

## Supporting Information

# Rapid Differentiation between Bacterial Infections and Cancer Using A Near-Infrared Fluorogenic Probe

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**Abstract:** The reliable differentiation between bacterial infections and other pathologies is crucial for both diagnostics and therapeutic approaches. To accommodate such needs, we herein report the development of an activatable near-infrared fluorescent probe **1** that could be applied in the ultrafast, ultrasensitive and specific detection of nitroreductase (NTR) activity in bacterial pathogens both *in vitro* and *in vivo*. Upon reacting with NTR, the nitro-group of the *para*-nitro phenyl sulfonic moiety presented in probe **1** was reduced to an amino-group, resulting in a near-infrared fluorescence turn-on of the latent cyanine 7 fluorophore. Probe **1** was capable of rapid and real-time quantitative detection of 0-150 ng/mL NTR with the limit of detection as low as 0.67 ng/mL *in vitro*. In addition, probe **1** exhibited an outstanding performance of ultrafast measurement and suitable selectivity toward NTR to accurately sense intracellular basal NTR in ESKAPE bacterial pathogens. Most remarkably, probe **1** was capable of noninvasively identifying bacterial infection sites without showing any significantly increased signal of tumour sites in the same animals within 30 min.

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## Experimental Procedures

### Abbreviations

ATCC = American Type Culture Collection

BHI = Brain Heart Infusion Broth

DCM = Dichloromethane

DIPEA = Diisopropyl-ethyl amine

DMF = Dimethylformamide

DMSO = Dimethyl sulfoxide

HRMS = High Resolution Mass Spectrometry

LB = Luria-Bertani Broth

MRS = M.R.S. Broth

NADH = Beta-Nicotinamide Adenine Dinucleotide Disodium Salt Hydrate, reduced form

NB = Nutrient Broth

NMR = Nuclear Magnetic Resonance

NTR = Nitroreductase

OD = Optical Density

rpm = Revolutions Per Minute

Tris = Tris(hydroxymethyl)aminomethane

TSB = Tryptone Soya Broth

## General methods

NADH (beta-nicotinamide adenine dinucleotide disodium salt hydrate, reduced form) was purchased from TOKYO CHEMICAL INDUSTRY CO., LTD. NTR (nitroreductase) extracted from *Escherichia coli* was purchased from SIGMA-ALDRICH CO., LTD. The relevant 16S rRNA sequence from 5'-3', GGCGUCACACCUUCGGGUGAAGUCGCC, was purchased from ruiibotech CO., LTD. All other chemicals were purchased from J&K. Commercially available reagents were used without further purification. Six bacterial strains *Staphylococcus aureus* (*S. aureus*, ATCC 29213), *Enterobacter cloacae* (*E. cloacae*, ATCC 13047), *Klebsiella pneumoniae* (*K. pneumoniae*, ATCC 700603) and *Pseudomonas aeruginosa* (*P. aeruginosa*, ATCC 27853) were purchased from American Type Culture Collection (ATCC), USA. *Enterococcus faecium* (*E. faecium*) (CICC 10840) and *Acinetobacter baumannii* (*A. baumannii*, CICC 22933) were purchased from China Center of Industrial Culture Collection, CICC®. The human peripheral blood mononuclear cell (PBMC) line, human hepatocellular carcinomas (HepG2) and Raw CT26 colon cancer cell lines were obtained from Prof. Xiaoguang Chen' Lab (Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China). Fluorescence emission spectra and full wavelength absorption spectra were performed on Tecan Spark™ 10M Multimode Microplate Reader. OD values were recorded in a 10 mm path quartz cell on a Metash UV-5100B spectrometer. Confocal laser scanning microscope imaging was conducted using a Leica TCS SP8 X Confocal Microscope. All <sup>1</sup>H NMR spectra were recorded at 500 or 600 MHz, and <sup>13</sup>C NMR spectra were recorded at 125 or 150 MHz (Zhongke-Niujin, WNMR 500 MHz, CN, Varian VNS, 600 MHz, USA), respectively. Mass spectra (MS) were recorded on a Thermo LCQ Deca XP Max mass spectrometer using electrospray ionization (ESI) modes. *In vitro* optical imaging was acquired on an IVIS Spectrum CT (PerkinElmer) instrument using the following experimental settings: field of view (FOV) 13.2 x 13.2 cm, binning 8, f/stop 2, excitation filter block, emission filter open. The fluorescent imaging data were analyzed using the Living Image 4.3.1 software package (PerkinElmer) and oval region demonstrated total radiant efficiency from the respective regions of interest (ROI) ((p/sec/cm<sup>2</sup>/sr)/(μM/cm<sup>2</sup>)).

### UV-vis absorption and fluorescence spectra

The probe in DMSO stock solution was diluted to 10 μM in Tris-buffered saline (TBS, 50 mM Tris/HCl, containing 1.5% DMSO as co-solvent, pH 7.4). UV-Visible spectra were recorded on a Tecan Spark™ 10M Multimode Microplate Reader.

### *In vitro* binding assay of probe 1 with 16S rRNA.

We investigated the 16S rRNA binding property of probe 1 by circular dichroism (CD) using the reported 27 nucleotides (nt) RNA oligonucleotide which adopts the same conformation as the A site of 16S rRNA in the 30S subunit. The 27 nt RNA (5 μM) was titrated with increasing concentrations of probe 1 (0 μM to 50 μM), and overlaid CD spectra were created to compare the RNA conformation at different probe: RNA ratios. As shown in Figure S12, the CD signal increases (most noticeably at 265 nm) with increasing probe 1 concentrations, which was indicative of the probe complexation with the A site of 16S rRNA (Figure S12).

### Bacteria and cell cultures

Medically important bacterial pathogens of the ESKAPE panel (comprising of two Gram-positive species *E. faecium* and *S. aureus*, and four Gram-negative species *K. pneumoniae*, *A. baumannii*, *P. aeruginosa* and *E. cloacae*) were studied. M. R. S. broth (MRS) medium was used for culture of *E. faecium*. Tryptic Soy Broth (TSB) medium was used for culture of *P. aeruginosa* and *S. aureus*. Nutrient broth (NB) was used for culture of *K. pneumoniae* and *E. cloacae*. Brain Heart Infusion (BHI) broth was used for culture of *A. baumannii*. A single colony from the stock agar plate was added to 10 mL of liquid medium. Then, the bacterial pathogens were incubated in a shaker incubator at 180 rpm and 37 °C overnight. The subculture was incubated until the OD<sub>600</sub> of a single colony was approximately 0.3-0.7. Human hepatocellular carcinomas (HepG2) cells were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal bovine serum (FBS) under humidified atmosphere of 5% CO<sub>2</sub> at 37 °C. Raw CT26 cells and human peripheral blood mononuclear cells (PBMC) were cultured in 1640 medium containing 10% fetal bovine serum (FBS) under a humidified atmosphere of 5% CO<sub>2</sub> at 37 °C.

### Confocal fluorescence microscopy imaging

*S. aureus* cells were cultured in Tryptic Soy Broth (TSB) medium at 37 °C overnight. Next, the cells were harvested and washed with

PBS (pH 7.4) twice. The washed cells were then resuspended in PBS with an OD<sub>600</sub> of 0.3-0.7. 200  $\mu$ L aliquots were treated with 10  $\mu$ M of probe **1**. After incubation at 37 °C for 1 h, the cells were washed with PBS twice and then centrifuged to remove the unbound probe, and treated with Hoechst 33342 at 37 °C for 30 min. Then, the suspension (8  $\mu$ L) was added into an 8-well chamber followed by covering with agarose pads. Fluorescence images were obtained on a Leica TCS SP8 X Confocal Microscope, using a white light laser and argon ion laser for excitation (probe signal:  $\lambda_{\text{ex}}$  = 670 nm,  $\lambda_{\text{em}}$  = 770  $\pm$  30 nm; Hoechst 33342 signal:  $\lambda_{\text{ex}}$  = 405 nm and  $\lambda_{\text{em}}$  = 460  $\pm$  30 nm).

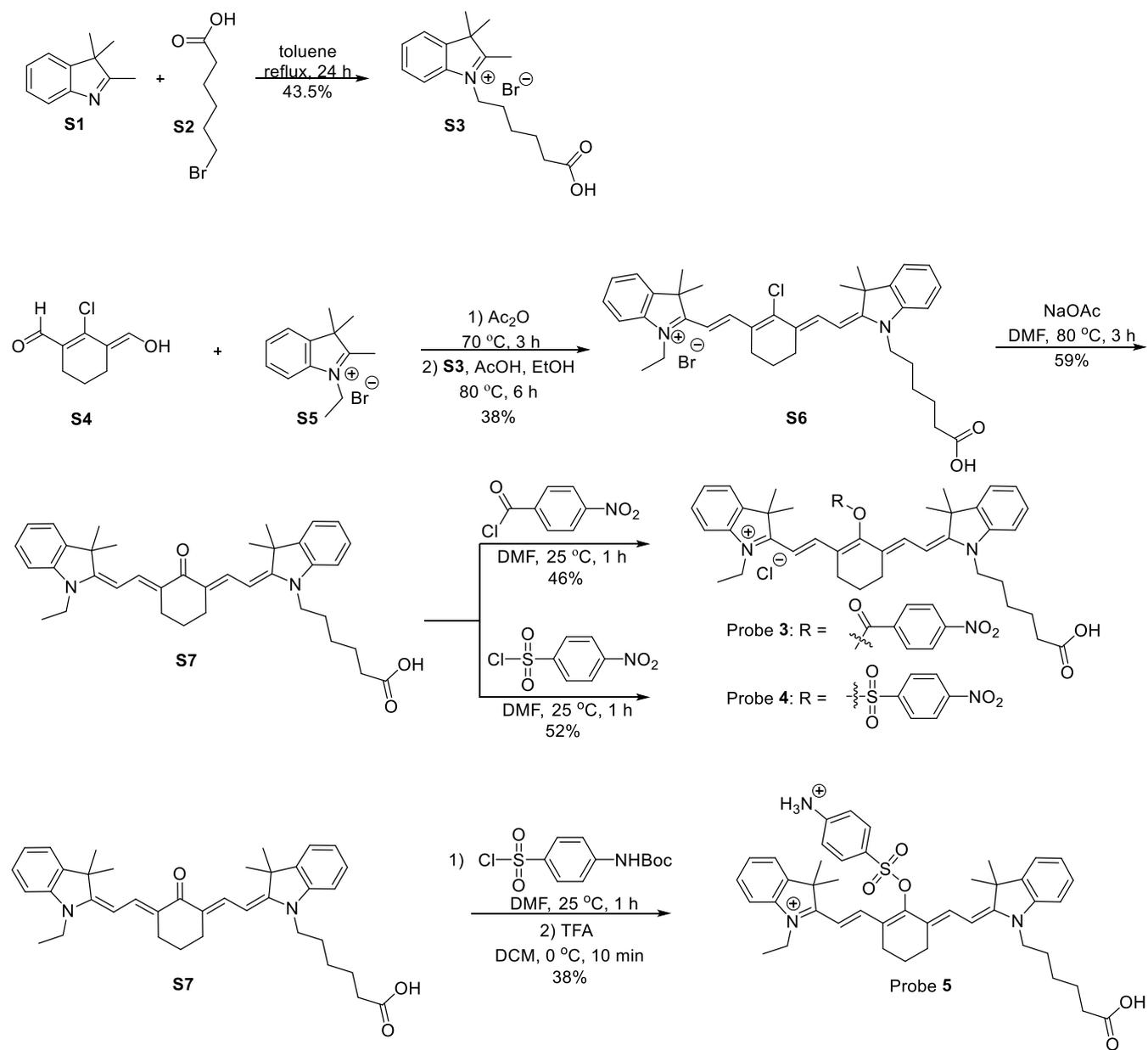
Upon reaching 80% confluence, HepG2 cells in DMEM containing 10% fetal bovine serum and Raw 26 cells in 1640 medium containing 10% fetal bovine serum were transferred into an 8-well chamber containing sterile coverslips at the bottom (300  $\mu$ L/well, 1  $\times$  10<sup>5</sup> cells/mL). After overnight culture at 37 °C under hypoxia (1% O<sub>2</sub>) conditions, the cells were washed with PBS and incubated with probe **1** (10  $\mu$ M) in the respective medium. After incubation for 1 h under normoxia conditions, the cells were further stained with Hoechst 33342 for 30 min under normoxia conditions. Next, the cells were washed with PBS once and the medium was then changed to phenol-red-free DMEM or 1640 medium (100  $\mu$ L). The cells were observed on a Leica TCS SP8 X Confocal Microscope using 63x magnification. Hoechst 33342 was excited at 405 nm and the fluorescence was monitored at 460  $\pm$  30 nm. Probe **1** was excited at 670 nm and the fluorescence was monitored at 770  $\pm$  30 nm.

The 8-well chambers coated with poly-L-lysine for human PBMC cells adhesion were used for confocal imaging assays. 10x poly-L-lysine (0.1%) was diluted to 1x in sterile H<sub>2</sub>O, and enough of the solution was pipetted to cover the surface of each well. Then, the resulting medium was incubated at 37 °C for 1 h. After aspirating the coating solution and washing for a total of three times with PBS, thoroughly covering of each well was ensured. Air dry in a tissue culture hood was added, until no PBS was left. Human PBMC cells with PHA (Phytohemagglutinin, 10 ng/mL) were cultured in 8-well chambers coated with poly-L-lysine at 37 °C for 24 h. The culture medium was removed and washed with PBS once. After incubation with probe **1** (10  $\mu$ M) at 37 °C for 1 h, the cells were then washed twice with PBS buffer and treated with Hoechst 33342 at 37 °C for 30 min. The cells were imaged on a Leica TCS SP8 X Confocal Microscope using 63x magnification. Hoechst 33342 was excited at 405 nm and the fluorescence was monitored at 460  $\pm$  30 nm. Probe **1** was excited at 670 nm and the fluorescence was monitored at 770  $\pm$  30 nm.

