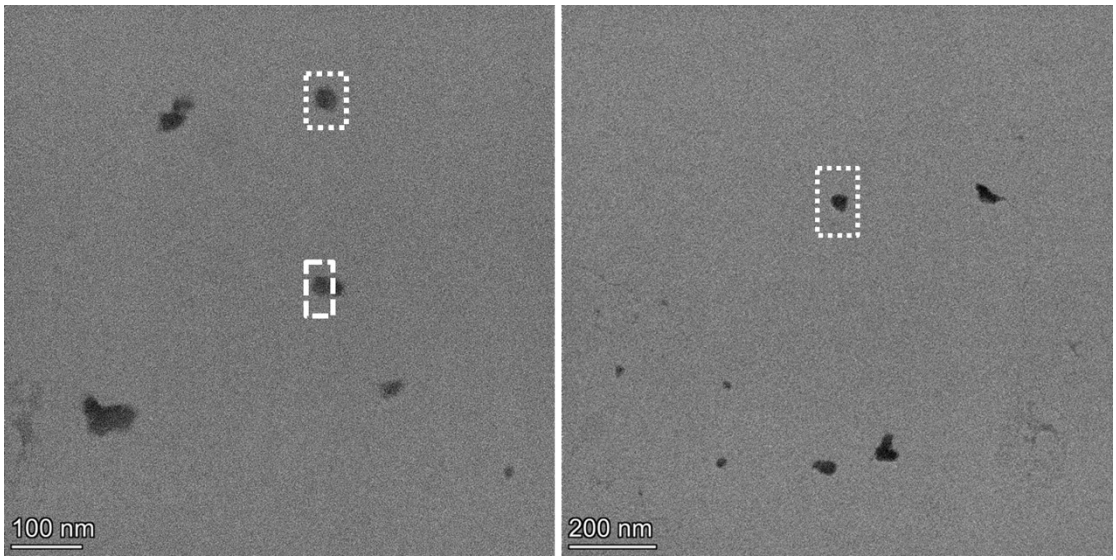


Fig.S20 Transmission electron microscopy images of BD-6-QM/NPs.

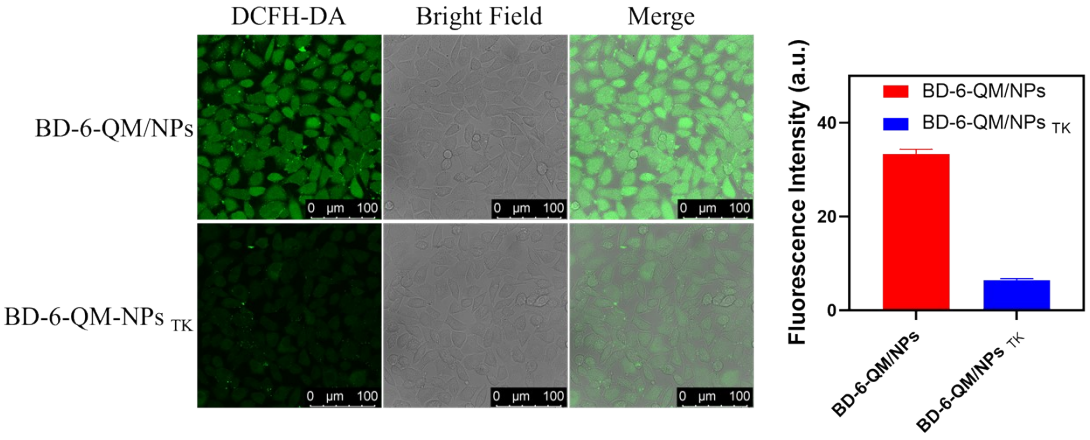


Fig.S21 Comparison of intracellular $^1O_2$ production by BD-6-QM/NPs and BD-6-QM/NPs-$_{TK}$.

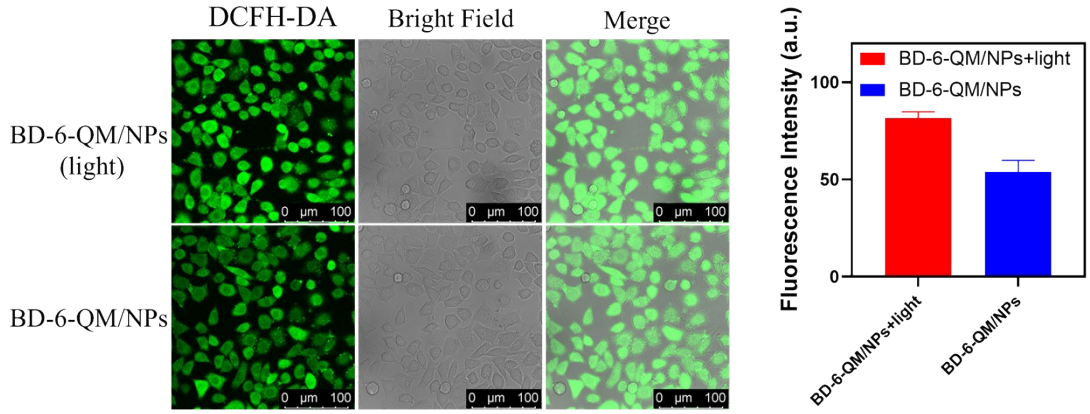


Fig.S22 Comparison of intracellular $^1O_2$ production by BD-6-QM/NPs under different conditions.

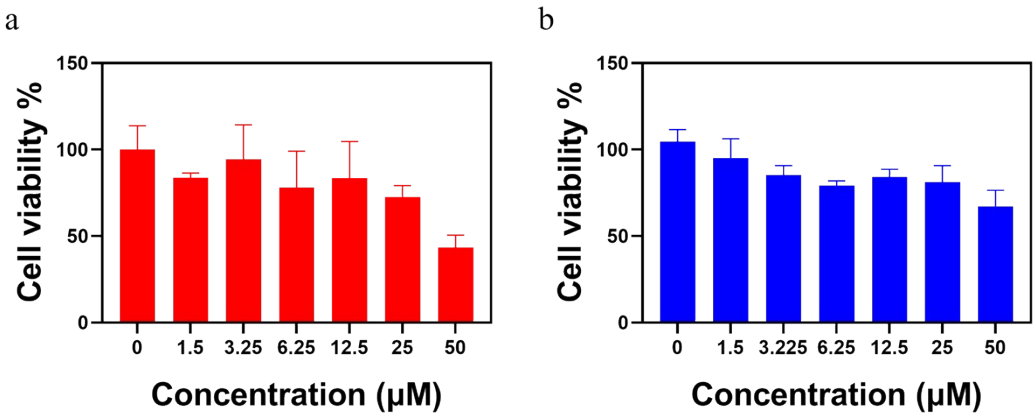


Fig.S23 Evaluation of cell viability with BD-6-QM/NPs.

(b) Survival rate of BV2 cells with different concentrations of BD-6-QM/NPs.

(c) Survival rate of SH-SY5Y cells with different concentrations of BD-6-QM/NPs.

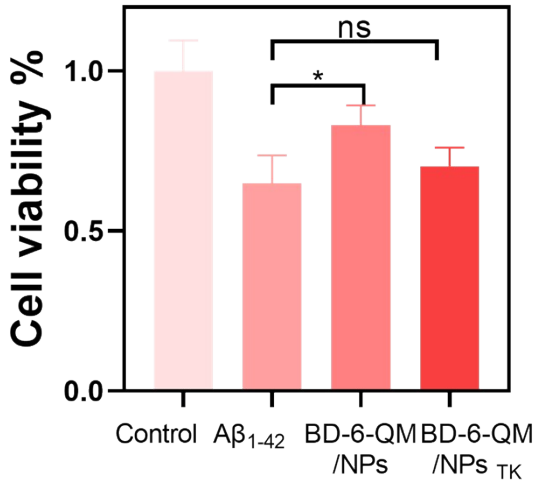


Fig.S24 Evaluation of whether BD-6-QM/NPs and BD-6-QM/NPs-$_{TK}$ can reduce $A\beta_{1-42}$-induced neurotoxicity.

Solvents	Ex [nm]	Em [nm]	Stocks shift [nm]	Quantum Yield (%)	Quantum Yield with $A\beta_{1-42}$ (%)	Fold [b]	K_d [nM] [c]
PBS	518	715	197	3.33	28	6	227.7

Table.S1 The spectral data of BD-6-QM.

[a] Kd value refers to dissociation constant, which was given as best-fit values ± Std.

Solvents	Ex [nm]	Em [nm]	Stocks shift [nm]
PBS	518	715	197
DMSO	507	683	176
MeOH	507	681	174
DCM	514	642	128
DMF	514	703	189
Methylbenzene	503	690	187
THF	493	695	202
EA	503	684	181

Table.S2 Spectral Properties of BD-6-QM in Different Solvents.