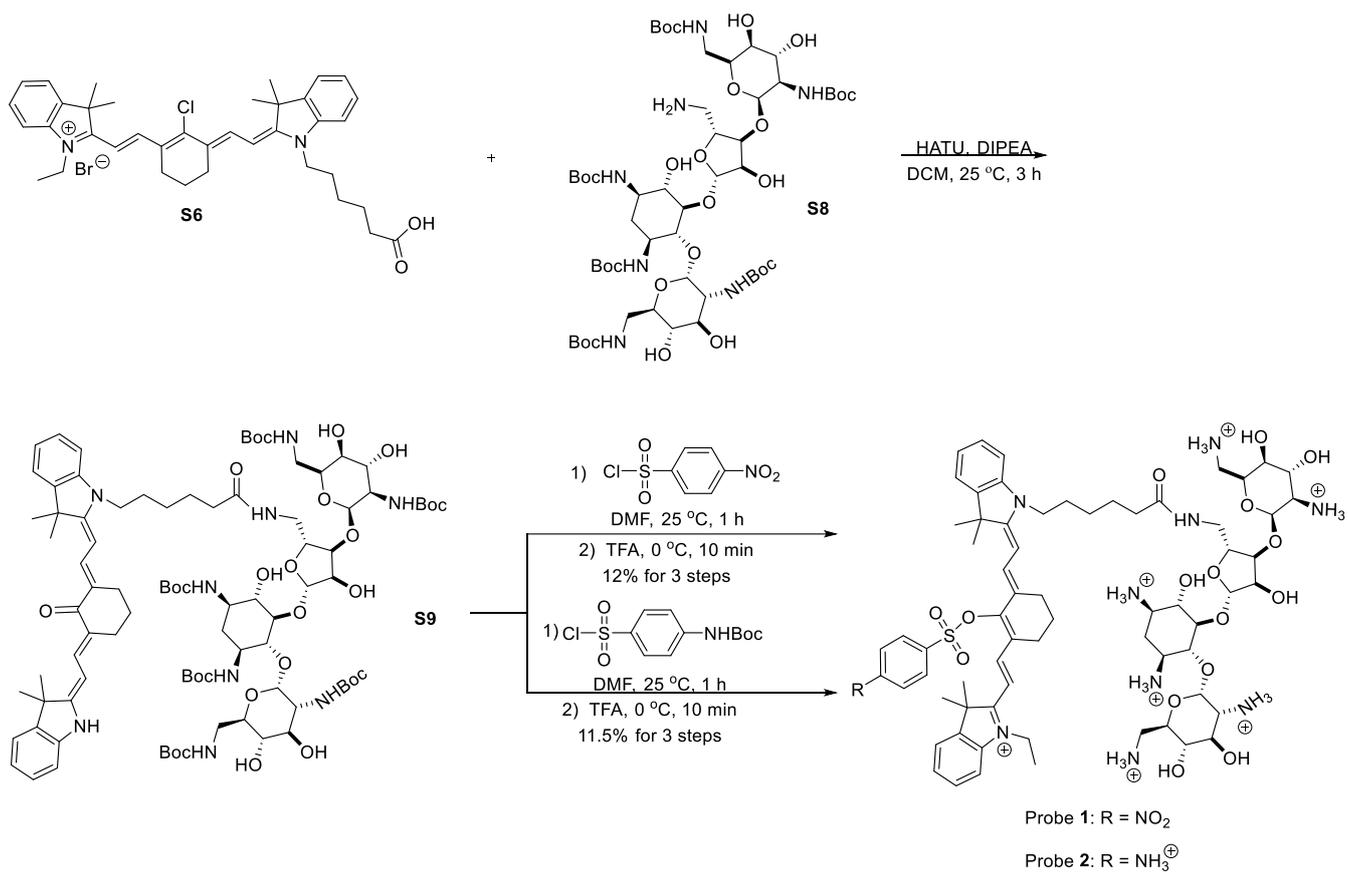
## **2D and 3D real-time *in vivo* optical imaging**

CT26 mouse colon cancer model preparation procedures were in accordance with the guidelines of the Institutional Animal Care and Use Committee. BALB/c mice with an average weight of 20 g at the age of 6-8 weeks were used throughout this study. A CT26 cell suspension (200  $\mu$ L, approximately 2  $\times$  10<sup>6</sup> cells) was ectopically injected into the left hind leg of mice. After inoculation for 7 days, small animal *in vivo* fluorescence imaging was carried out on mice when tumor sizes of mice reached about 100-150 mm<sup>3</sup>. The right hind legs of the mice were infected with *S. aureus* strain (1  $\times$  10<sup>9</sup> CFU). Then, probe **1** (20  $\mu$ M, 100  $\mu$ L) was injected intravenously through the tail veins of the mice. After 0 h, 0.5 h, 1h, 2 h, 4 h and 6 h, images on the IVIS Spectrum CT system (PerkinElmer, USA) were acquired using the following experimental settings: FOV 13.2  $\times$  13.2 cm, binning 8, f/stop 2, excitation filter 745 nm wavelength, emission filter 820 nm wavelength.

## Synthesis Schemes



Scheme S1. Synthesis of probes 3-5.



**Scheme S2.** Synthesis of probes 1-2.

## Synthesis and Spectroscopic Characterization

### 1-(5-carboxypentyl)-2,3,3-trimethyl-3H-indol-1-ium bromide (S3)

To a solution of compound **S1** (10 g, 62.8 mmol) in toluene (16 mL), compound **S2** (12.2 g, 62.8 mmol) was added slowly at 25 °C under argon. The reaction mixture was stirred under reflux for 24 h. After then, the solvent was removed under vacuum, and the residue was washed with diethyl ether (3 × 32 mL) and DCM (3 × 32 mL). The product was dried under reduced pressure, and used directly without further purification. The product **S3** was white solid, 9.7 g, yield 43.5%. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.07 – 7.95 (m, 1H), 7.91 – 7.80 (m, 1H), 7.67 – 7.56 (m, 2H), 4.47 (t, *J* = 7.7 Hz, 2H), 2.87 (s, 3H), 2.22 (t, *J* = 7.3 Hz, 2H), 1.84 (p, *J* = 7.8 Hz, 2H), 1.59 – 1.51 (m, 8H), 1.42 (p, *J* = 8.0, 7.4 Hz, 2H); <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ 196.99, 174.80, 142.33, 141.52, 129.84, 129.40, 124.00, 115.99, 54.63, 47.93, 33.83, 27.42, 25.86, 24.49, 22.47, 14.59. HRMS (ESI): *m/z* calcd for C<sub>17</sub>H<sub>24</sub>NO<sub>2</sub><sup>+</sup>: 274.1802 [M]<sup>+</sup>; found: 274.1802.

### 2-((E)-2-((E)-3-(2-((E)-1-(5-carboxypentyl)-3,3-dimethylindolin-2-ylidene)ethylidene)-2-chlorocyclohex-1-en-1-yl)vinyl)-1-ethyl-3,3-dimethyl-3H-indol-1-ium bromide (S6)

To a solution of compound **S4** (3.1 g, 11.6 mmol) in Ac<sub>2</sub>O (16.5 mL), compound **S5** (2.0 g, 11.6 mmol) in Ac<sub>2</sub>O (16.5 mL) was added slowly at 25 °C under argon. The reaction mixture was stirred at 70 °C for 3 h. After then, the reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. After the residue was diluted with EtOH (33 mL), compound **S3** (4.9 g, 13.9 mmol) and AcONa (2.85 g, 34.8 mmol) was added subsequently at 25 °C under argon. The reaction mixture was stirred at 80 °C for 6 h. After then, the reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was diluted with DCM (33 mL), and washed with brine (2 × 33 mL). The organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (6% MeOH in DCM) to obtain product **S6** (2.9 g, 38%) as green solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.37 (d, *J* = 14.1 Hz, 1H), 8.32 (d, *J* = 13.9 Hz, 1H), 7.44 – 7.33 (m, 4H), 7.25 – 7.17 (m, 2H), 7.13 (d, *J* = 8.0 Hz, 1H), 6.26 (d, *J* = 14.1 Hz, 1H), 6.13 (d, *J* = 14.0 Hz, 1H), 4.20 – 4.12 (m, 4H), 2.74 (t, *J* = 6.1 Hz, 2H), 2.70 (t, *J* = 6.0 Hz, 2H), 2.60 (t, *J* = 7.2 Hz, 2H), 2.00 (p, *J* = 6.2 Hz, 2H), 1.87 (p, *J* = 7.8 Hz, 2H), 1.79 (p, *J* = 7.3 Hz, 2H), 1.71 (s, 12H), 1.57 (q, *J* = 7.5, 7.0 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 176.01, 172.97, 171.33, 150.88, 145.20, 144.10, 142.09, 141.95, 141.21, 141.12, 129.10, 128.92, 128.06, 127.62, 125.69, 125.15, 122.39, 122.33, 111.27, 110.47, 101.93, 100.42, 49.59, 49.28, 44.75, 39.62, 34.73, 28.25, 28.22, 27.01, 26.71, 26.65, 26.31, 24.64, 20.79, 12.43. HRMS (ESI): *m/z* calcd for C<sub>38</sub>H<sub>46</sub>ClN<sub>2</sub>O<sub>2</sub><sup>+</sup>: 597.3242 [M]<sup>+</sup>; found: 597.3242.

### 6-((E)-2-((E)-2-((E)-3-(2-((E)-1-ethyl-3,3-dimethylindolin-2-ylidene)ethylidene)-2-oxocyclohexylidene)ethylidene)-3,3-dimethylindolin-1-yl)hexanoic acid (S7)<sup>[1]</sup>

To a solution of compound **S6** (200 mg, 0.295 mmol) in DMF (7.9 mL), sodium acetate (73 mg, 0.885 mmol) was added slowly at 25 °C under argon. The reaction mixture was stirred at 80 °C for 2 h. After then, the reaction mixture was diluted with DCM (40 mL), and washed with H<sub>2</sub>O (2 × 14 mL) and brine (3 × 14 mL). The organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (2% MeOH in DCM) to obtain product **S7** (100 mg, 59%) as red solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.20 (dd, *J* = 13.4, 5.6 Hz, 2H), 7.18 (p, *J* = 6.6 Hz, 4H), 6.91 (q, *J* = 7.1 Hz, 2H), 6.68 (t, *J* = 7.0 Hz, 2H), 5.48 (dd, *J* = 13.3, 6.8 Hz, 2H), 3.74 (q, *J* = 7.2 Hz, 2H), 3.68 (t, *J* = 7.5 Hz, 2H), 2.61 (q, *J* = 5.3 Hz, 4H), 2.40 (t, *J* = 7.4 Hz, 2H), 1.87 (p, *J* = 6.3 Hz, 2H), 1.74 (t, *J* = 7.5 Hz, 4H), 1.67 (d, *J* = 3.5 Hz, 12H), 1.54 – 1.43 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 186.58, 177.69, 162.79, 162.45, 144.08, 143.62, 139.87, 139.72, 133.87, 133.72, 127.71, 126.43, 126.30, 121.83, 120.68, 106.78, 106.59, 92.69, 92.36, 53.50, 46.66, 42.41, 37.11, 34.15, 30.59, 28.72, 28.66, 26.71, 26.03, 25.81, 24.62, 22.49, 11.18. HRMS (ESI): *m/z* calcd for C<sub>38</sub>H<sub>47</sub>N<sub>2</sub>O<sub>3</sub><sup>+</sup>: 579.3581 [M+H]<sup>+</sup>; found: 579.3581.

**2-((E)-2-((E)-3-(2-((E)-1-(5-carboxypentyl)-3,3-dimethylindolin-2-ylidene)ethylidene)-2-((4-nitrobenzoyl)oxy)cyclohex-1-en-1-yl)vinyl)-1-ethyl-3,3-dimethyl-3H-indol-1-ium chloride (Probe 3)**

To a solution of compound **S7** (40 mg, 0.069 mmol) in DCM (1.7 mL), 4-nitrobenzoyl chloride (32 mg, 0.173 mmol) was added slowly at 0 °C under argon. The reaction mixture was stirred at 25 °C for 1 h. After then, the reaction mixture was quenched with absolute methanol (2 µL). The organic solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (4% MeOH in DCM) to obtain product probe **3** (23 mg, 46%) as green solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.65 - 8.46 (m, 4H), 7.67 (dd, *J* = 23.7, 13.9 Hz, 2H), 7.36 (q, *J* = 7.5 Hz, 2H), 7.26 – 7.15 (m, 5H), 7.13 (d, *J* = 8.0 Hz, 1H), 6.20 (d, *J* = 14.1 Hz, 1H), 6.10 (d, *J* = 14.0 Hz, 1H), 4.21 – 4.08 (m, 4H), 2.86 – 2.70 (m, 4H), 2.60 (t, *J* = 7.2 Hz, 2H), 2.08 (q, *J* = 6.1 Hz, 2H), 1.91 – 1.81 (m, 2H), 1.81 – 1.72 (m, 1H), 1.53 (p, *J* = 7.9 Hz, 3H), 1.46 – 1.32 (m, 14H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 175.91, 172.27, 170.74, 162.27, 159.40, 151.72, 141.97, 141.78, 140.88, 140.77, 140.64, 139.58, 133.46, 131.41, 129.14, 128.97, 125.72, 125.24, 124.65, 122.44, 122.23, 122.17, 111.35, 110.60, 101.49, 100.11, 49.18, 48.90, 44.71, 39.63, 34.75, 28.06, 28.00, 27.02, 26.31, 24.63, 20.79, 12.37. HRMS (ESI): *m/z* calcd for C<sub>45</sub>H<sub>50</sub>N<sub>3</sub>O<sub>6</sub><sup>+</sup>: 728.3694 [M]<sup>+</sup>; found: 728.3659.

**2-((E)-2-((E)-3-(2-((E)-1-(5-carboxypentyl)-3,3-dimethylindolin-2-ylidene)ethylidene)-2-(((4-nitrophenyl)sulfonyl)oxy)cyclohex-1-en-1-yl)vinyl)-1-ethyl-3,3-dimethyl-3H-indol-1-ium chloride (Probe 4)**

To a solution of compound **S7** (40 mg, 0.069 mmol) in DCM (1.7 mL), 4-Nitrobenzenesulphonyl chloride (38 mg, 0.173 mmol) was added slowly at 0 °C under argon. The reaction mixture was stirred at 25 °C for 1 h. After then, the reaction mixture was quenched with absolute methanol (2 µL). The organic solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (4% MeOH in DCM) to obtain product probe **4** (27 mg, 52%) as green solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.46 (d, *J* = 8.4 Hz, 2H), 8.23 (d, *J* = 8.4 Hz, 2H), 7.79 (dd, *J* = 14.1, 6.8 Hz, 2H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.32 (t, *J* = 6.6 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 2H), 7.13 (t, *J* = 8.3 Hz, 2H), 6.06 (dd, *J* = 20.6, 14.0 Hz, 2H), 4.12 (q, *J* = 7.3 Hz, 2H), 4.07 (d, *J* = 7.7 Hz, 2H), 2.57 (q, *J* = 6.9 Hz, 3H), 2.41 (t, *J* = 7.1 Hz, 2H), 1.82 (q, *J* = 6.9 Hz, 4H), 1.70 (h, *J* = 9.2 Hz, 3H), 1.53 (s, 6H), 1.51 (s, 8H), 1.40 (t, *J* = 7.4 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 172.53, 171.73, 157.13, 152.98, 151.46, 148.03, 141.93, 141.65, 141.24, 141.16, 141.07, 140.83, 140.54, 130.10, 129.04, 127.67, 125.82, 125.64, 124.87, 123.73, 123.29, 122.38, 111.24, 110.78, 101.64, 100.86, 49.40, 49.33, 44.56, 39.67, 34.30, 30.65, 27.66, 27.62, 27.00, 26.31, 25.48, 24.53, 20.36, 19.26, 12.38; HRMS (ESI): *m/z* calcd for C<sub>44</sub>H<sub>50</sub>N<sub>3</sub>O<sub>7</sub>S<sup>+</sup>: 764.3364 [M+H]<sup>+</sup>; found: 764.3368.

**2-((E)-2-((E)-2-(((4-ammoniophenyl)sulfonyl)oxy)-3-(2-((E)-1-(5-carboxypentyl)-3,3-dimethylindolin-2-ylidene)ethylidene)cyclohex-1-en-1-yl)vinyl)-1-ethyl-3,3-dimethyl-3H-indol-1-ium chloride (Probe 5)**

To a solution of compound **S7** (40 mg, 0.069 mmol) in DCM (1.7 mL), tert-butyl (4-(chlorosulfonyl)phenyl) carbamate (50 mg, 0.173 mmol) was added slowly at 0 °C under argon. The reaction mixture was stirred at 25 °C for 1 h. After then, the reaction mixture was quenched with absolute methanol (2 µL). The organic solvent was removed under reduced pressure, and trifluoroacetic acid (0.069 mmol) was added to the residue at 0 °C, and the reaction mixture was stirred at 0 °C for 10 min. The solvent was removed under vacuum, and the residue was purified by column chromatography on silica gel (6% MeOH in DCM) to obtain product probe **5** (19.2 mg, 38%) as green solid. <sup>1</sup>H NMR (500 MHz, Chloroform-*d*) δ 8.07 (d, *J* = 14.0 Hz, 1H), 7.95 (d, *J* = 14.0 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.39 – 7.31 (m, 4H), 7.20 (td, *J* = 7.5, 2.4 Hz, 2H), 7.09 (dd, *J* = 8.1, 3.9 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 5.95 (d, *J* = 14.0 Hz, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 4.01 (t, *J* = 7.5 Hz, 2H), 2.56 – 2.40 (m, 6H), 1.81 (p, *J* = 7.4 Hz, 2H), 1.71 (t, *J* = 7.3 Hz, 4H), 1.67 (s, 6H), 1.60 (s, 6H), 1.46 (t, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 175.66, 172.67, 171.85, 159.78, 154.91, 142.48, 142.04, 141.78, 141.53, 141.38, 131.08, 128.85, 128.75, 125.48, 125.28, 124.27, 122.52, 122.45, 117.37, 113.58, 110.91, 110.38, 100.80, 100.03, 49.54, 49.48, 44.36, 39.50, 34.50, 27.85, 27.77, 27.02, 26.27, 25.17, 24.62, 20.40, 12.34; HRMS (ESI): *m/z* calcd for C<sub>44</sub>H<sub>52</sub>N<sub>3</sub>O<sub>5</sub>S<sup>+</sup>: 734.3622 [M]<sup>+</sup>; found: 734.3601.