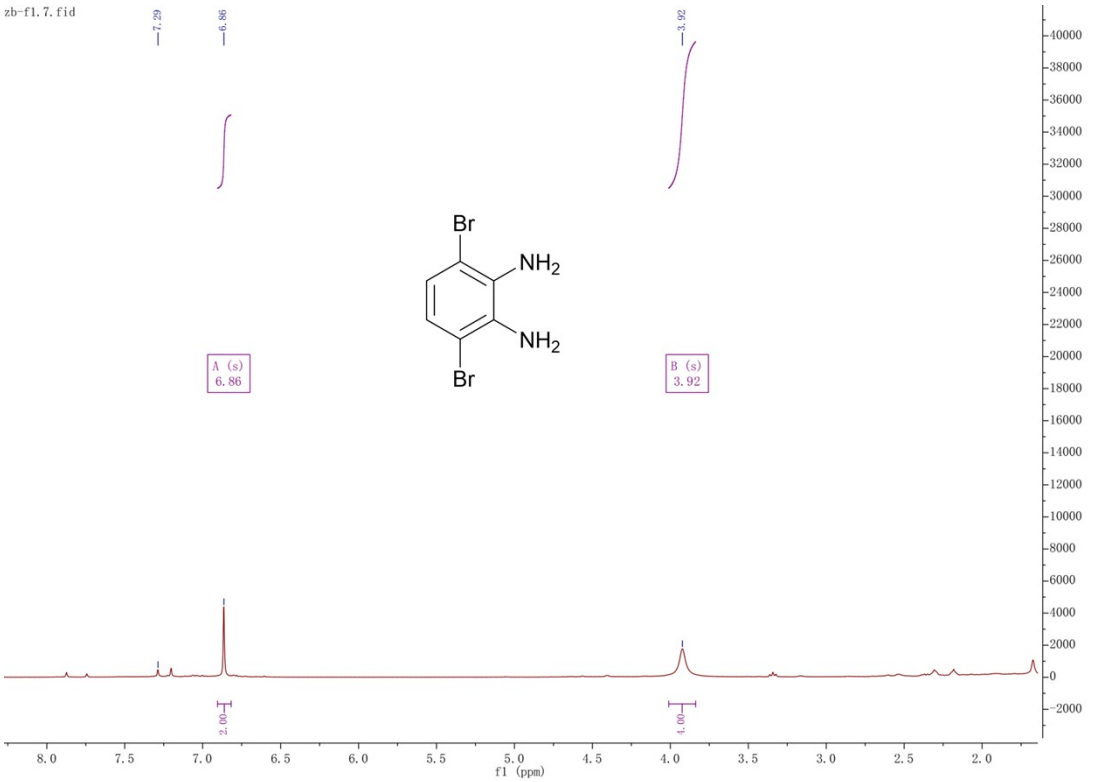


Fig.S25 The ^{1}H NMR of 3,6-Dibromo-1,2-phenylenediamine.

^{1}H NMR (400 MHz, Chloroform-d) δ 6.86 (s, 2H), 3.92 (s, 4H).

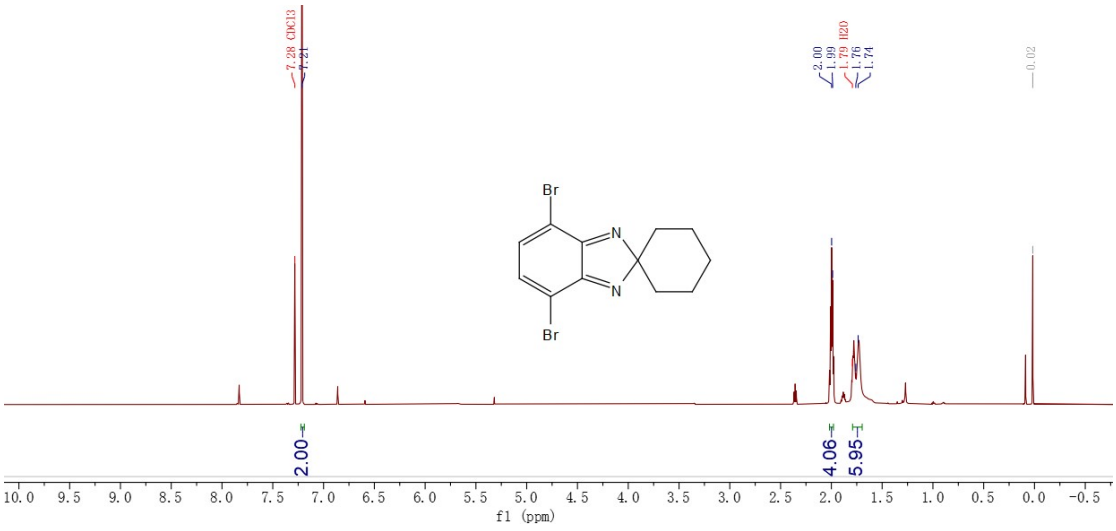


Fig.S26 The ^{1}H NMR of BD-6.

^{1}H NMR (400 MHz, Chloroform-d) δ 7.21 (s, 2 H), 1.99 (d, J = 6.0 Hz, 4 H), 1.78 (s, 2 H), 1.74 (s, 4 H).

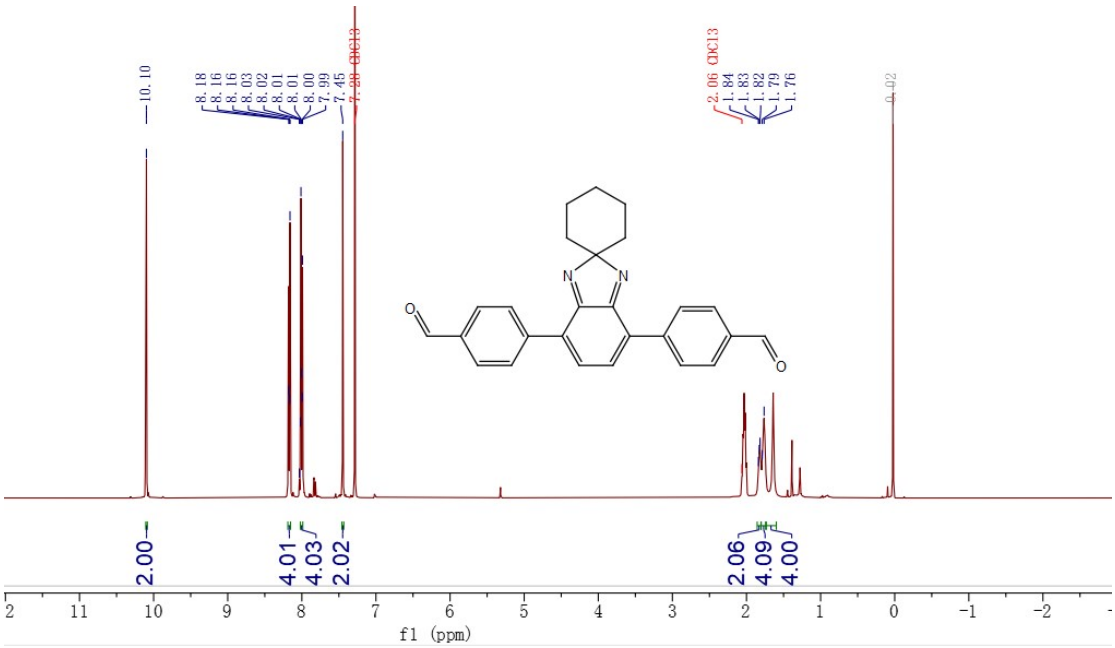


Fig.S27 The ^{1}H NMR of BD-6-CHO.

^{1}H NMR (400 MHz, Chloroform-d) δ 10.10 (s, 2 H), 8.16 (s, 4 H), 8.00 (d, J = 8.4 Hz, 4 H), 7.45 (s, 2 H), 1.91(m, 2 H), 1.69(m, 4 H), 1.64 (s, 4 H).

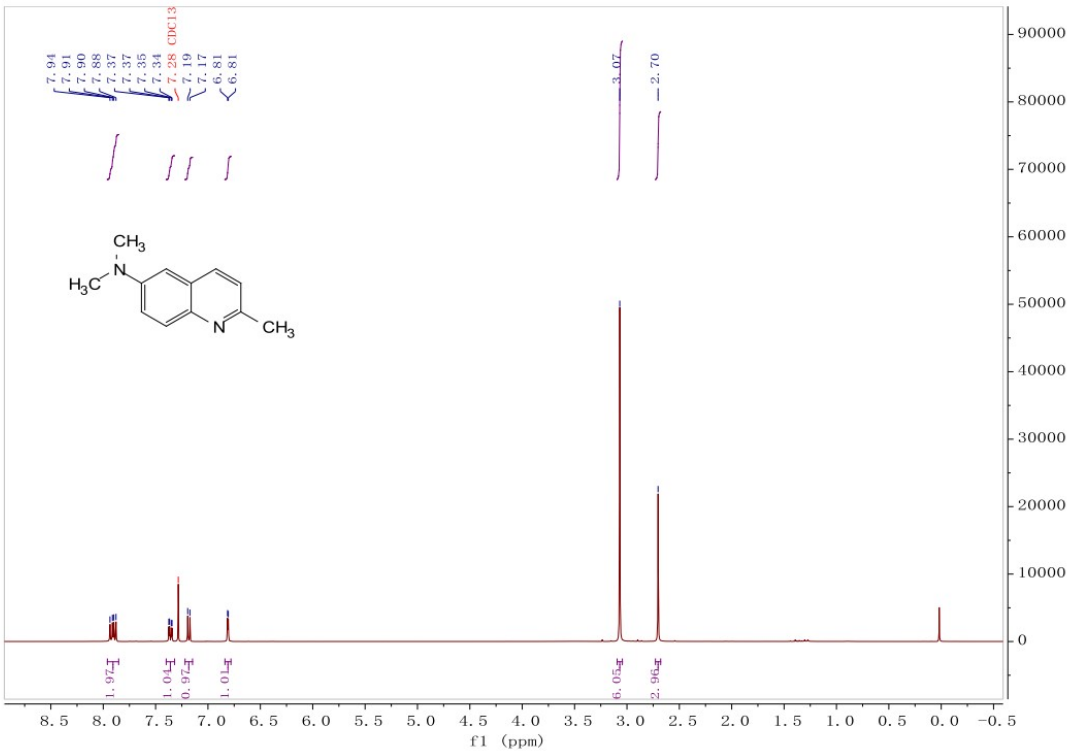


Fig.S28 The ^{1}H NMR of intermediate 1.