**2-((E)-2-((E)-3-(2-((E)-1-(6-(((2R,3S,4R,5S)-3-(((2R,3R,4R,5S,6S)-3-ammonio-6-(ammoniomethyl)-4,5-dihydroxytetrahydro-2H-pyran-2-yl)oxy)-5-(((1R,2R,3S,5R,6S)-3,5-dihydroxytetrahydro-2H-pyran-2-yl)oxy)-6-hydroxycyclohexyl)oxy)-4-hydroxytetrahydrofuran-2-yl)methyl)amino)-6--diammonio-2-(((2R,3R,4R,5S,6R)-3-ammonio-6-(ammoniomethyl)-4,5-dioxohexyl)-3,3-dimethylindolin-2-ylidene)ethylidene)-2-(((4-nitrophenyl)sulfonyl)oxy)cyclohex-1-en-1-yl)vinyl)-1-ethyl-3,3-dimethyl-3H-indol-1-ium (Probe 1)<sup>[2]</sup>**

To a solution of compound **S6** (68 mg, 0.098 mmol) and compound **S8** (100 mg, 0.082 mmol) in DCM (1.0 mL), HATU (62 mg, 0.164 mmol) and DIPEA (32 mg, 0.246 mmol) were added subsequently at 25 °C under argon. After stirred at 25 °C for 3 h, the reaction mixture was diluted with DCM (3.0 mL), and washed with H<sub>2</sub>O (4.0 mL), and brine (4.0 mL). The organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and evaporated under vacuum. The residue was purified by column chromatography on silica gel (3% MeOH in DCM) quickly and the product was used directly.

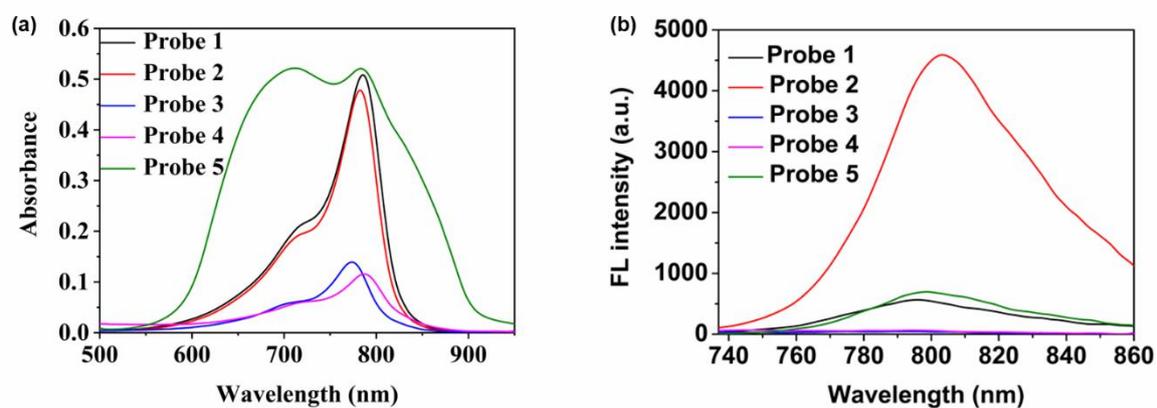
The above product (60 mg, 0.034 mmol) was dissolved in DCM (680 uL), 4-Nitrobenzenesulphonyl chloride (19 mg, 0.085 mmol) was added slowly at 0 °C under argon. The reaction mixture was stirred at 25 °C for 1 h. After then, the reaction mixture was quenched with absolute methanol (1 µL). The organic solvent was removed under reduced pressure. Trifluoroacetic acid (680 uL) was added to the residue slowly at 0 °C under argon. The reaction was stirred at 0 °C for 10 min. The reaction mixture was concentrated in vacuo, and the residue was purified by HPLC to obtain probe **1** as green solid, 24 mg, yield 12% for three steps. <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O) δ 8.34 – 8.17 (m, 2H), 7.95 – 7.78 (m, 2H), 7.57 – 7.36 (m, 3H), 7.23 (d, *J* = 24.2 Hz, 2H), 7.10 (s, 3H), 6.89 (s, 3H), 6.75 (s, 1H), 5.90 (s, 1H), 5.38 – 5.30 (m, 1H), 5.22 (s, 1H), 4.31 (s, 1H), 4.29 – 4.19 (m, 3H), 4.17 (s, 3H), 4.11 – 4.01 (m, 3H), 4.00 – 3.94 (m, 2H), 3.95 – 3.83 (m, 5H), 3.76 (s, 2H), 3.70 (t, *J* = 9.5 Hz, 2H), 3.54 (s, 2H), 3.53 – 3.41 (m, 6H), 3.41 – 3.28 (m, 2H), 3.27 – 3.16 (m, 2H), 2.45 (s, 1H), 2.14 (s, 6H), 1.89 (q, *J* = 13.1 Hz, 2H), 1.61 – 1.51 (m, 2H), 1.48 – 1.36 (m, 7H), 1.24 (s, 5H), 1.22 – 1.13 (m, 13H), 1.13 – 0.99 (m, 9H); <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O) δ 176.67, 171.36, 167.68, 167.62, 166.76, 164.94, 162.92, 162.64, 162.35, 162.07, 155.91, 151.19, 141.69, 141.36, 140.77, 140.54, 139.35, 139.22, 132.37, 130.96, 130.61, 129.71, 129.60, 129.52, 128.96, 128.56, 124.70, 122.82, 121.38, 119.87, 117.54, 115.22, 112.89, 109.02, 100.94, 98.46, 95.78, 94.91, 91.33, 84.93, 82.73, 80.88, 77.44, 75.04, 73.42, 72.25, 70.42, 70.24, 70.12, 69.85, 68.12, 67.53, 67.42, 66.58, 64.82, 53.24, 50.84, 49.52, 48.65, 48.53, 41.08, 40.45, 40.05, 38.72, 35.58, 30.43, 27.87, 26.91, 25.94, 25.04, 18.93, 17.95, 16.65, 13.31, 11.50; HRMS (ESI): *m/z* calcd for C<sub>67</sub>H<sub>95</sub>N<sub>10</sub>O<sub>18</sub>S<sup>+</sup>: 1359.6541 [M]<sup>+</sup>; found: 1359.6548.

**2-((E)-2-((E)-3-(2-((E)-1-(6-(((2R,3S,4R,5S)-3-(((2R,3R,4R,5S,6S)-3-ammonio-6-(ammoniomethyl)-4,5-dihydroxytetrahydro-2H-pyran-2-yl)oxy)-5-(((1R,2R,3S,5R,6S)-3,5-diammonio-2-(((2R,3R,4R,5S,6R)-3-ammonio-6-(ammoniomethyl)-4,5-dihydroxytetrahydro-2H-pyran-2-yl)oxy)-6-hydroxycyclohexyl)oxy)-4-hydroxytetrahydrofuran-2-yl)methyl)amino)-6-oxohexyl)-3,3-dimethylindolin-2-ylidene)ethylidene)-2-(((4-ammoniophenyl)sulfonyl)oxy)cyclohex-1-en-1-yl)vinyl)-1-ethyl-3,3-dimethyl-3H-indol-1-ium (Probe 2)**

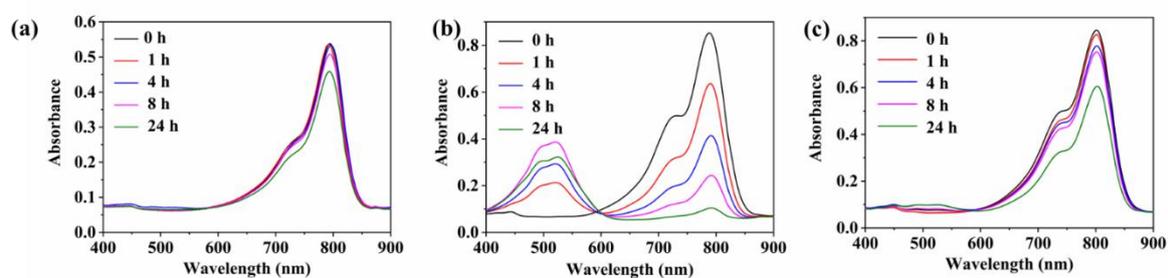
The compound **S9** (60 mg, 0.034 mmol) was dissolved in DCM (680 uL), tert-butyl (4-(chlorosulfonyl)phenyl) carbamate (24.7 mg, 0.085 mmol) was added slowly at 0 °C under argon. The reaction mixture was stirred at 25 °C for 1 h. After then, the reaction mixture was quenched with absolute methanol (1 µL). The organic solvent was removed under reduced pressure. Trifluoroacetic acid (680 uL) was added to the residue slowly at 0 °C under argon. The reaction was stirred at 0 °C for 10 min. The reaction mixture was concentrated in vacuo, and the residue was purified by HPLC to obtain probe **2** as green solid, 21 mg, yield 11.5% for three steps. <sup>1</sup>H NMR (600 MHz, D<sub>2</sub>O) δ 7.69 (s, 1H), 7.60 (s, 1H), 7.28 (s, 2H), 7.21 (s, 3H), 7.10 (s, 2H), 7.00 (s, 3H), 6.87 (s, 1H), 6.50 (s, 2H), 5.90 (d, *J* = 3.9 Hz, 1H), 5.40 – 5.37 (m, 1H), 5.35 (d, *J* = 4.4 Hz, 1H), 5.22 (s, 1H), 4.30 (d, *J* = 5.1 Hz, 1H), 4.24 (d, *J* = 5.1 Hz, 1H), 4.21 (d, *J* = 4.6 Hz, 1H), 4.19 – 4.14 (m, 3H), 4.07 (t, *J* = 9.6 Hz, 2H), 3.97 (t, *J* = 9.6 Hz, 2H), 3.94 – 3.85 (m, 4H), 3.85 – 3.74 (m, 3H), 3.70 (t, *J* = 9.5 Hz, 2H), 3.59 – 3.47 (m, 4H), 3.48 – 3.41 (m, 3H), 3.41 – 3.29 (m, 6H), 3.25 (dd, *J* = 13.6, 6.8 Hz, 2H), 2.53 – 2.38 (m, 1H), 2.23 – 2.01 (m, 6H), 1.88 (q, *J* = 12.6 Hz, 2H), 1.59 (s, 3H), 1.50 (s, 4H), 1.37 (s, 3H), 1.29 (s, 8H), 1.25 (s, 8H), 1.15 (s, 5H); <sup>13</sup>C NMR (150 MHz, D<sub>2</sub>O) δ 188.68, 179.27, 177.92, 176.84, 171.67, 171.44, 163.05, 162.81, 162.58, 162.35, 157.95, 157.84, 157.06, 156.58, 154.47, 141.86, 141.48, 140.77, 139.41, 137.52, 130.78, 130.15, 128.83, 128.73, 127.14, 125.19, 123.51, 121.78, 119.32, 117.38, 115.44, 113.51, 111.17, 109.09, 95.84, 94.96, 87.14, 84.94, 83.38, 82.46, 80.79, 77.51, 75.14, 73.40, 72.30, 70.47, 70.12,

69.85, 68.13, 67.84, 67.56, 67.47, 56.92, 53.91, 53.25, 50.85, 49.87, 49.54, 48.84, 48.77, 48.53, 41.20, 40.50, 40.09, 39.11, 35.65, 27.90, 27.06, 26.43, 25.95, 25.08, 25.01, 24.34, 19.74, 11.54; HRMS (ESI): m/z calcd for  $C_{67}H_{97}N_{10}O_{16}S^+$ : 1329.6799 [M]<sup>+</sup>; found: 1329.6794.

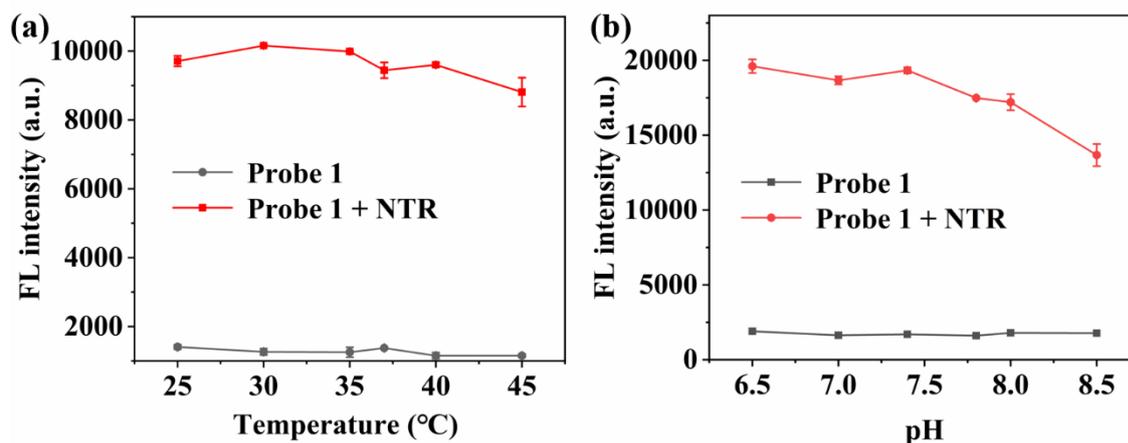
## Supplementary Figures



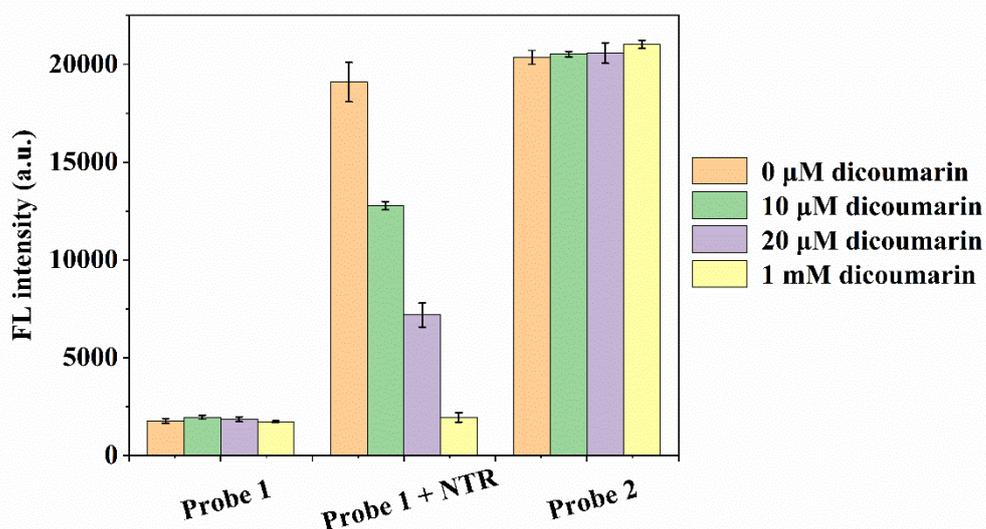
**Figure S1.** (a) Absorption and (b) normalized fluorescence emission spectra of probes 1-5 in Tris-buffered saline (TBS, 50 mM Tris/HCl, with 1.5% DMSO as co-solvent, pH 7.4). ( $\lambda_{\text{ex}} = 700 \text{ nm}$ )



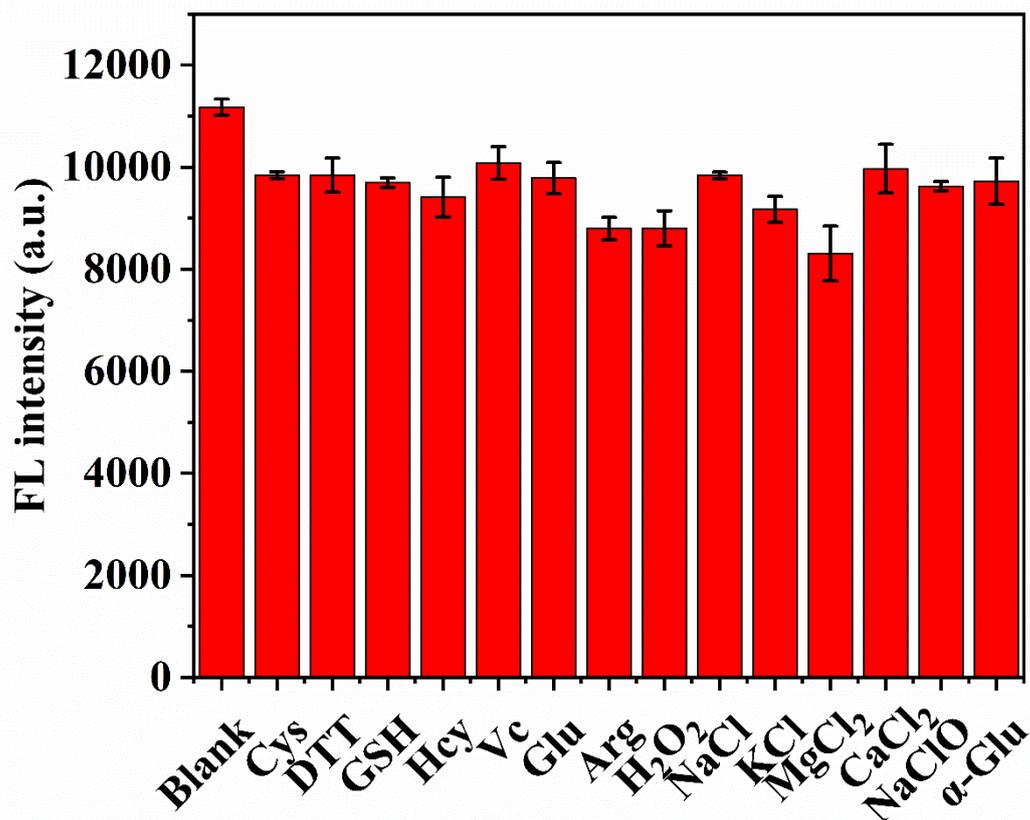
**Figure S2.** Time-dependent stability of (a) probe 1, (b) probe 3 and (c) probe 4 in Tris buffer (containing 1.5% DMSO and 0.5% Kolliphor RH40 as co-solvent, pH = 7.4) at 37 °C.



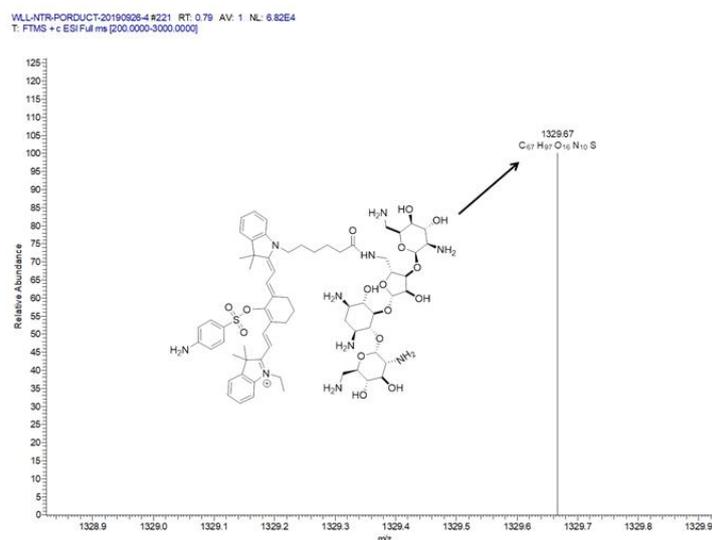
**Figure S3.** (a) Effect of temperature (25 °C, 30 °C, 35 °C, 37 °C, 40 °C and 45 °C) on the fluorescence intensity of probe 1 and probe 1 (10  $\mu$ M) reacting with NTR (0.25  $\mu$ g/mL) in Tris-buffered saline (TBS, 50 mM Tris/HCl, with 1.5% DMSO as co-solvent) after blending, in the presence of NADH (500  $\mu$ M) at 37 °C. ( $\lambda_{ex}$  = 750 nm,  $\lambda_{em}$  = 801 nm). (b) Effect of pH value (6.5, 7.0, 7.4, 7.8, 8.0 and 8.5) on the fluorescence intensity of probe 1 and probe 1 (10  $\mu$ M) reacting with NTR (0.25  $\mu$ g/mL) in Tris-buffered saline (TBS, 50 mM Tris/HCl, with 1.5% DMSO and 0.1% Kolliphor RH40 as co-solvent) for 2 min, in the presence of NADH (500  $\mu$ M) at 37 °C. ( $\lambda_{ex}$  = 750 nm,  $\lambda_{em}$  = 801 nm)



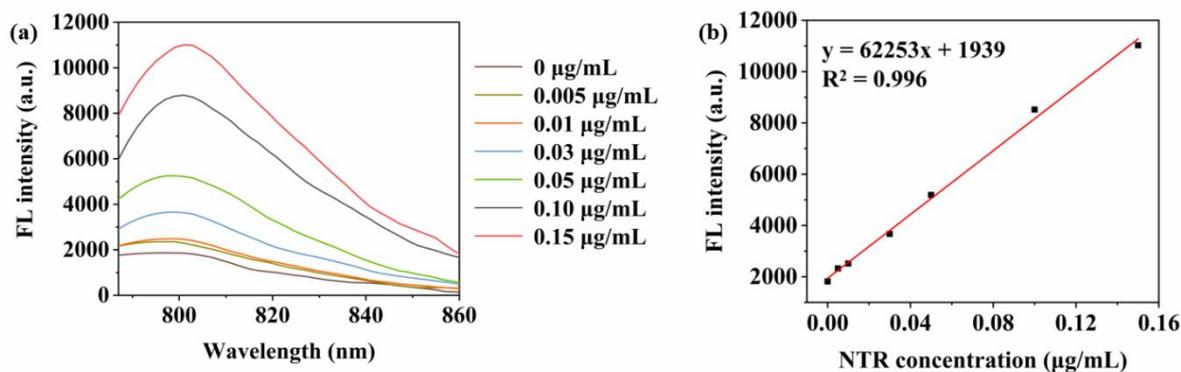
**Figure S4.** Fluorescence emission spectra of probe 1 (10  $\mu$ M), probe 2 (10  $\mu$ M) and probe 1 (10  $\mu$ M) reacted with NTR (0.25  $\mu$ g/mL) in Tris-buffered saline (TBS, 50 mM Tris/HCl, with 1.5% DMSO and 0.1% Kolliphor RH40 as co-solvent, pH 7.4) with or without dicoumarin (0  $\mu$ M, 10  $\mu$ M, 20  $\mu$ M or 1 mM) for 2 min, in the presence of NADH (500  $\mu$ M) at 37 °C. ( $\lambda_{ex}$  = 750 nm,  $\lambda_{em}$  = 801 nm).



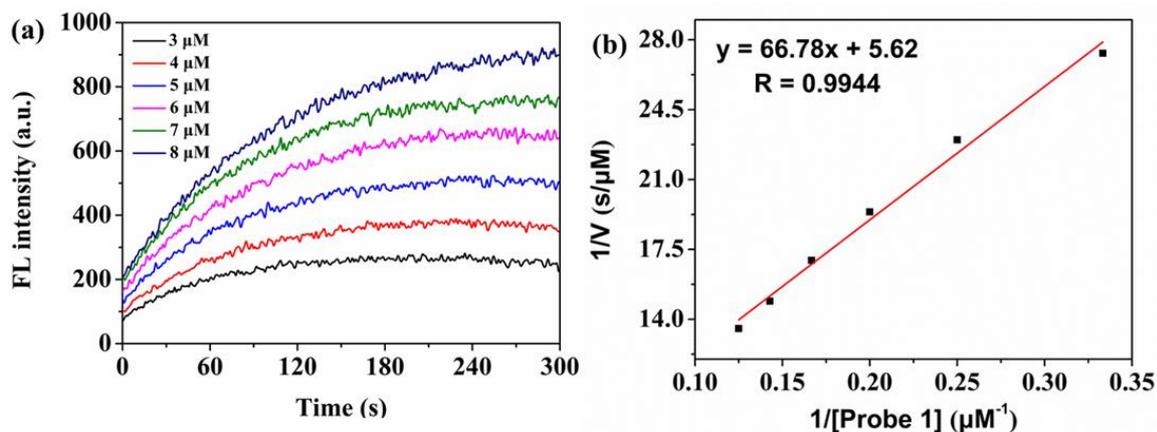
**Figure S5.** Fluorescence intensities at 801 nm for probe 1 (10  $\mu$ M) reacted with NTR (0.25  $\mu$ g/mL) in Tris-buffered saline (TBS, 50 mM Tris/HCl, with 1.5% DMSO as co-solvent, pH 7.4) after blending, in the presence of NADH (500  $\mu$ M) and different compound species at 37  $^{\circ}$ C. NaCl (50 mM), MgCl<sub>2</sub> (50 mM), KCl (50 mM), CaCl<sub>2</sub> (50 mM), H<sub>2</sub>O<sub>2</sub> (1 mM), NaClO (1 mM), Arg (arginine, 1 mM), Cys (cysteine, 1 mM), Hcy (Homocysteine, 1 mM), DTT (dithiothreitol, 1 mM), GSH (glutathione, 1 mM), Glu (glucose, 10 mM), Vc (Vitamin c, 1 mM) and  $\alpha$ -Glu ( $\alpha$ -glucuronidase, 10 U/mL) ( $\lambda_{ex}$  = 750 nm,  $\lambda_{em}$  = 801 nm).



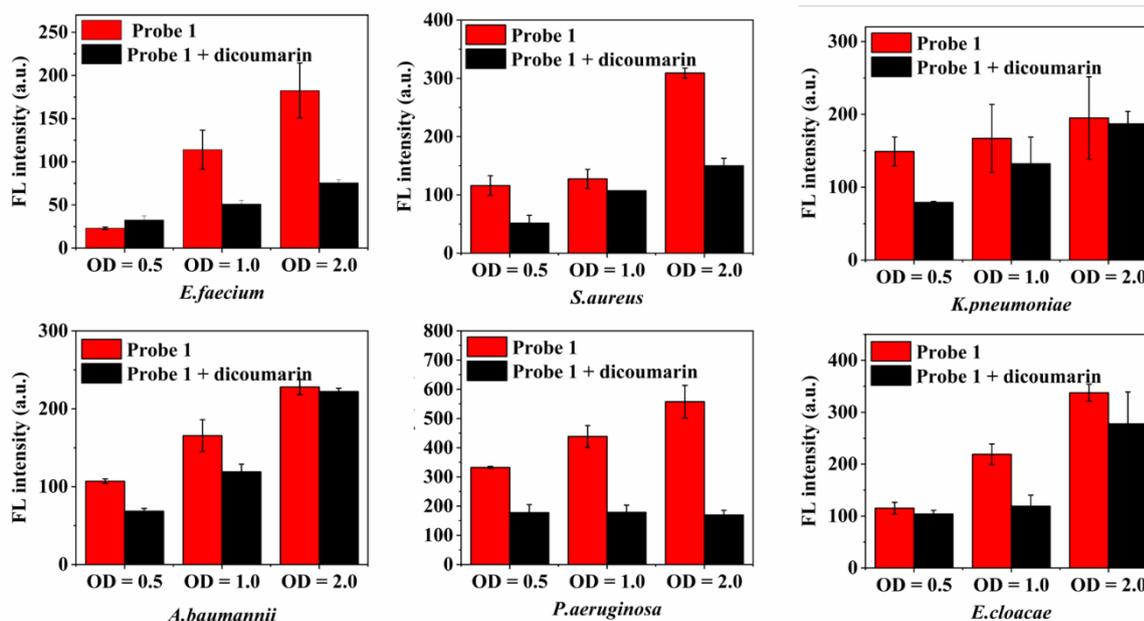
**Figure S6.** ESI interface-Exacte Plus Orbitrap mass spectrum of probe 1 (10  $\mu$ M) reacted with NTR (0.25  $\mu$ g/mL) in Tris-buffered saline (TBS, 50 mM Tris/HCl, with 1.5% DMSO as co-solvent, pH 7.4) after blending, in the presence of NADH (500  $\mu$ M) at 37  $^{\circ}$ C.



**Figure S7.** (a) Fluorescence emission spectra of probe 1 (10  $\mu\text{M}$ ) reacted with different amounts of NTR (0  $\mu\text{g/mL}$ , 0.005  $\mu\text{g/mL}$ , 0.01  $\mu\text{g/mL}$ , 0.03  $\mu\text{g/mL}$ , 0.05  $\mu\text{g/mL}$ , 0.10  $\mu\text{g/mL}$  and 0.15  $\mu\text{g/mL}$ ) in Tris-buffered saline (TBS, 50 mM Tris/HCl, with 1.5% DMSO as co-solvent, pH 7.4), in the presence of NADH (500  $\mu\text{M}$ ) at 37  $^{\circ}\text{C}$ ,  $\lambda_{\text{ex}} = 750 \text{ nm}$ . (b) Linear correlation between fluorescence intensity ( $\lambda_{\text{em}} = 801 \text{ nm}$ ) and various NTR concentrations. The detection limit ( $3\sigma/k$ , in which  $\sigma$  is the standard deviation of blank measurements,  $n = 11$ , and  $k$  is the slope of the linear equation) was determined.



**Figure S8.** (a) Dynamic curves of probe 1 (3, 4, 5, 6, 7 and 8  $\mu\text{M}$ ) reacted with NTR (0.125  $\mu\text{g/mL}$ ) in Tris-buffered saline (TBS, 50 mM Tris/HCl, with 1.5% DMSO as co-solvent, pH 7.4) after blending, in the presence of NADH (500  $\mu\text{M}$ ) at 37  $^{\circ}\text{C}$ . ( $\lambda_{\text{ex}} = 750 \text{ nm}$ ). (b) Lineweaver-Burk plot for the enzyme-catalyzed reaction. The Michaelis-Menten equation was calculated as:  $V = V_{\text{max}} [\text{probe}] / (K_{\text{m}} + [\text{probe}])$ , where  $V$  was the initial reaction rate,  $[\text{probe}]$  was the probe concentration, and  $K_{\text{m}}$  was the Michaelis constant. Conditions: 0.125  $\mu\text{g/mL}$  of NTR, 500  $\mu\text{M}$  of NADH, 3-8  $\mu\text{M}$  of probe 1,  $\lambda_{\text{ex}}/\lambda_{\text{em}} = 750/801 \text{ nm}$ . Points were fitted using a linear regression model (correlation coefficient:  $R = 0.9944$ ).