^{1}H NMR (400 MHz, Chloroform-d): δ=7.91 (dd, J = 14.3, 8.9 Hz, 2H), 7.36 (dd, J = 9.3, 2.8 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 2.9 Hz, 1H), 3.07 (s, 6H), 2.70 (s, 3H).

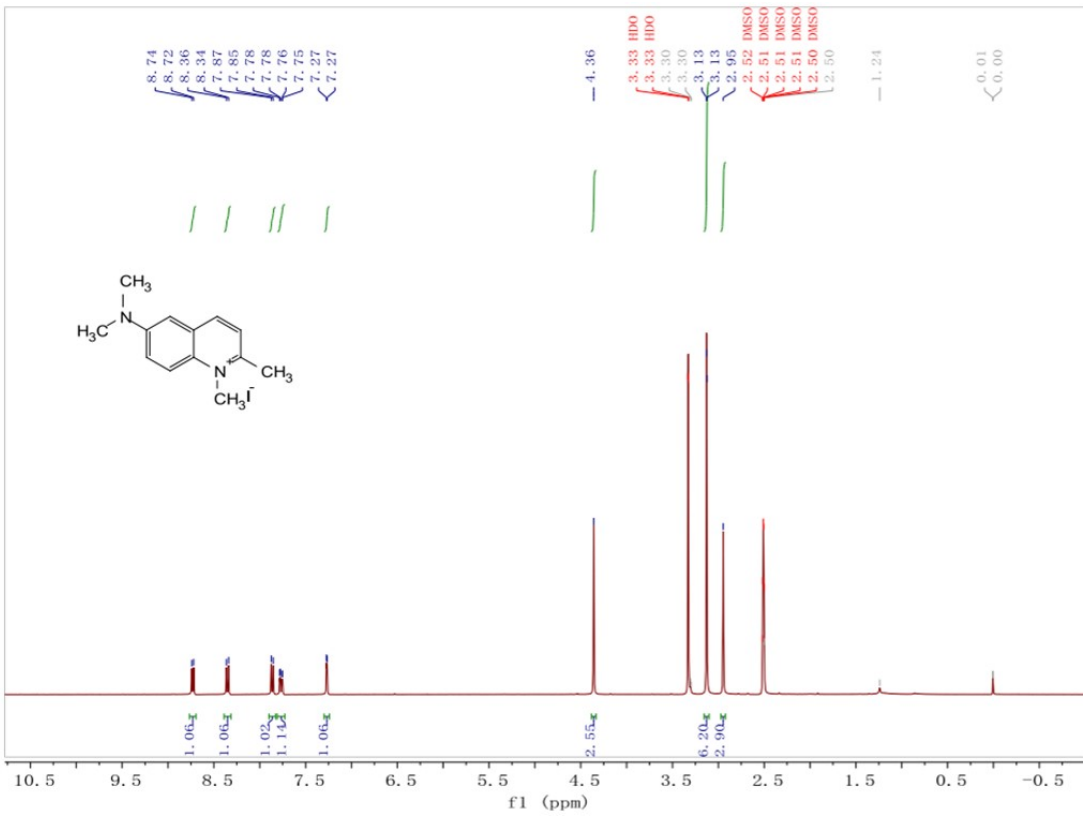


Fig.S29 The ^{1}H NMR of intermediate 2.

^{1}H NMR (400 MHz, DMSO-d_6): δ=8.73 (d, J = 8.6 Hz, 1H), 8.35 (d, J = 9.7 Hz, 1H), 7.86 (d, J = 8.6 Hz, 1H), 7.77 (dd, J = 9.9, 3.0 Hz, 1H), 7.27 (d, J = 3.0 Hz, 1H), 4.36 (s, 3H), 3.13 (d, J = 1.2 Hz, 6H), 2.95 (s, 3H).

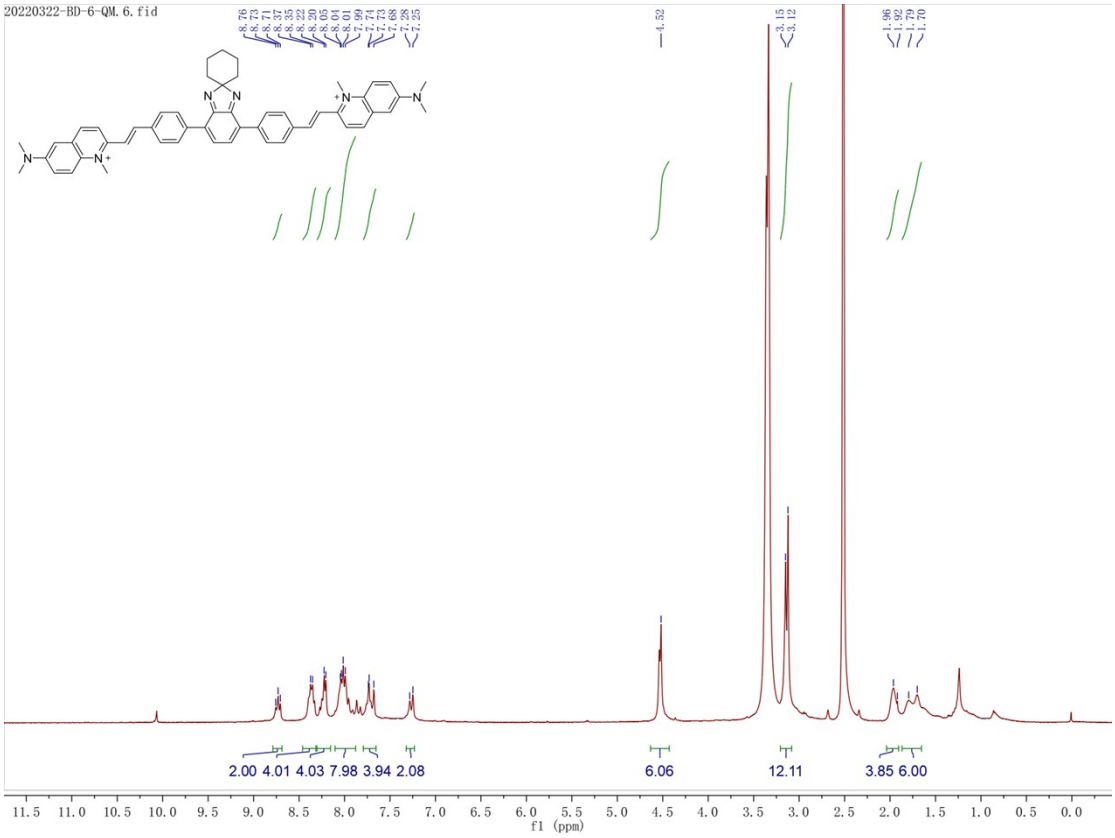


Fig.S30 The ^{1}H NMR of BD-6-QM.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (d, J = 9.9 Hz, 2H), 8.33 (d, J = 8.7 Hz, 4H), 8.20 (s, 4H), 8.01 (t, J = 8.8 Hz, 8H), 7.75 – 7.65 (m, 4H), 7.26 (d, J = 11.4 Hz, 2H), 4.53 (s, 6H), 3.13 (d, J = 11.5 Hz, 12H), 1.96 (s, 4H), 1.81 – 1.54 (m, 6H).

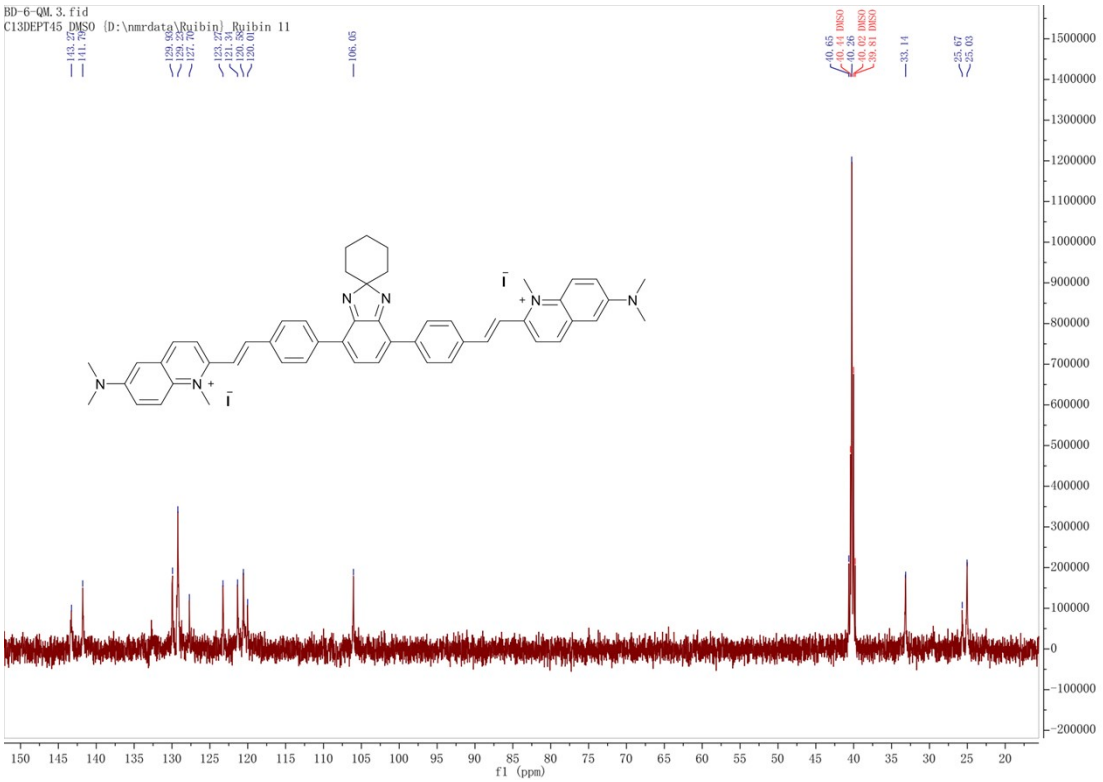


Fig.S31 The DEPT (45°) of BD-6-QM.

^{13}C NMR (101 MHz, DMSO-d_6) δ 143.27, 141.79, 129.93, 129.23, 127.70, 123.27, 121.34, 120.58, 120.01, 106.05, 40.65, 40.26, 33.14, 25.67, 25.03.

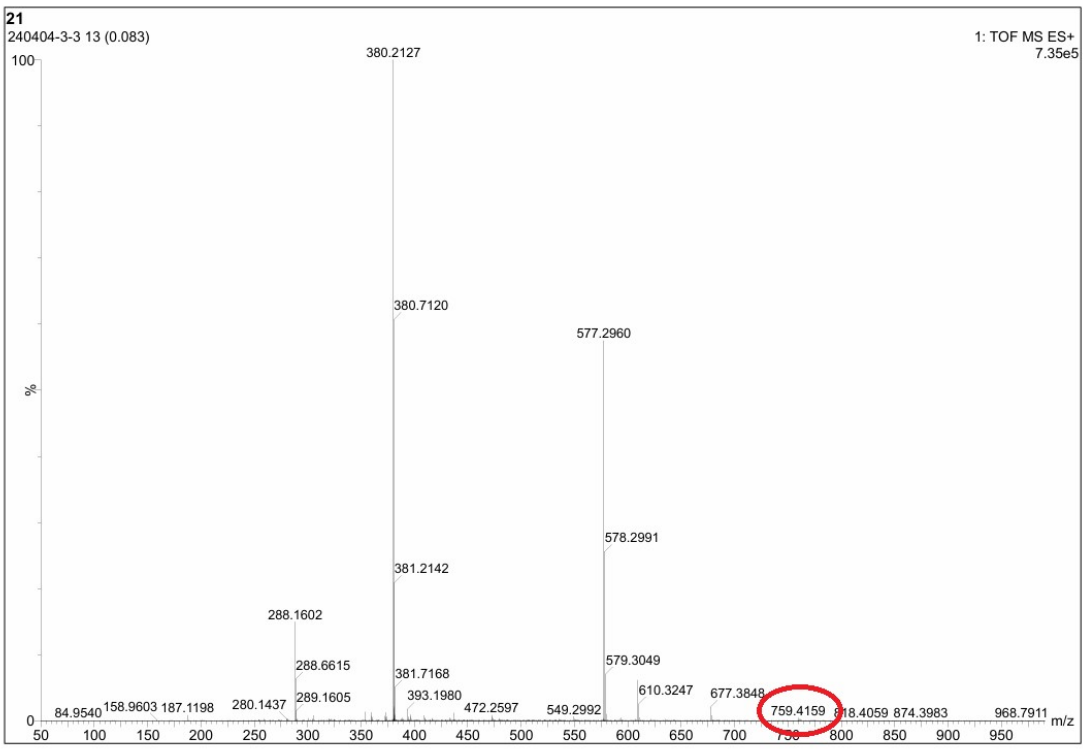


Fig.S32 The Mass spectrum of BD-6-QM. $[C_{52}H_{52}N_6]^{2+}$=380.2127.

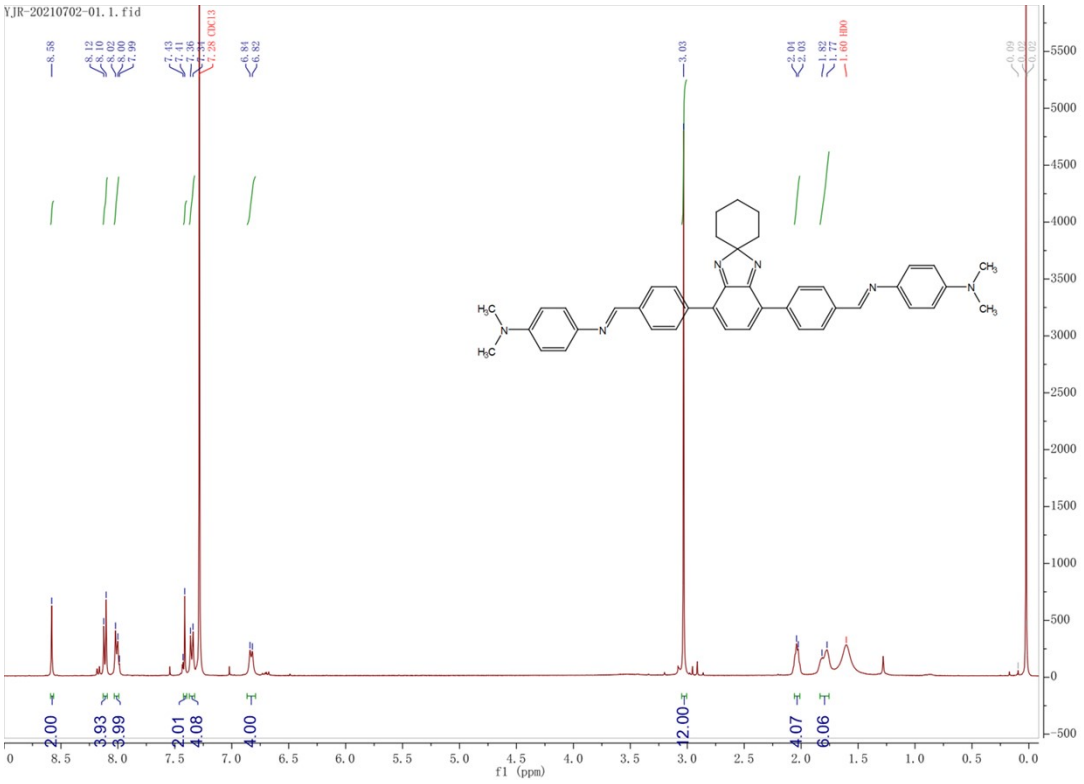


Fig.S33 The ^{1}H NMR of BD-6-1.

^{1}H NMR (400 MHz, Chloroform-d) δ 8.58 (s, 2H), 8.11 (d, J = 8.3 Hz, 4H), 8.01 (d, J = 8.3 Hz, 4H), 7.41 (s, 2H), 7.35 (d, J = 8.5 Hz, 4H), 6.83 (d, J = 8.4 Hz, 4H), 3.03 (s, 12H), 2.03 (d, J = 6.0 Hz, 4H), 1.79 (d, J = 17.6 Hz, 6H).

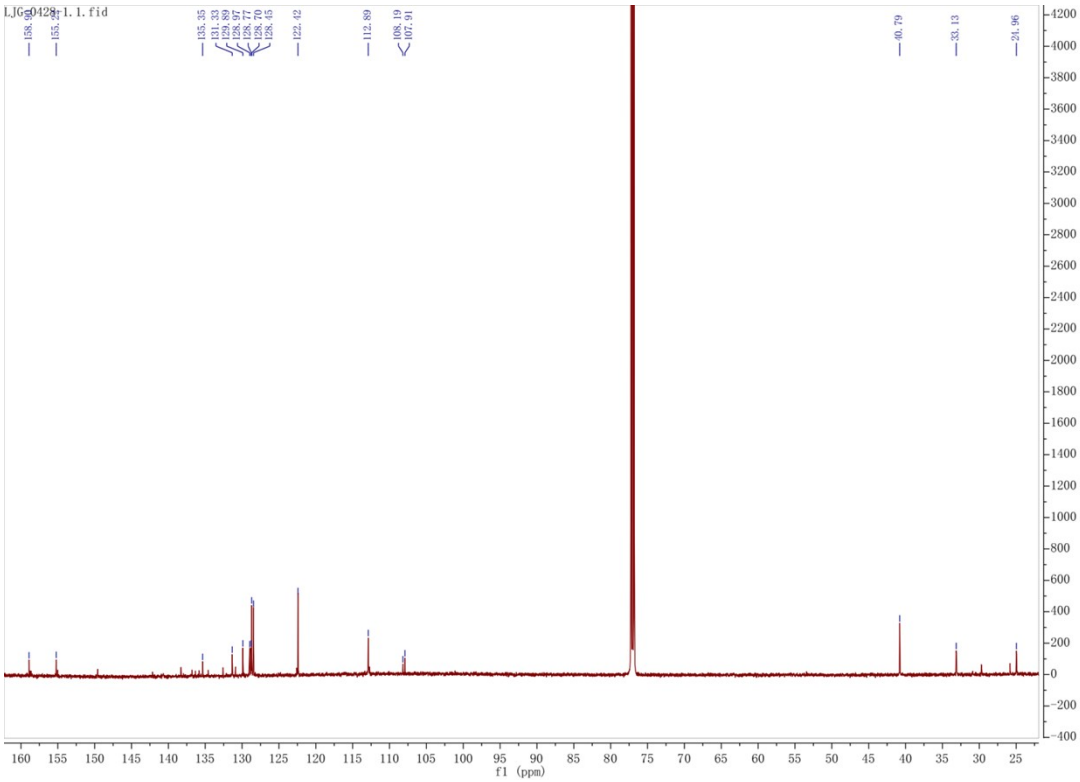


Fig.S34 The ^{13}C NMR of BD-6-1.