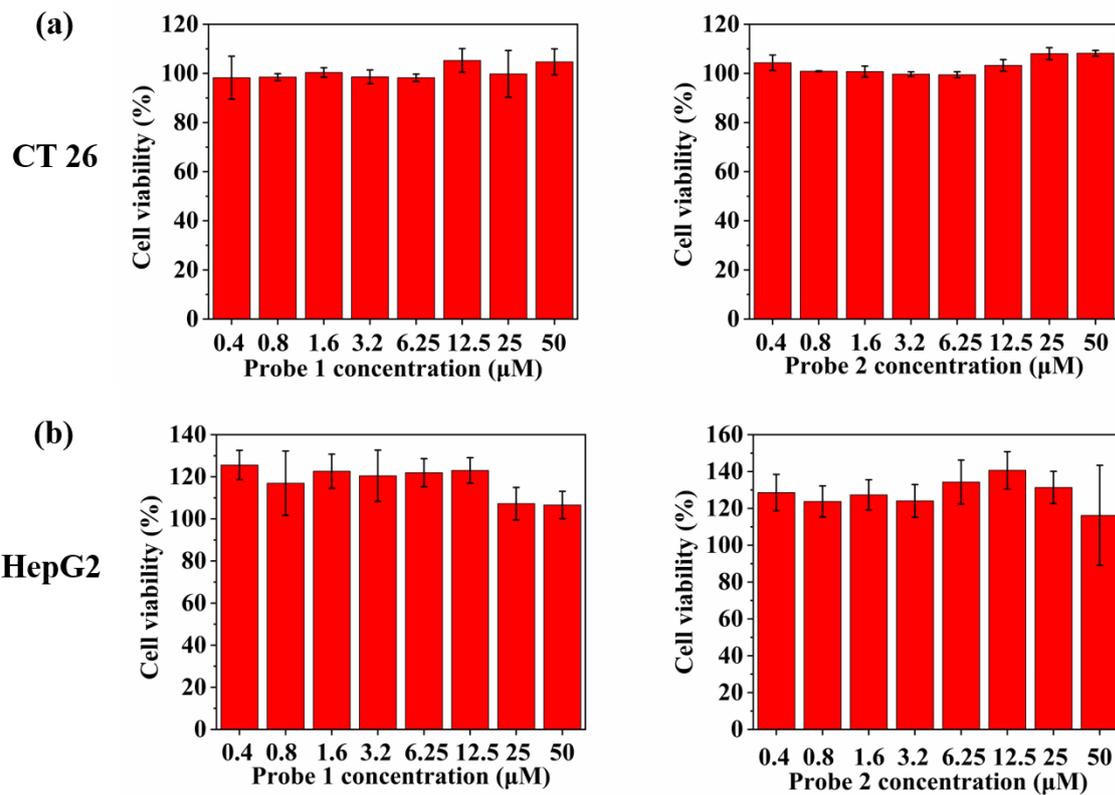
**Figure S9.** Quantification analysis of the response of fluorescence intensity of probe 1 (10  $\mu$ M) in Tris-buffered saline (TBS, 50 mM Tris/HCl, with 0.1% Kolliphor RH40 as co-solvent, pH 7.4) after incubation with ESKAPE pathogens (comprising of two Gram-positive species *E. faecium* and *S. aureus*, and four Gram-negative species *K. pneumoniae*, *A. baumannii*, *P. aeruginosa* and *E. cloacae*) at 37  $^{\circ}$ C for 1 h. For the inhibition test of dicoumarin, bacteria and dicoumarin (1 mM) were incubated in Tris-buffered saline (TBS, 50 mM Tris/HCl, with 1.5% DMSO and 0.1% Kolliphor RH40 as co-solvent, pH 7.4) at 37  $^{\circ}$ C for 0.5 h, and then probe 1 (10  $\mu$ M) was added and incubated at 37  $^{\circ}$ C for 1 h.  $\lambda_{ex}$  = 750 nm,  $\lambda_{em}$  = 809 nm. Optical density (OD) value of bacteria was measured at a wavelength of 600 nm.

**Table S1.** Representative Minimal Inhibitory Concentrations (MIC) in  $\mu$ mol/L for Various Bacterial Strains.

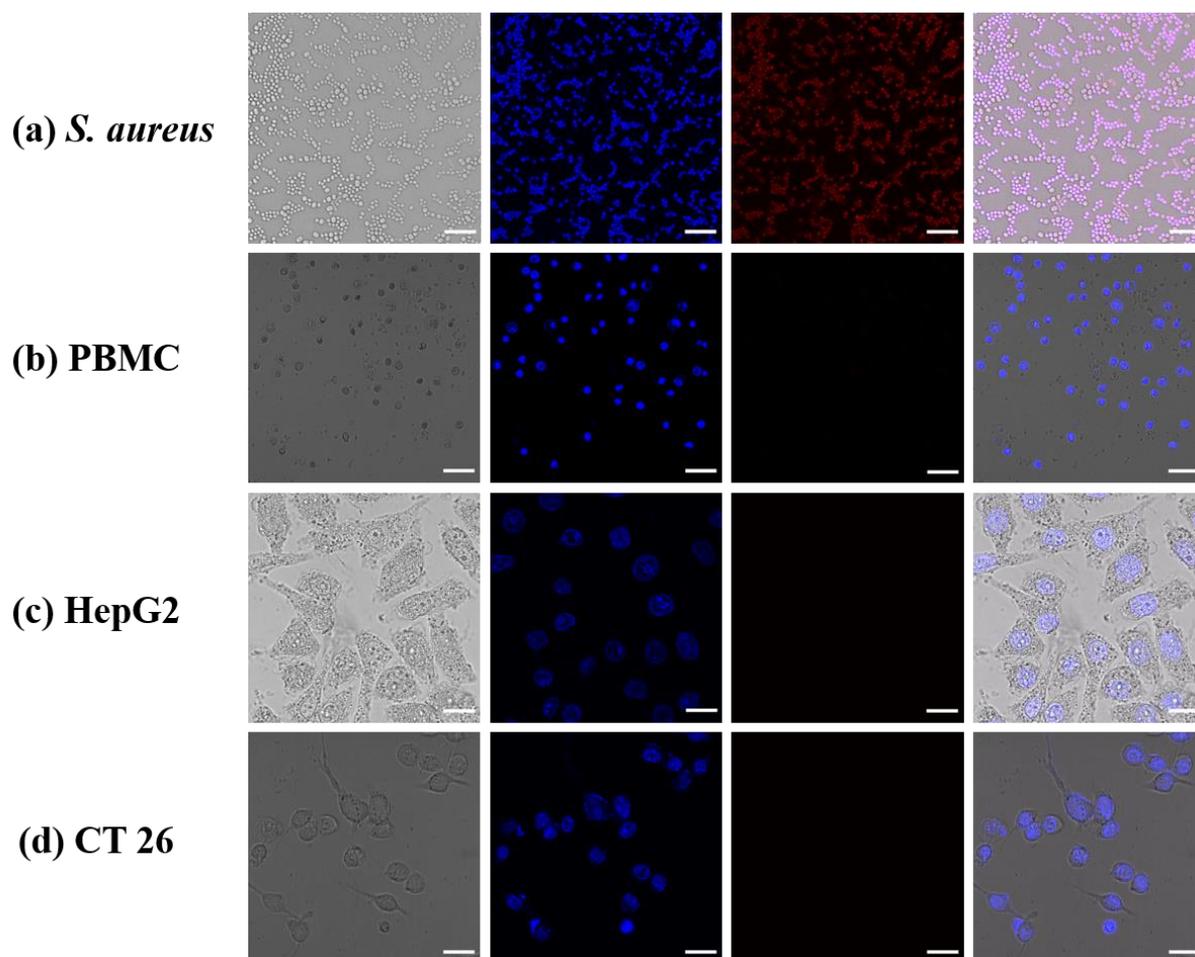
Compound	MIC ( $\mu$ mol/L)					
	<i>E. faecium</i> <sup>a</sup>	<i>S. aureus</i> <sup>b</sup>	<i>K. pneumoniae</i> <sup>c</sup>	<i>A. baumannii</i> <sup>d</sup>	<i>P. aeruginosa</i> <sup>e</sup>	<i>E. cloacae</i> <sup>f</sup>
<b>Probe 1</b>	>50	50	>50	>50	>50	>50
<b>Probe 2</b>	>50	50	>50	>50	>50	>50
<b>Neomycin</b>	>50	10	25	50	>50	1.25

<sup>a</sup> CICC 10840. <sup>b</sup> ATCC 29213. <sup>c</sup> ATCC 700603. <sup>d</sup> CICC 22933. <sup>e</sup> ATCC 27853. <sup>f</sup> ATCC 13047.

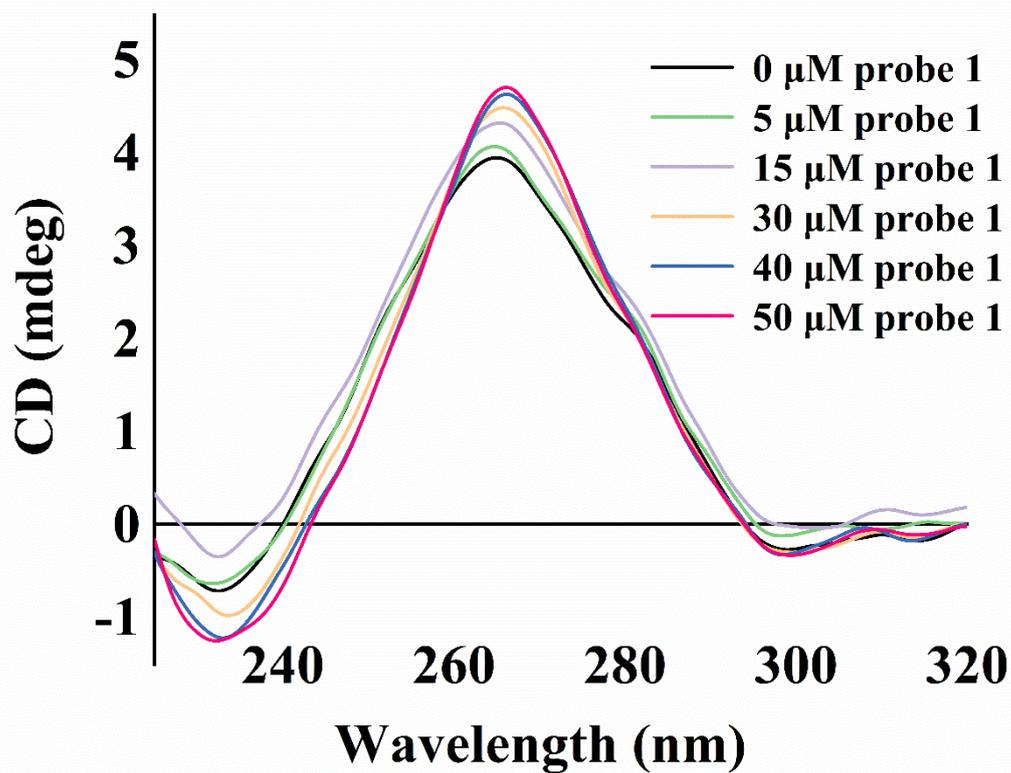
The MIC values were defined as the lowest concentration of the drug necessary to inhibit bacterial growth. Each bacterial strain was incubated in the required broths with different concentrations of compounds in a 96-well plate for 24 h. The MIC values were determined from OD<sub>600</sub> values in three separate experiments. The OD<sub>600</sub> values of the wells in the absence of bacteria were used as the control.



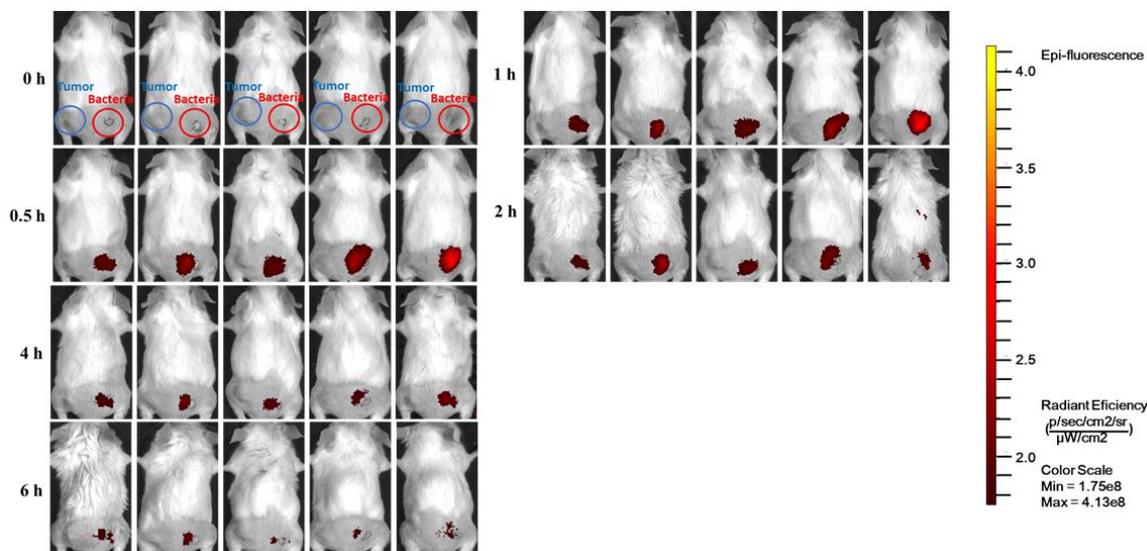
**Figure S10.** Cell viabilities (%) estimated by MTS proliferation tests of probe 1 and 2 (0.4, 0.8, 1.6, 3.2, 6.25, 12.5, 25, 50  $\mu\text{M}$ ) towards (a) CT26 and (b) HepG2 cells, after 24 h incubation at 37 °C.



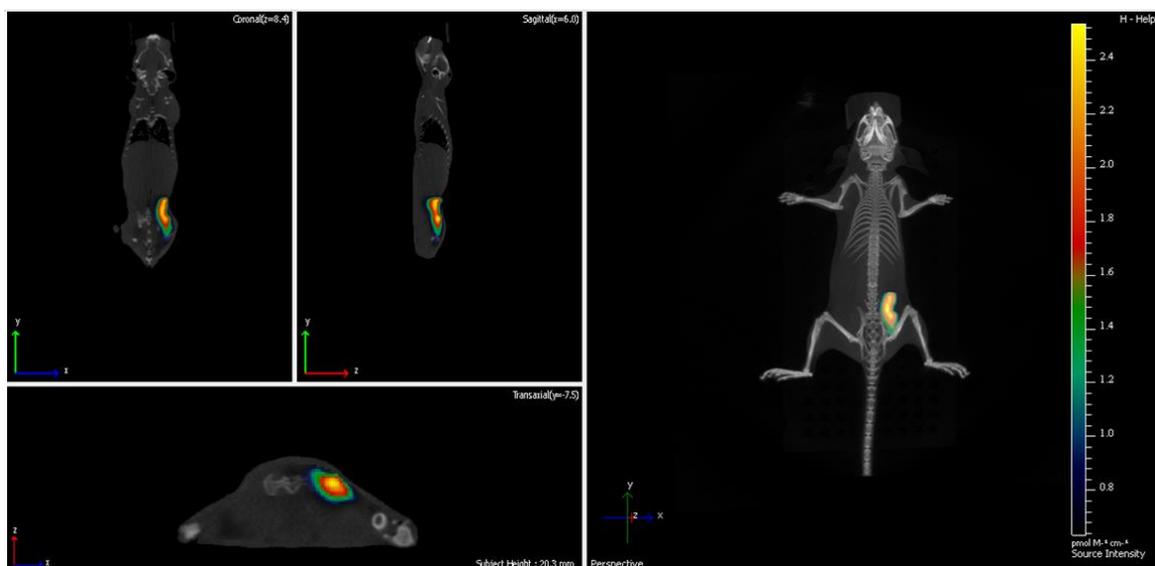
**Figure S11.** (a) *S. aureus*, (b) PBMC, (c) HepG2 and (d) CT26 incubated with probe 1 (10  $\mu$ M) at 37  $^{\circ}$ C for 1 h, followed by treatment with Hoechst 33342 at 37  $^{\circ}$ C for 30 min before confocal fluorescence microscopy imaging. The fluorescence imaging of Hoechst 33342 was excited at the 405 nm ( $\lambda_{ex}$  = 405 nm,  $\lambda_{em}$  = 460  $\pm$  30 nm), and that of probe 1 was excited at 670 nm ( $\lambda_{ex}$  = 670 nm,  $\lambda_{em}$  = 770  $\pm$  30 nm). Scale bar = 8  $\mu$ m (a), 25  $\mu$ m (b, c, and d).



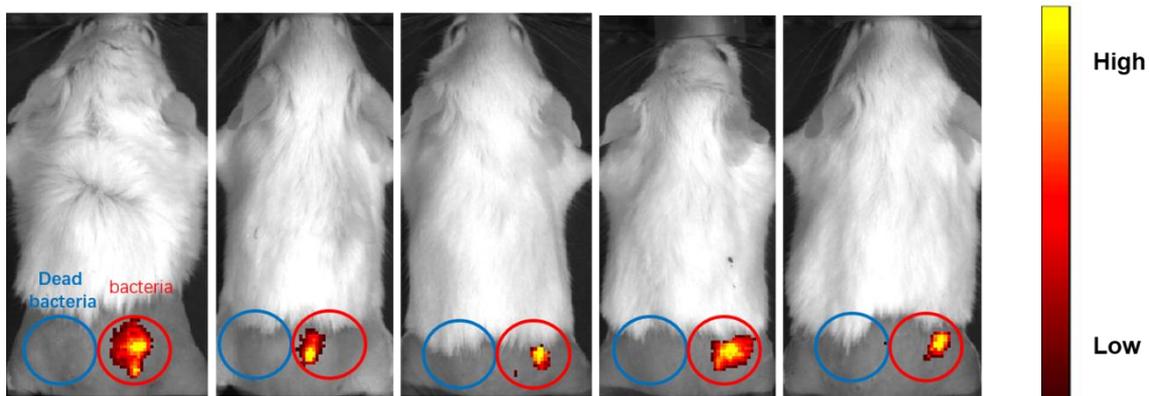
**Figure S12.** CD scans for the 27 nt A-site oligonucleotide of *E. coli* 16S rRNA (5  $\mu\text{M}$ ) in the absence and presence of probe 1 (5, 15, 30, 40 and 50  $\mu\text{M}$ ) in  $\text{H}_2\text{O}$ . The relevant 16S rRNA sequence from 5'-3' was GGCGUCACACCUUCGGGUGAAGUCGCC.



**Figure S13.** Time-dependent *in vivo* 2D fluorescence images of the CT26 mouse tumor model (the left hind leg of mice, blue circle) and bacterial infection model (the right hind leg of mice, red circle) before (0 h) and after (0.5-6.0 h) injection of probe 1 in Tris-buffered saline (TBS, 50 mM Tris/HCl, pH 7.4) (20  $\mu\text{M}$ , 100  $\mu\text{L}$ ) via tail vein injection. The fluorescence signal was collected at  $\lambda_{\text{em}} = 820 \text{ nm}$ , with excitation at a wavelength of 745 nm.



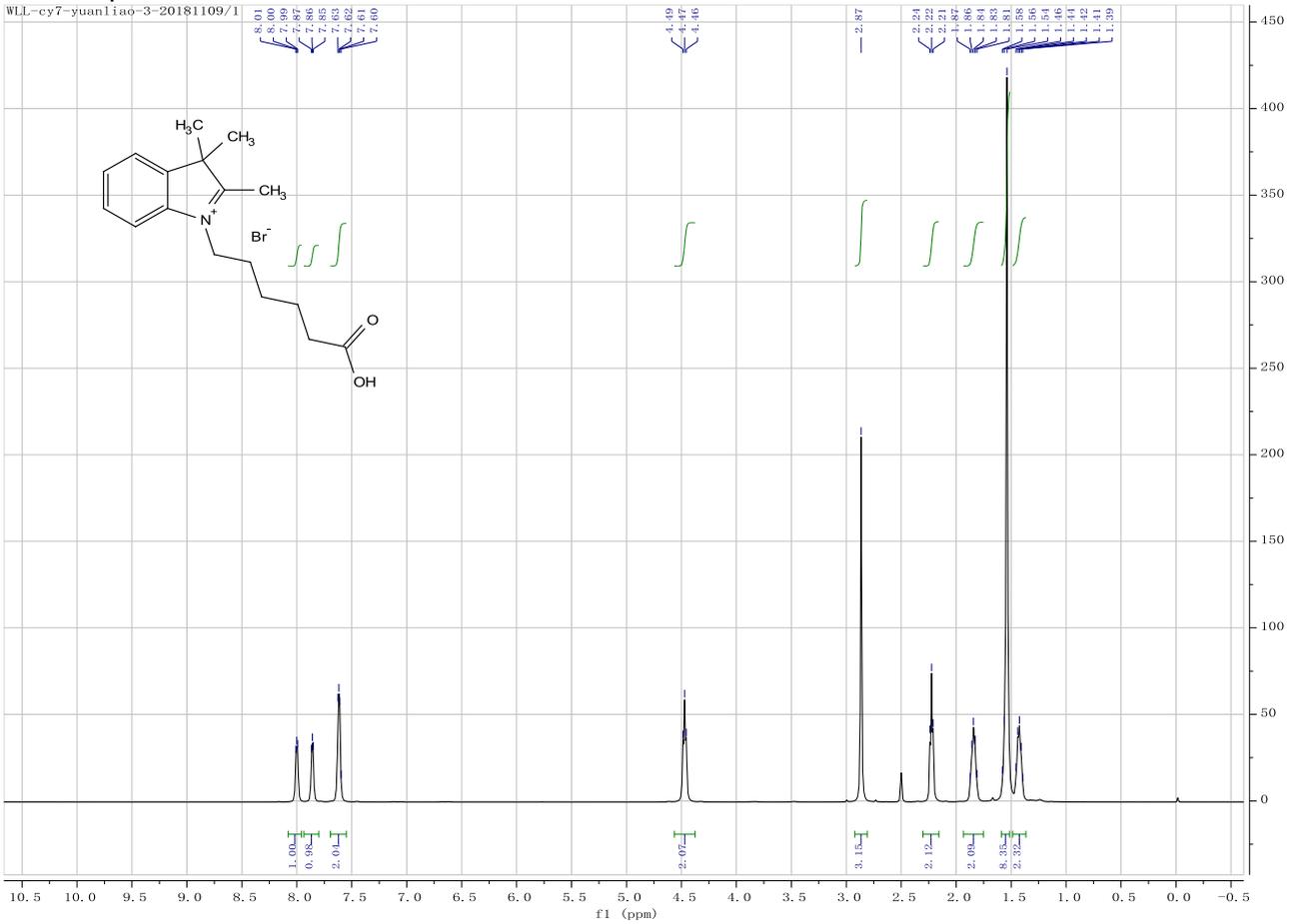
**Figure S14.** *In vivo* 3D fluorescence images of the CT26 mouse tumor model (left hind leg of mice) and bacterial infection model (right hind leg of mice) after injection of probe 1 (20  $\mu$ M, 100  $\mu$ L) via tail vein injection for 30 min. Bacterial infection region as a single source of luminescence was detected in the right hind leg visualized by 3D fluorescent light imaging tomography with integrated  $\mu$ CT. Panels I, II, and III demonstrated  $\mu$ CT xy-, yz-, and zx- projections, respectively, and panel IV showed the 3D reconstruction of fluorescent light imaging tomography with integrated  $\mu$ CT.



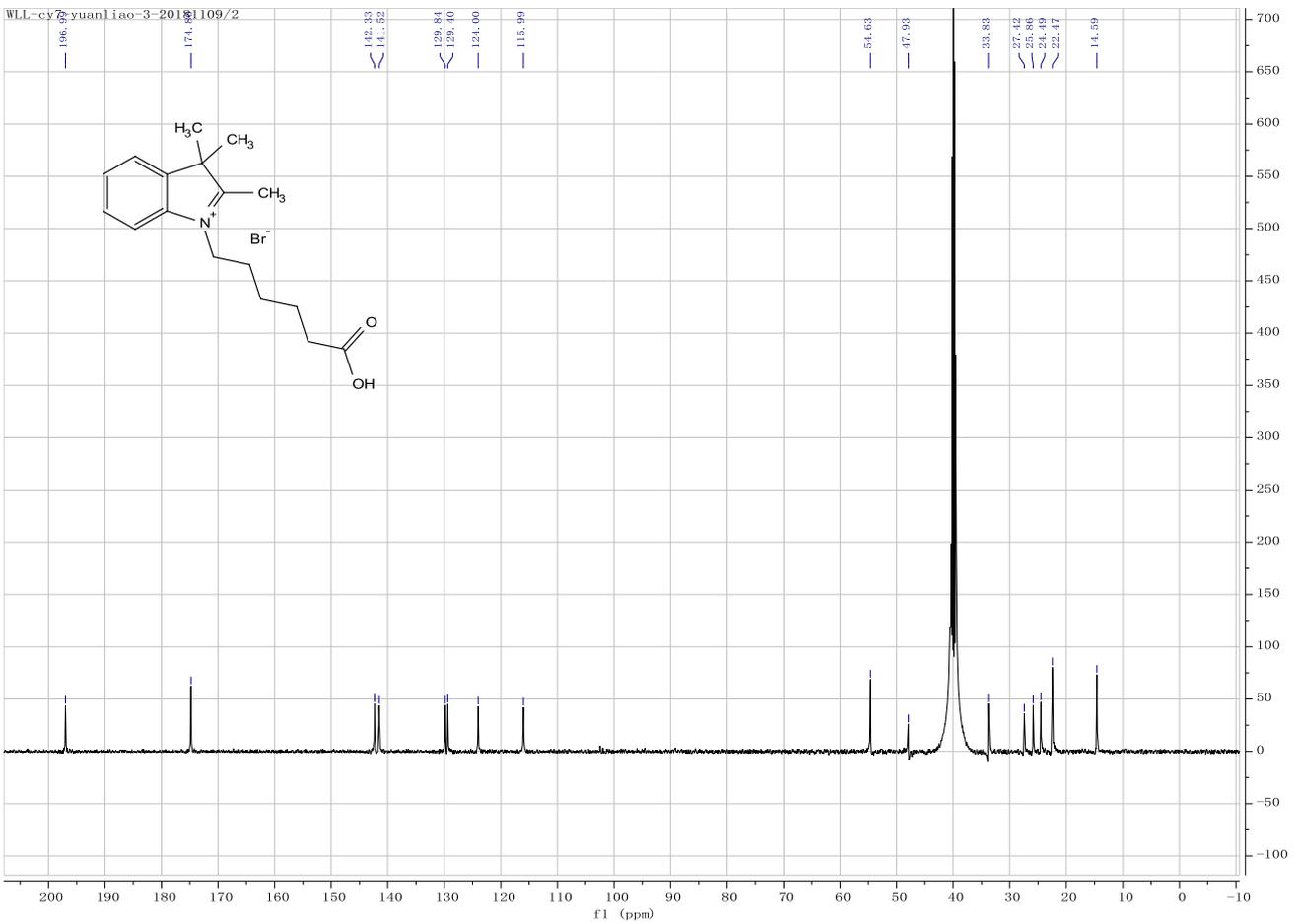
**Figure S15.** *In vivo* 2D fluorescence images of the neomycin-treated bacteria model (neomycin-treated *S. aureus*,  $1 \times 10^9$  CFU, the left hind leg of mice, blue circle) and bacterial infection model (*S. aureus*,  $1 \times 10^8$  CFU, the right hind leg of mice, red circle) 30 min post *i.v.* injection of probe 1 (20  $\mu$ M, 100  $\mu$ L, in Tris-buffered saline (TBS, 50 mM Tris/HCl, with 0.1% Kolliphor RH40 as co-solvent, pH 7.4)), the fluorescence signal was collected at  $\lambda_{em} = 820$  nm, with excitation at a wavelength of 745 nm,  $n = 5$ .

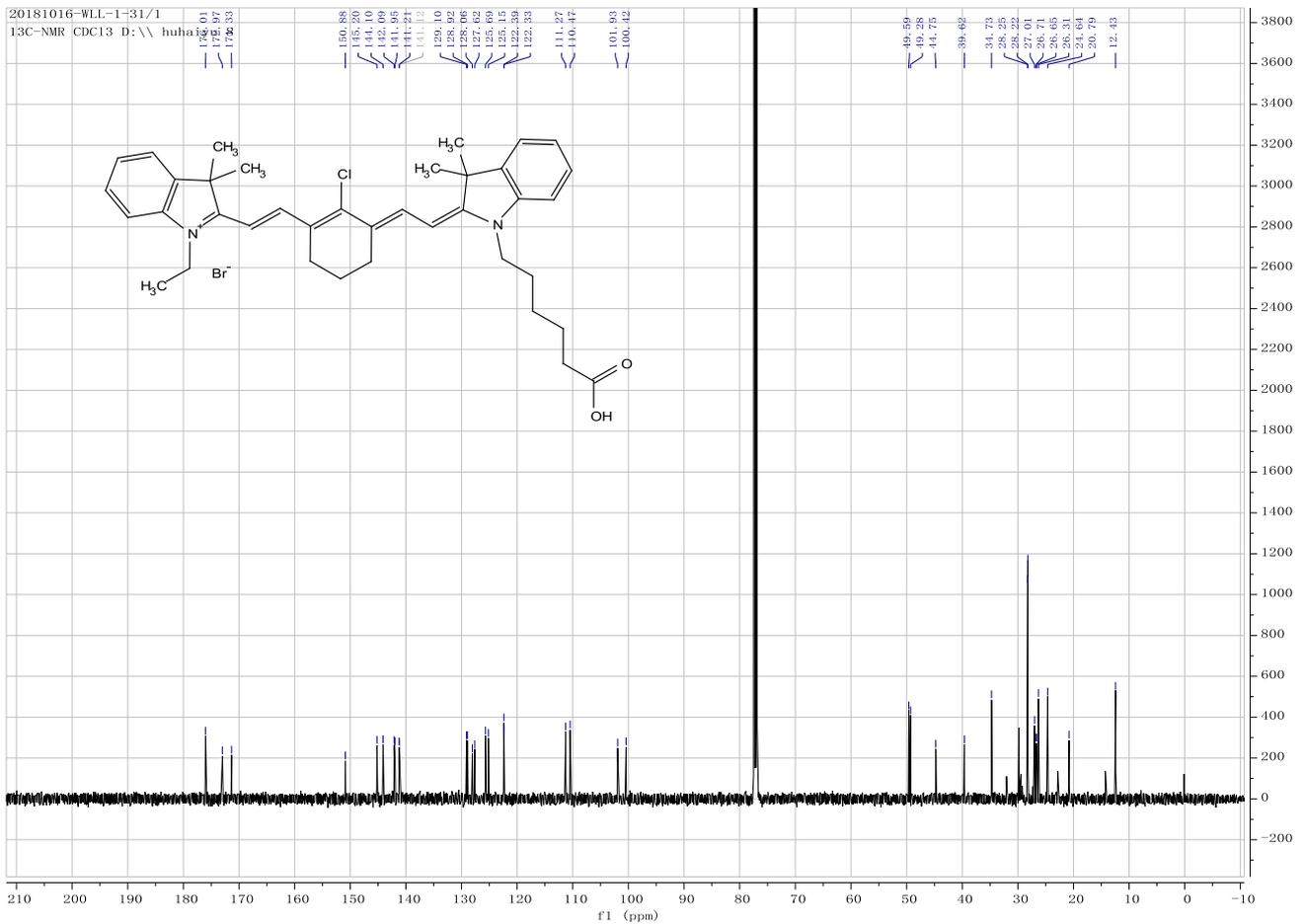
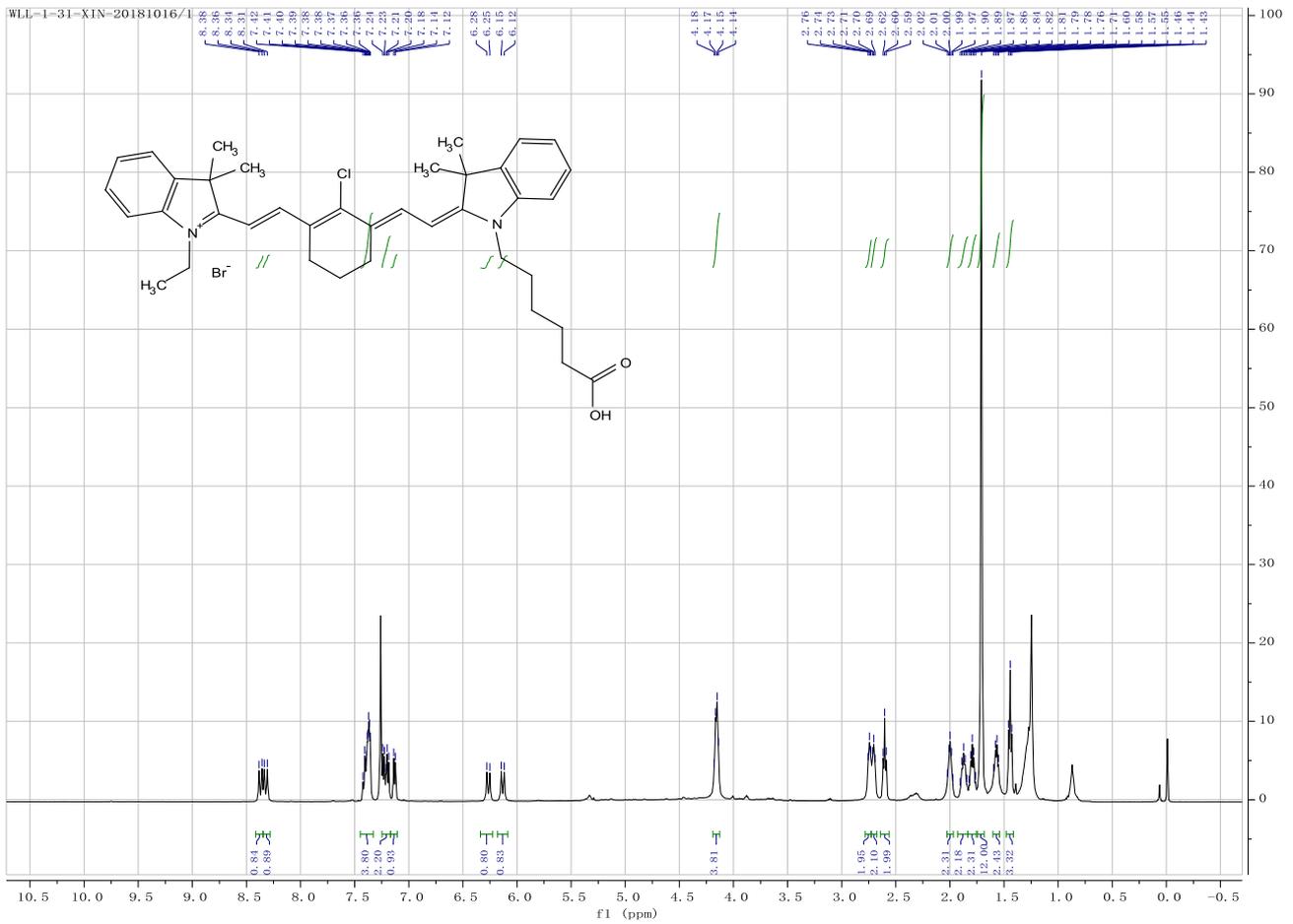
# NMR Spectra