^{13}C NMR (151 MHz, $CDCl_3$) δ 158.90, 155.22, 135.35, 131.33, 129.89, 128.97, 128.77, 128.70, 128.45, 122.42, 112.89, 108.19, 107.91, 40.79, 33.13, 24.96.

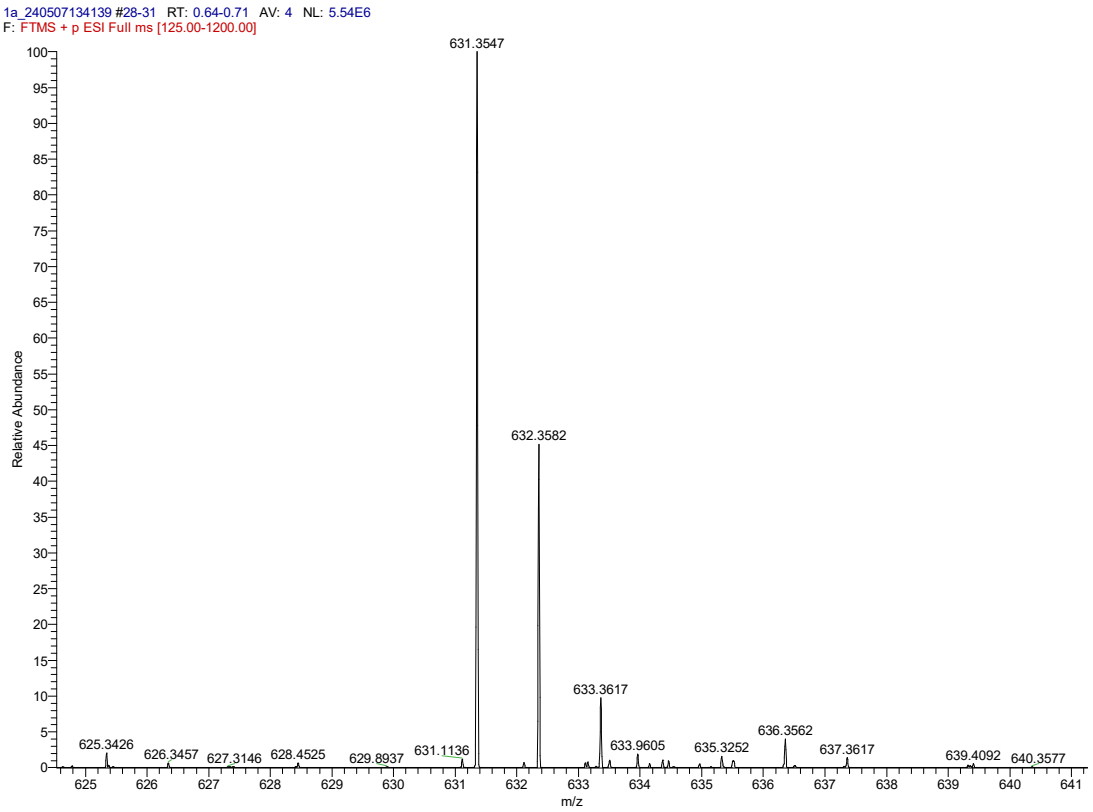


Fig.S35 The Mass spectrum of BD-6-1.

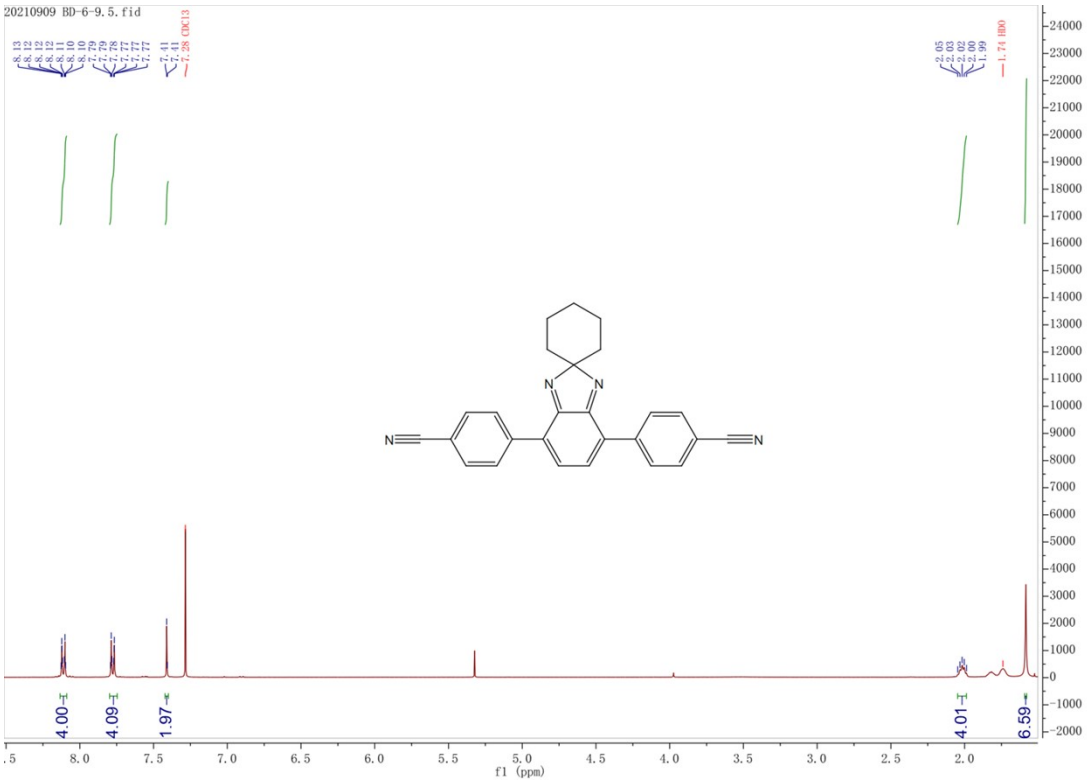


Fig.S36 The ^{1}H NMR of BD-6-9.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 – 7.99 (m, 4H), 7.86 – 7.62 (m, 4H), 7.41 (s, 2H), 2.02 (p, *J* = 6.1 Hz, 4H), 1.59 (s, 6H).

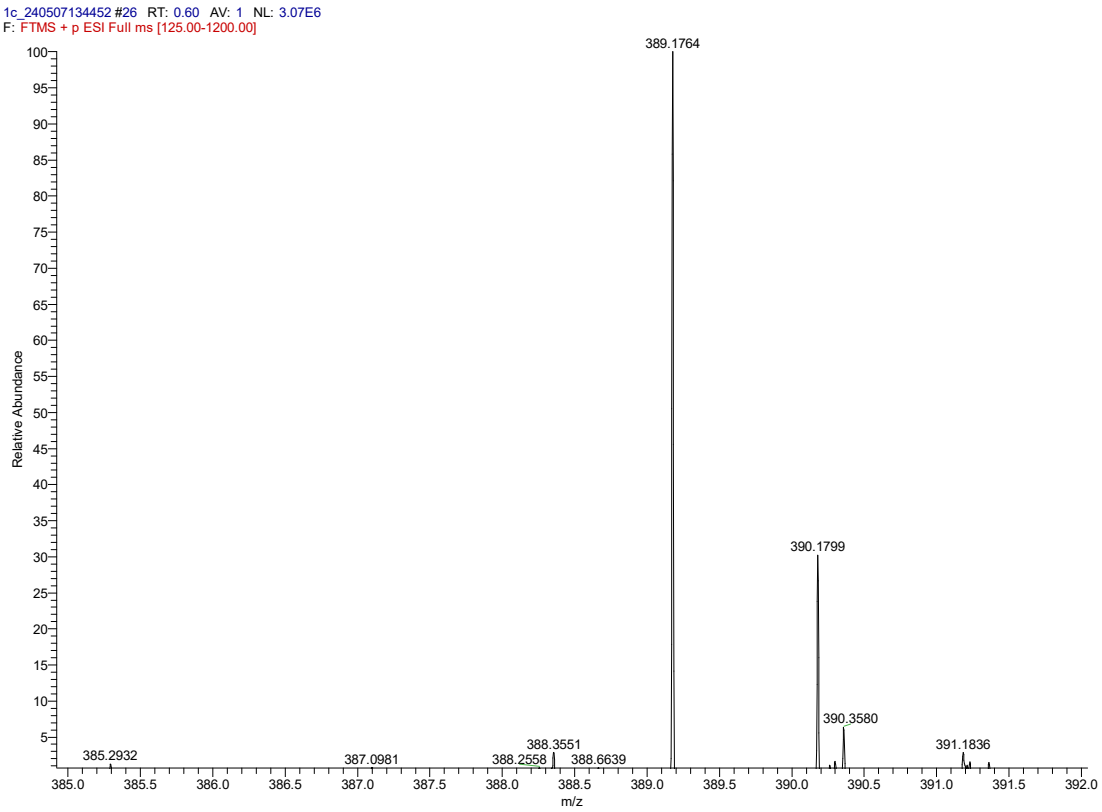


Fig.S37 The Mass spectrum of BD-6-9.

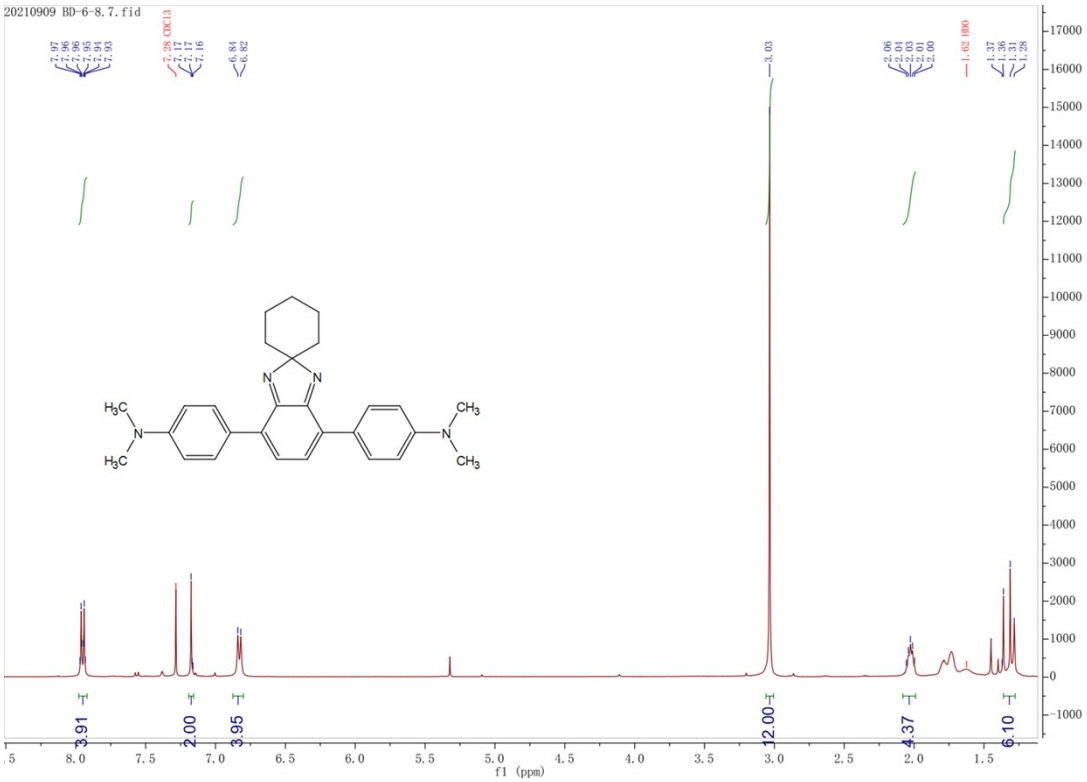


Fig.S38 The ^{1}H NMR of BD-6-8.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 (d, *J* = 8.9 Hz, 4H), 7.17 (s, 2H), 6.83 (d, *J* = 8.5 Hz, 4H), 3.03 (s, 12H), 2.03 (p, *J* = 5.9 Hz, 4H), 1.44 – 1.12 (m, 6H).

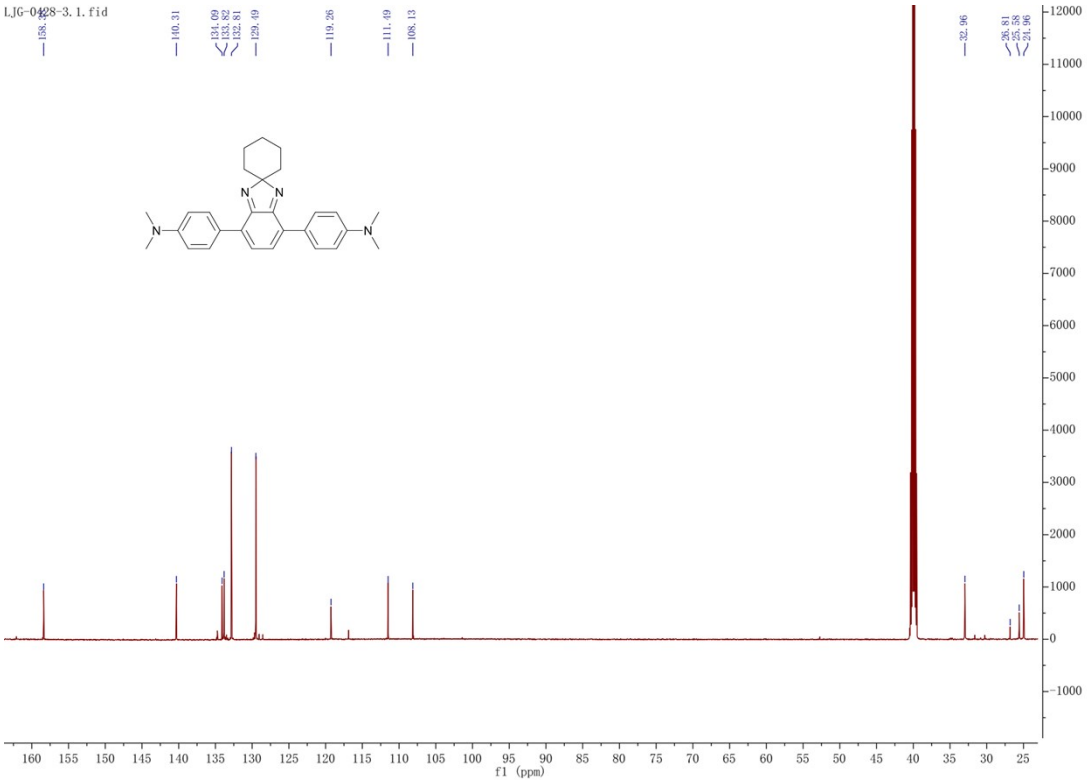


Fig.S39 The ^{13}C NMR of BD-6-8.

^{13}C NMR (151 MHz, DMSO) δ 158.38, 140.31, 134.09, 133.82, 132.81, 129.49, 119.26, 111.49, 108.13, 32.96, 26.81, 25.58, 24.96.

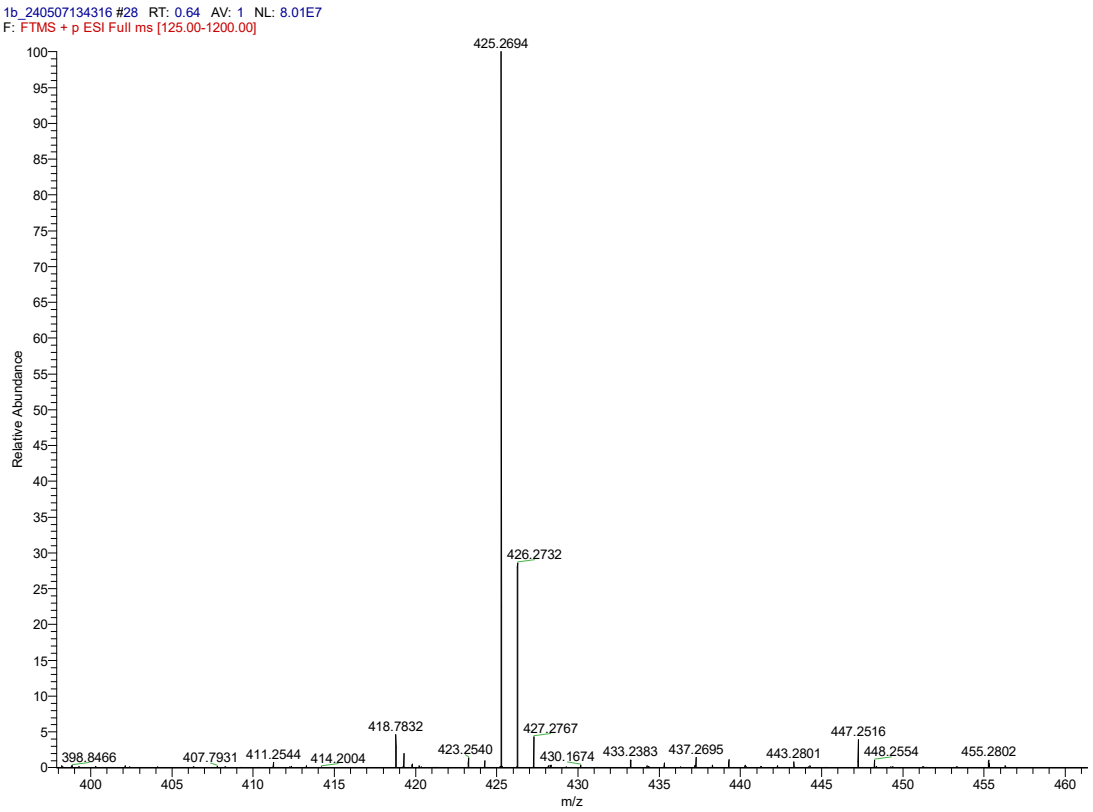


Fig.S40 The Mass spectrum of BD-6-8.