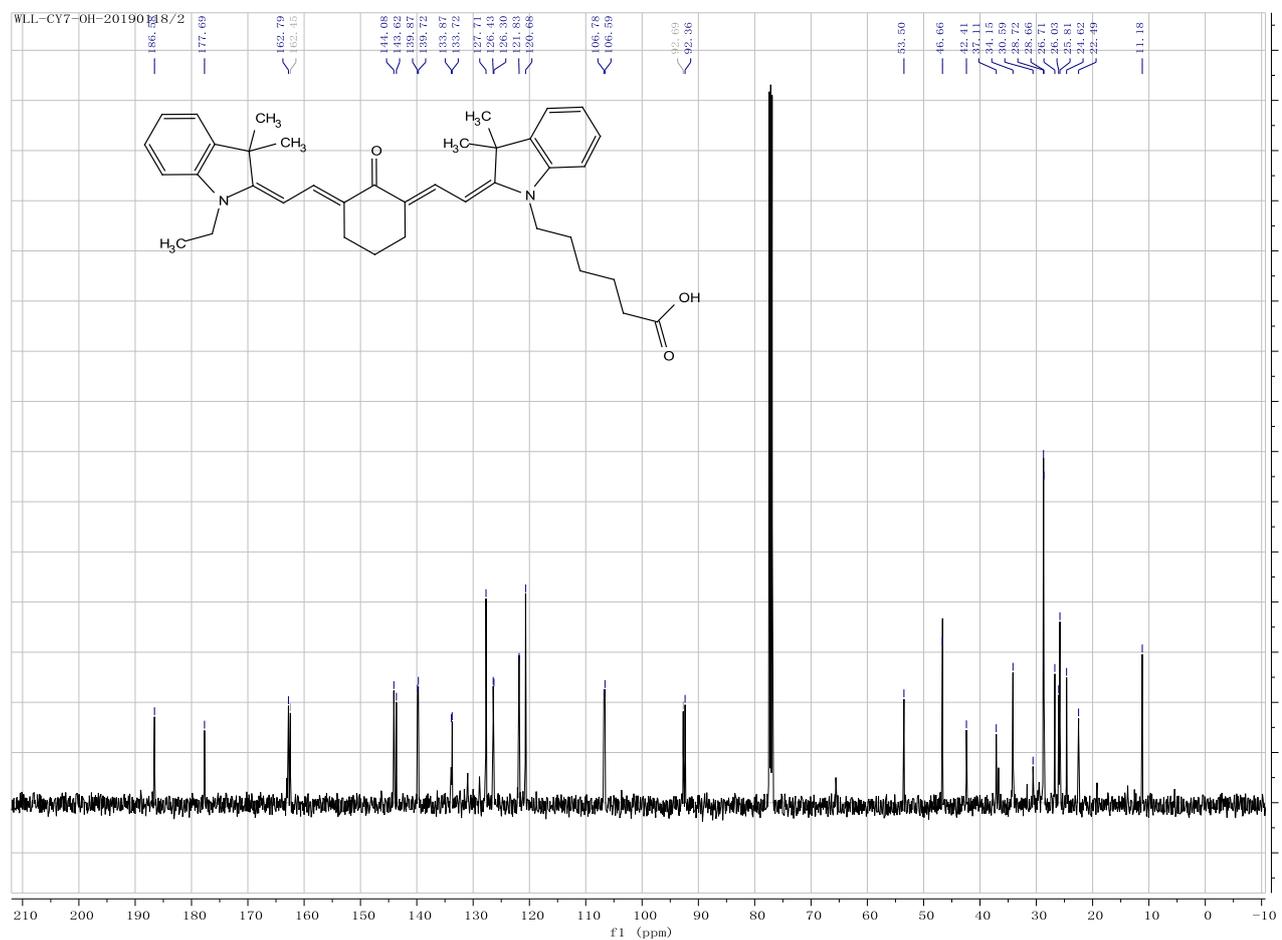
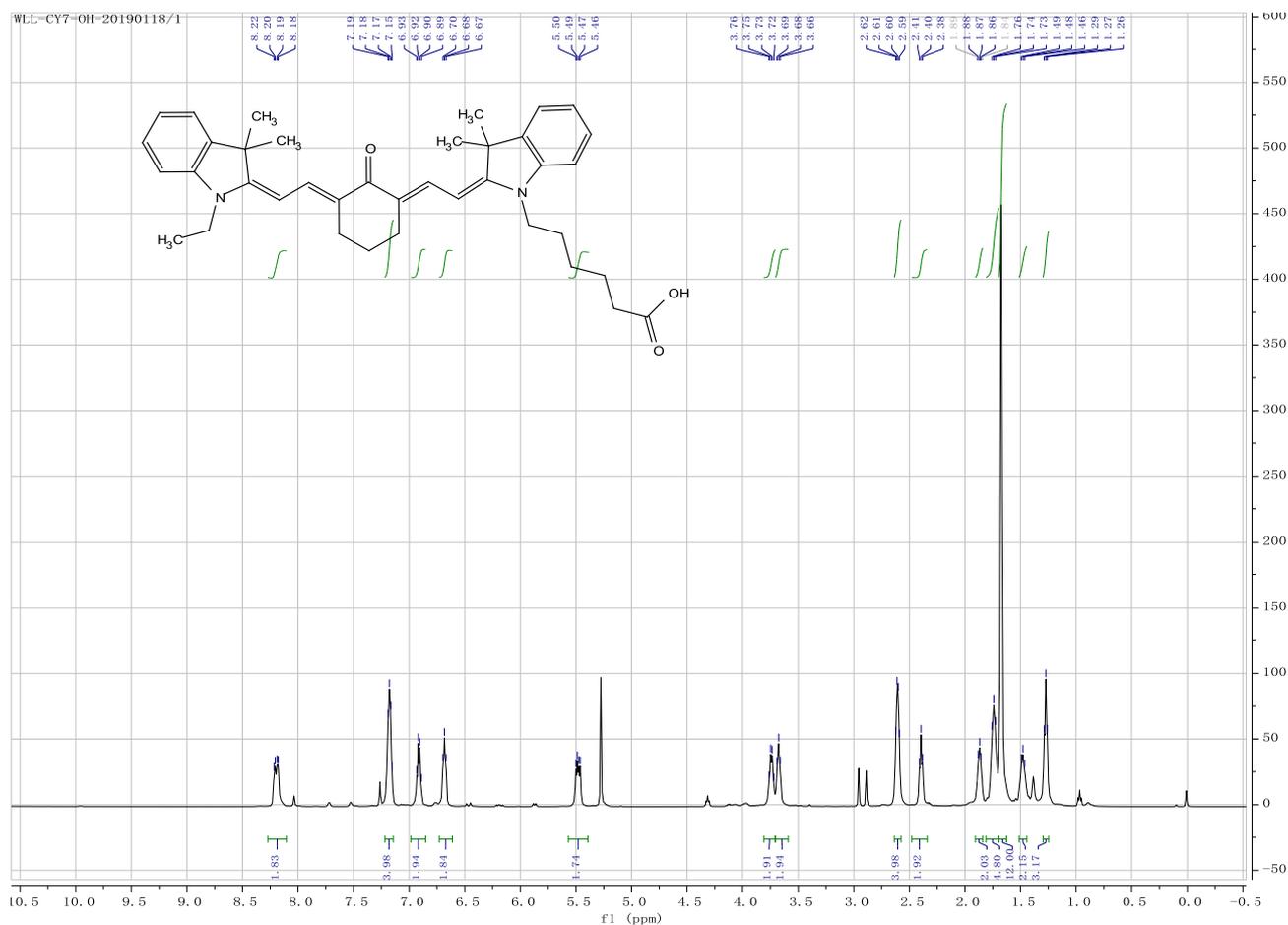
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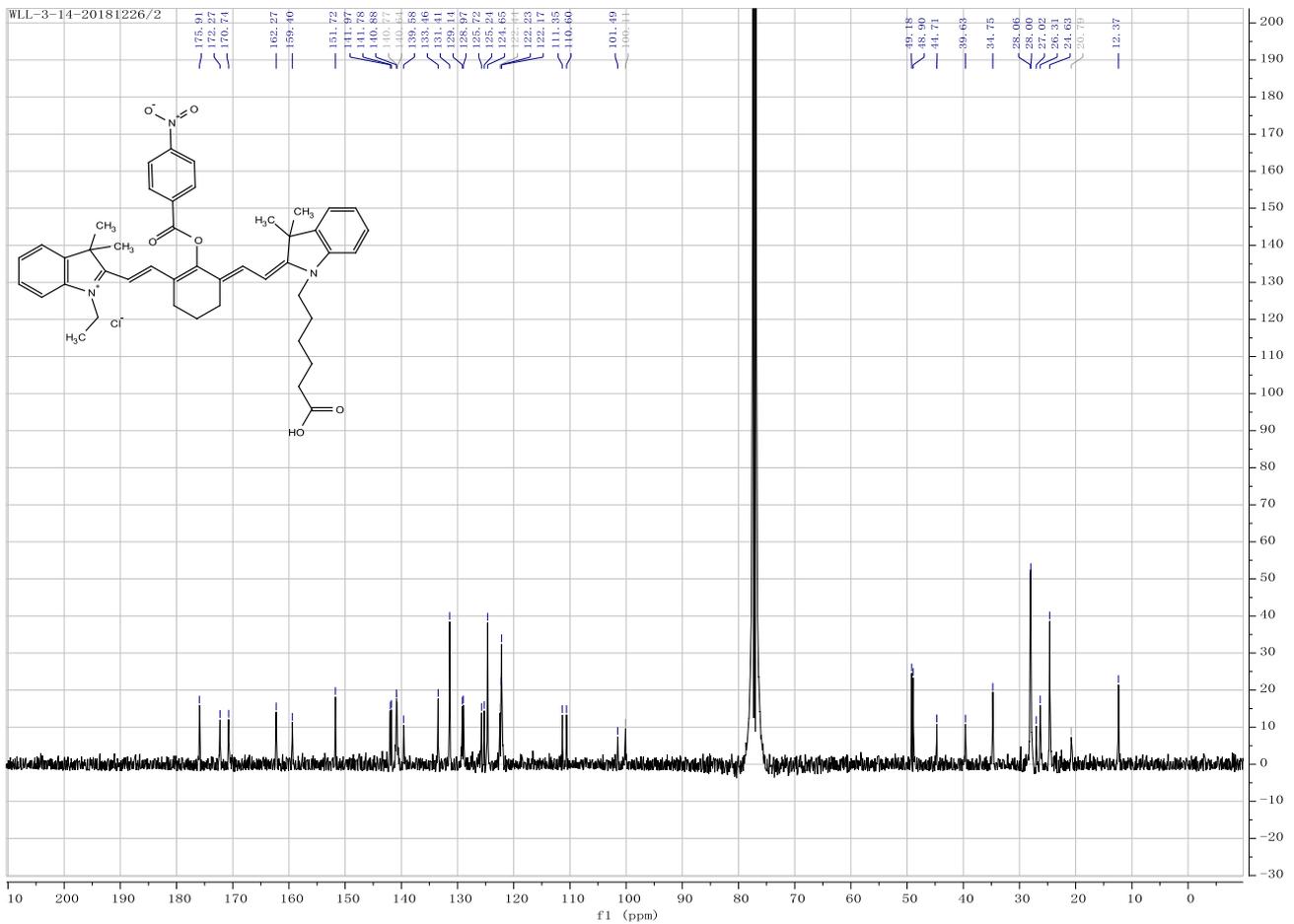
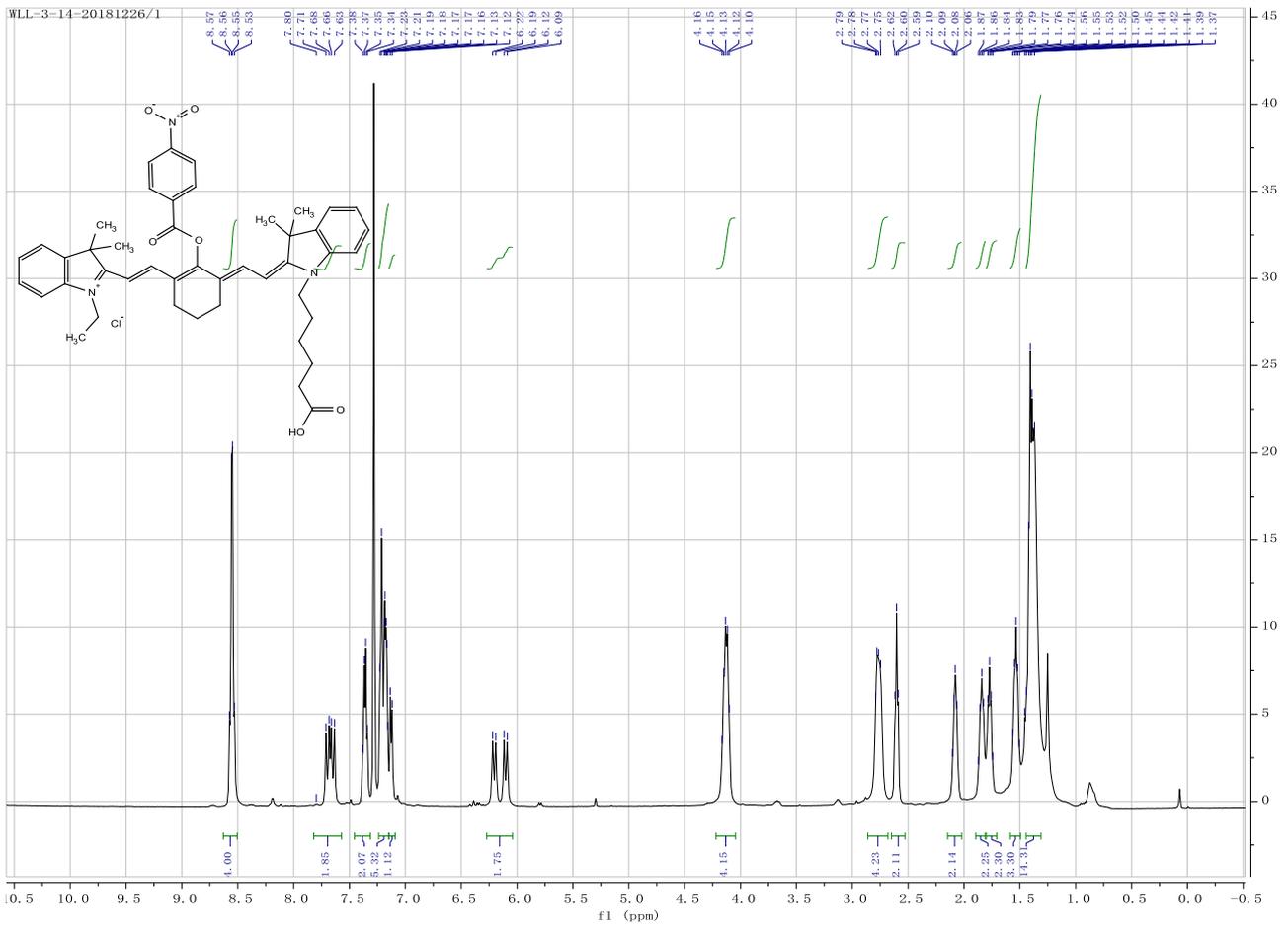