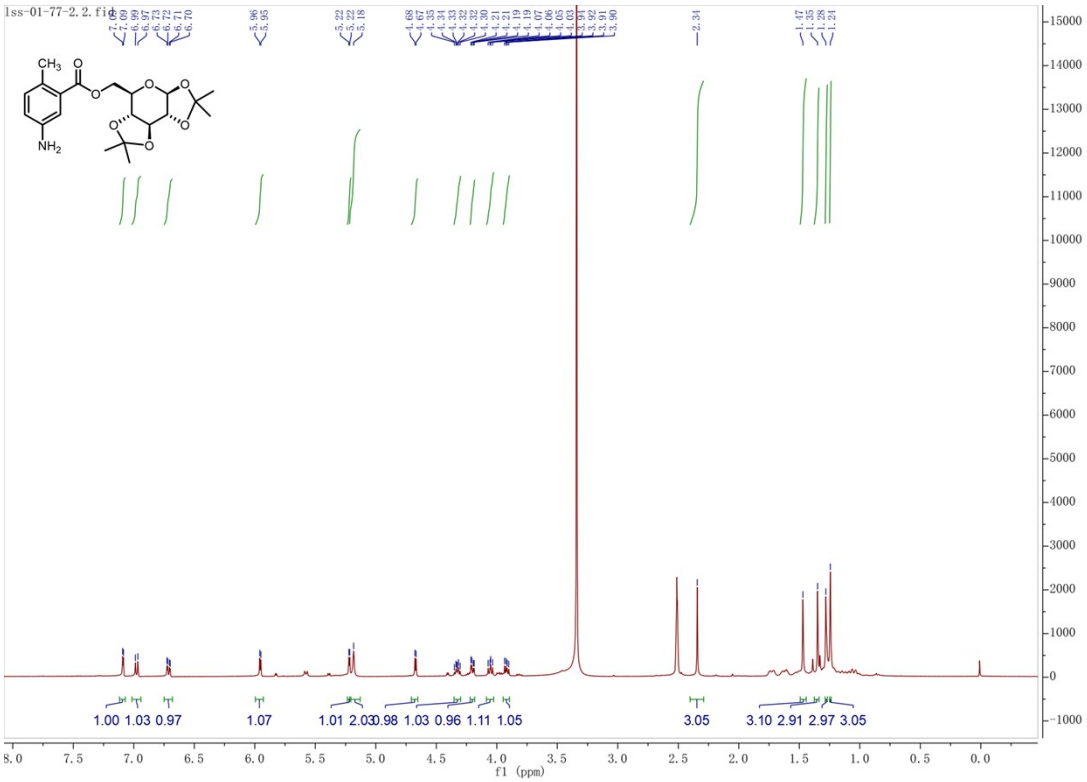


Fig.S41 The ^{1}H NMR of intermediate 4.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.09 (d, J = 2.5 Hz, 1H), 6.98 (d, J = 8.2 Hz, 1H), 6.71 (dd, J = 8.1, 2.6 Hz, 1H), 5.95 (d, J = 3.8 Hz, 1H), 5.22 (d, J = 3.0 Hz, 1H), 5.18 (s, 2H), 4.67 (d, J = 3.7 Hz, 1H), 4.33 (dt, J = 7.7, 5.5 Hz, 1H), 4.20 (dd, J = 7.7, 3.0 Hz, 1H), 4.05 (dd, J = 8.5, 6.1 Hz, 1H), 3.92 (dd, J = 8.5, 5.2 Hz, 1H), 2.34 (s, 3H), 1.47 (s, 3H), 1.35 (s, 3H), 1.28 (s, 3H), 1.24 (s, 3H).

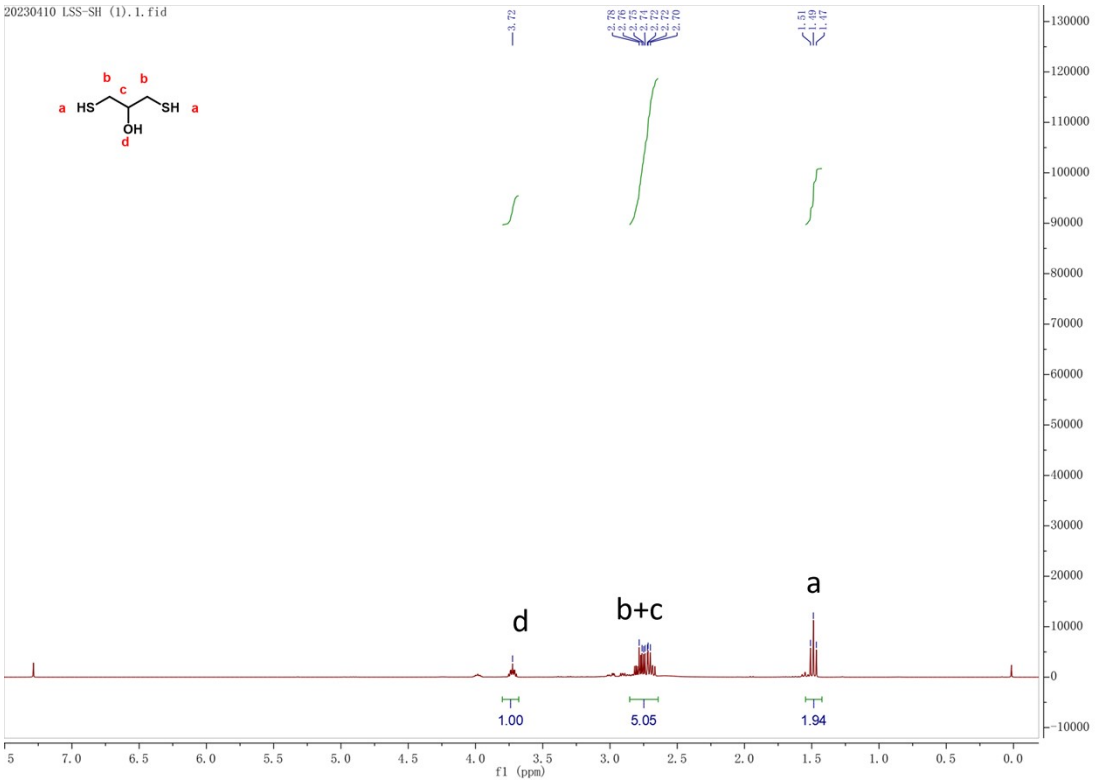


Fig.S42 The ^{1}H NMR of 1,3-dimercaptopropan-2-ol.

^{1}H NMR (400 MHz, Chloroform-d): δ 3.72 (tq, J = 7.5, 4.3 Hz, 1H), 2.85 – 2.63 (m, 5H), 1.55 – 1.42 (m, 2H).

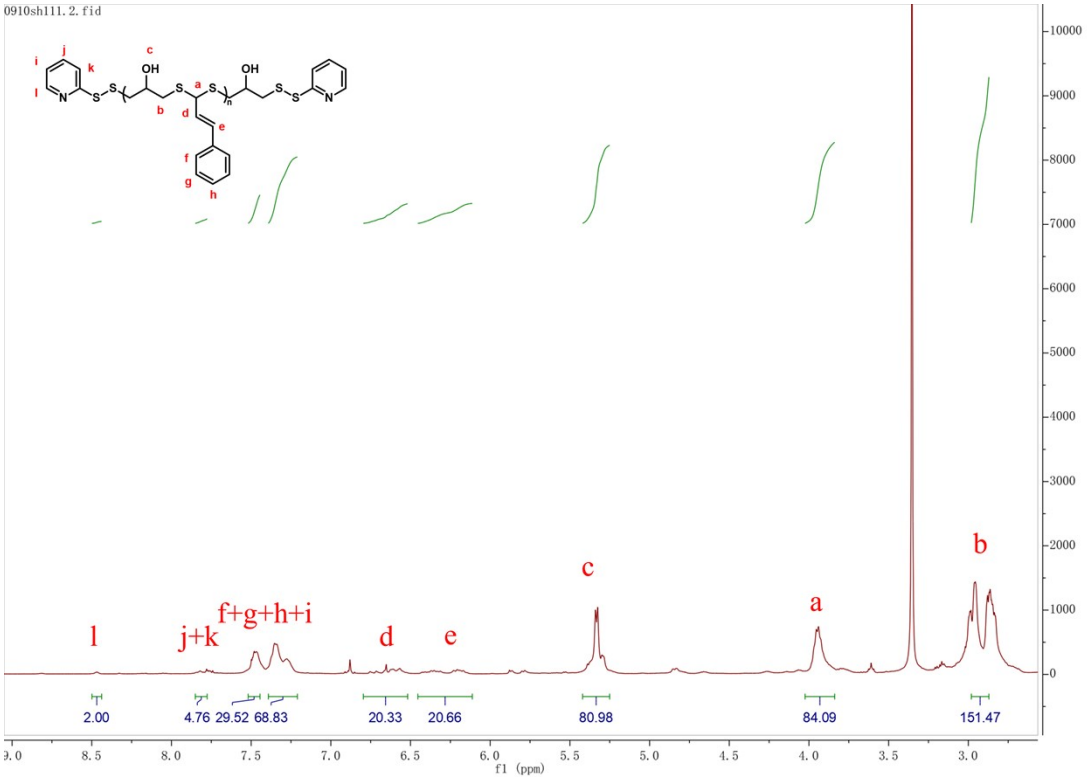


Fig.S43 The ^{1}H NMR of PTA-SS.

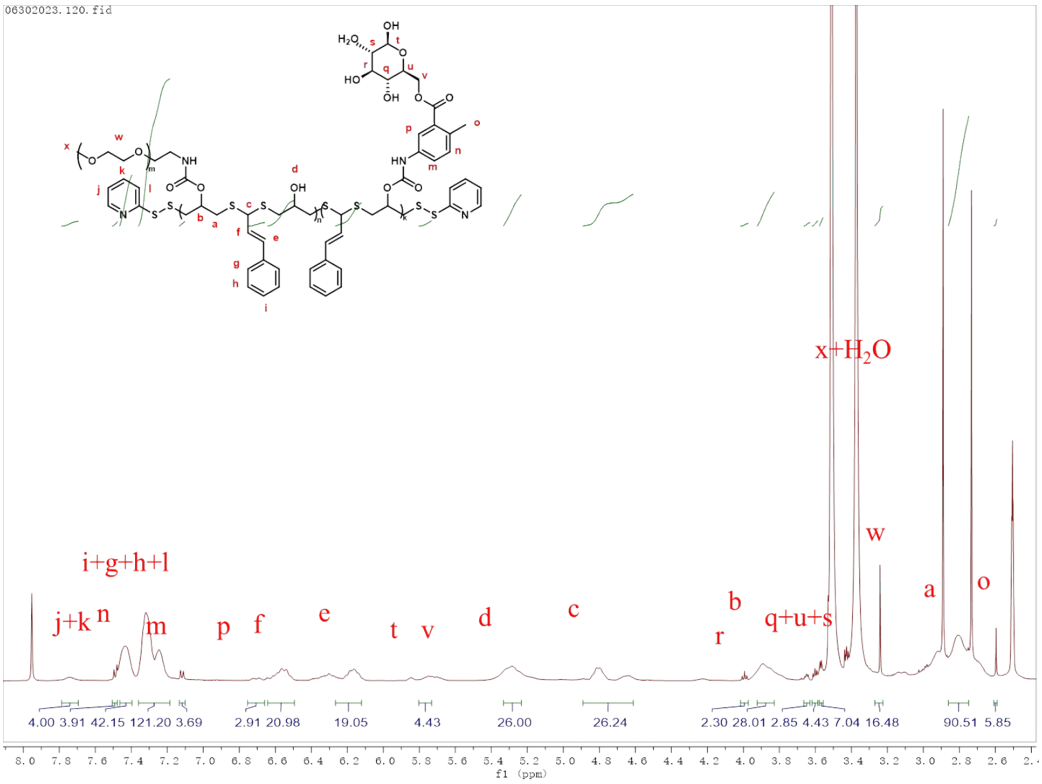


Fig.S44 The ^{1}H NMR ofG-Poly(thioacetal).

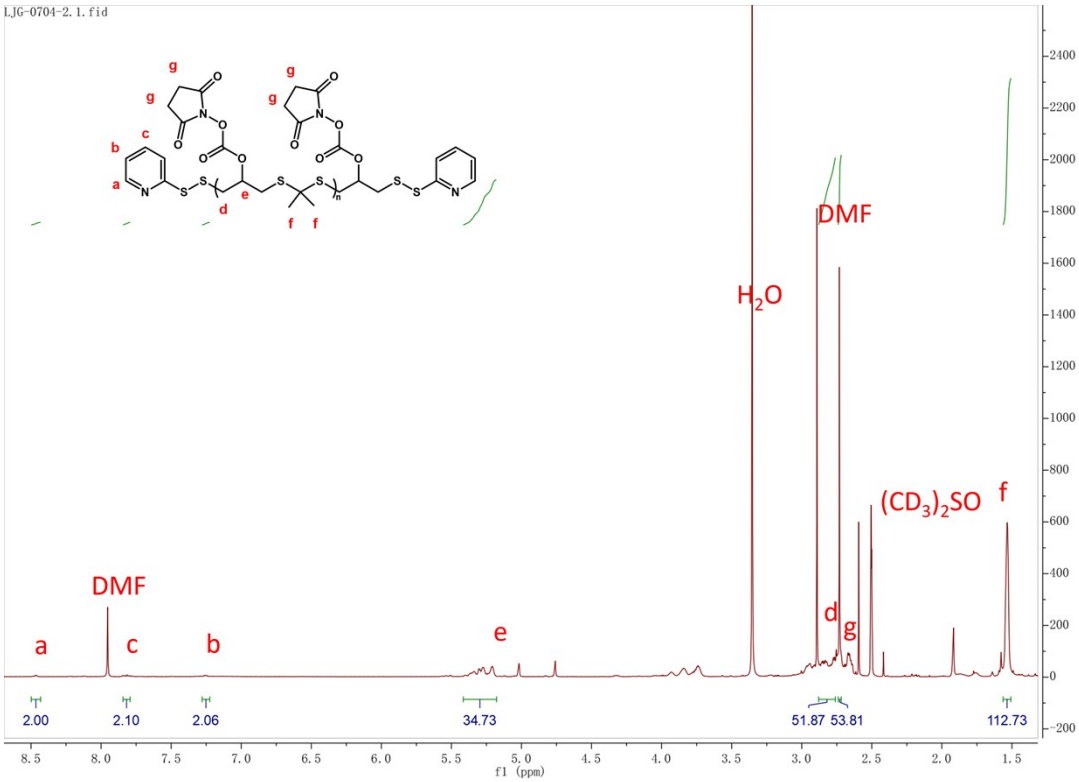


Fig.S45 The ^{1}H NMR of TK-DSC.

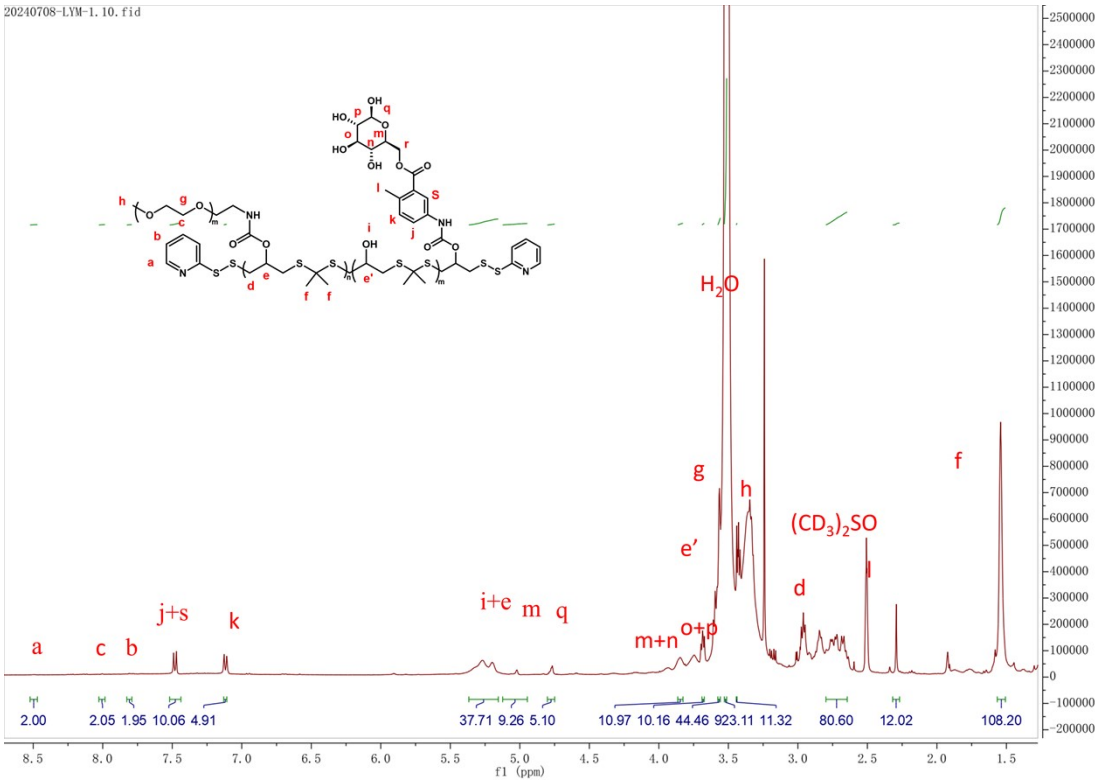


Fig.S46 The ^{1}H NMR of G-Poly(thioacetal) $_{TK}$.