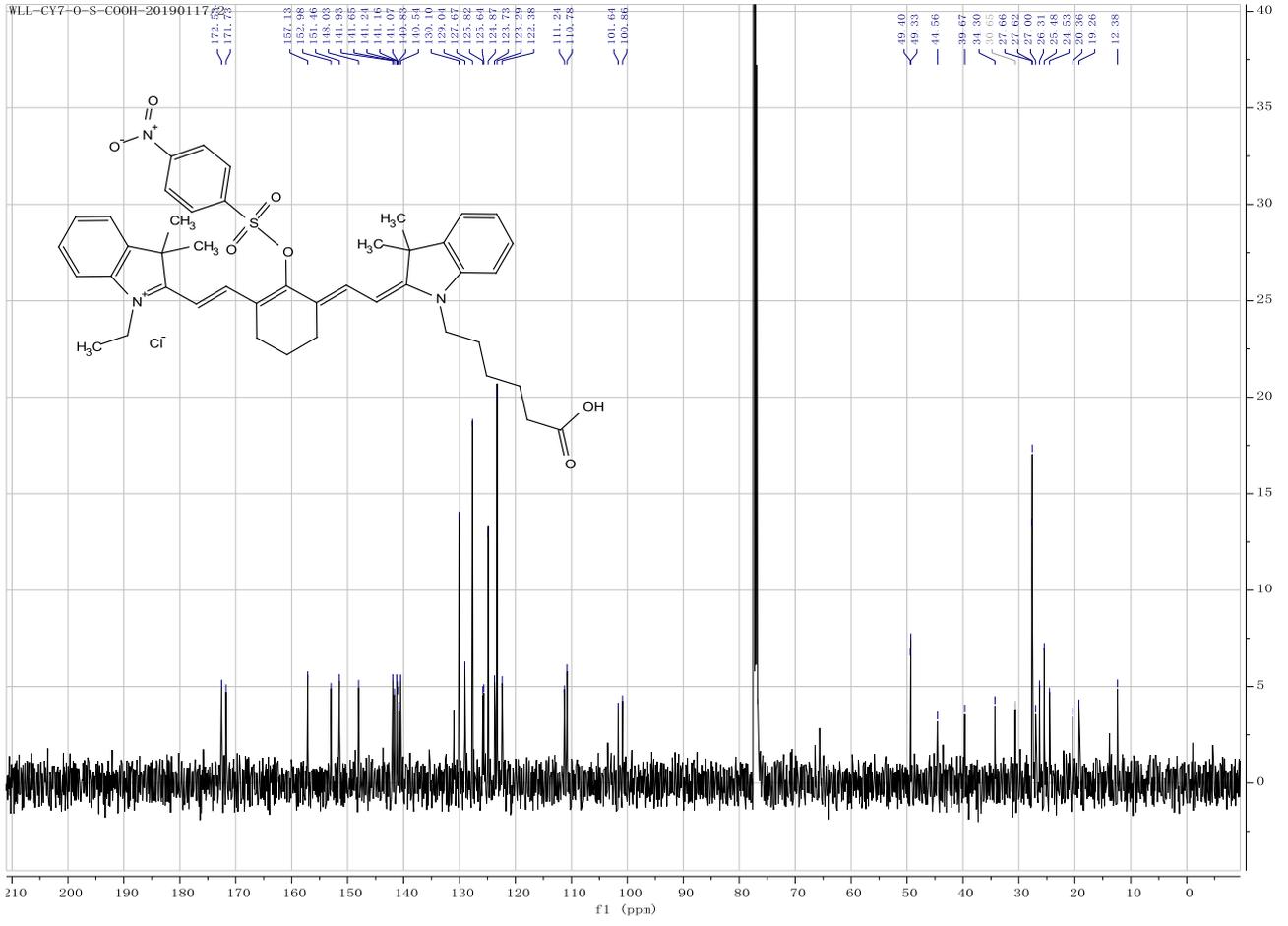
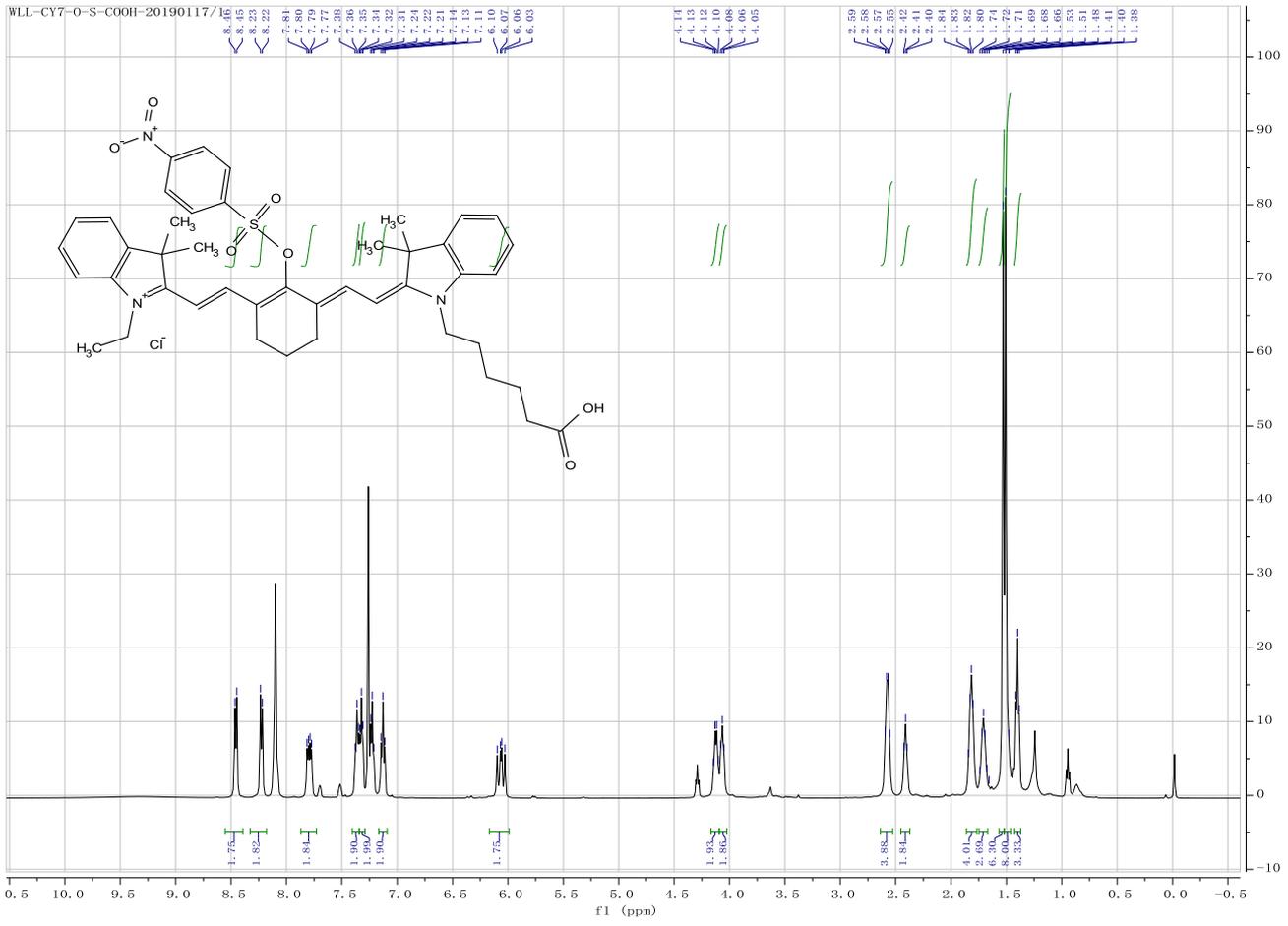
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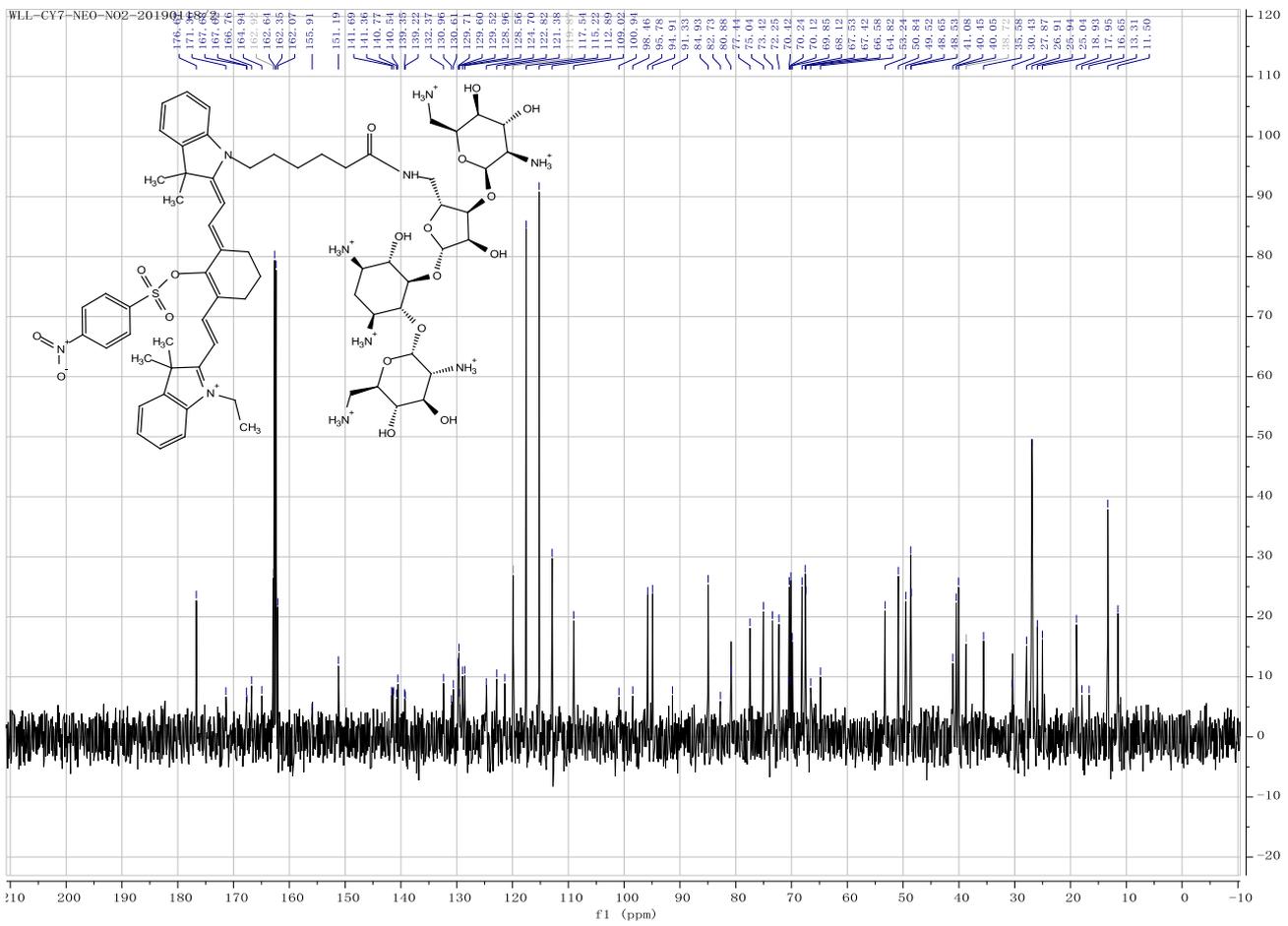
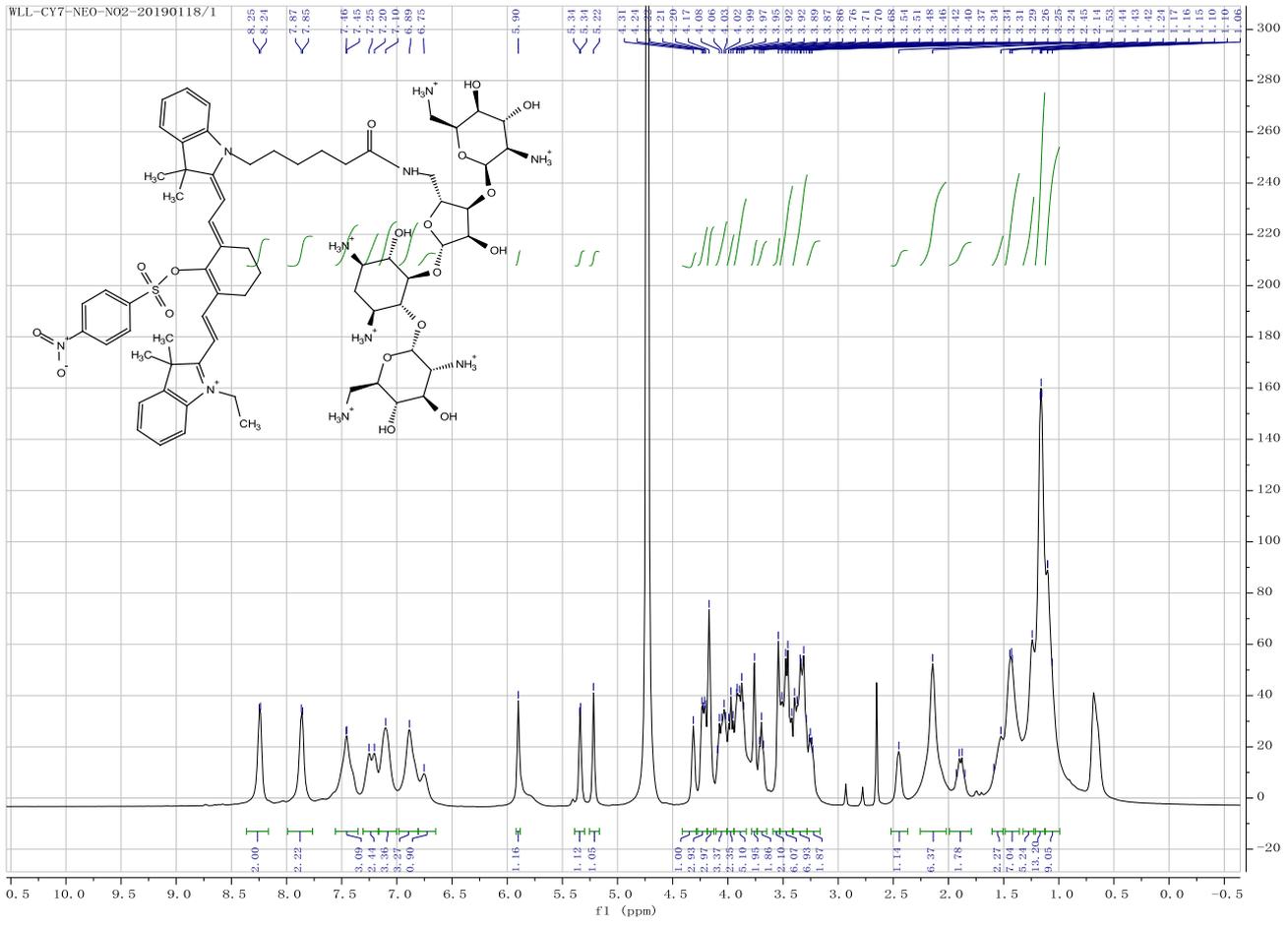














## References

- [1] Y. Li, Y. Sun, J. Li, Q. Su, W. Yuan, Y. Dai, C. Han, Q. Wang, W. Feng, F. Li, *J. Am. Chem. Soc.* **2015**, *137*, 6407-6416.
- [2] Q. Zhang, Q. Wang, S. Xu, L. Zuo, X. You, H.-Y. Hu, *Chem. Commun.* **2017**, *53*, 1366-1369.