Electronic Supplementary Material (ESI) for Chemical Communications.

Supporting Information

A receptor-targeting AIE photosensitizer for selective bacterial killing and real-time monitoring of photodynamic therapy outcome

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Experimental Section

Chemicals and materials. Phenanthroline, cuprous chloride, iodotrimethylsilane, triphenylphosphine, and tris(2-methylphenyl)phosphine were ordered from Heowns Biochem Technologies LLC. Palladium acetate ($Pd(OAc)_2$) and tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$) were obtained from Energy Chemical. 4-Methoxydiphenylamine, 1-bromo-4-iodobenze, and cephalothin were purchased from Bide Pharmatech Ltd. Sodium 2-ethylhexanoate, allyl bromide, rose bengal (RB), triethylamine (TEA), *N*,*N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) were ordered from Shanghai Adamas Reagent Co., Ltd. Dichloromethane (DCM), ethyl acetate (PE), petroleum ether (EA), methanol (MeOH), tetrahydrofuran (THF), 1,4-dioxane, toluene, acetonitrile, acetone, and potassium hydroxide (KOH) were purchased from Tianjin Bohai Chemical Industry Group Co., Ltd. 2',7'-Dichlorofluorescin diacetate (DCFH-DA) and 9,10-anthracenediyl-bis(methylene)-dimalonic acid (ABDA) were purchased from Sigma-Aldrich. Dihydrorhodamine 123 (DHR-123) and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) were ordered from Shanghai Macklin Biochemical Co., Ltd. and Beyotime Biotechnology, respectively. Tetracycline hydrochloride, ampicillin sodium, phosphate buffer saline (PBS, 10 mM, pH = 7.4), and vitamin C (Vc) were ordered from Solarbio Life Science. Dulbecco's modified eagle medium (DMEM) and penicillin-streptomycin solution (100×) were ordered from Thermal Fisher Scientific. Luria-Bertani broth (LB) and tryptone soy broth (TSB) were purchased from Oxoid Ltd. All chemicals were used as received without further purification. The water used in all experiments was obtained by filtering through a set of HEAL FORCE cartridges (Smart-N15VF).

Synthesis of compound 2. Compound **1** was synthesized by referring to a previously published paper.[1] Palladium acetate (0.4 mmol, 90 mg), tris-*o*-tolylphosphine (0.8 mmol, 244 mg), and compound **1** (4 mmol, 1.4 g) were placed in a 100 mL flask, which was evacuated under vacuum and purged with dry argon gas three times. After adding TEA/DMF (4:1, v/v, 10 mL) and 4-ethenylpyridine (6 mmol, 647 μL), the reaction mixture was heated to 90 °C and stirred for 6 h. Upon completion of the reaction, the solvent was removed under reduced pressure, and the crude

product was purified by column chromatography on a silica gel (PE/EA = 1:1, v/v) to afford compound **2** in 89% yield. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.53 (d, J = 4.6 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 5.3 Hz, 2H), 7.24 (t, J = 7.7 Hz, 2H), 7.20 (s, 1H), 7.08 (d, J = 8.5 Hz, 4H), 7.00 (dd, J = 12.7, 7.9 Hz, 3H), 6.87–6.81 (m, 3H), 3.80 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.68, 150.10, 148.86, 147.49, 145.17, 140.14, 132.87, 129.36, 129.02, 128.02, 127.74, 124.05, 123.45, 122.99, 121.53, 120.69, 114.99, 77.55, 77.23, 76.91, 55.54. HRMS (ESI, m/z, $C_{26}H_{22}N_2O$, [M + H^+]): calcd., 379.1805; found, 379.1808.

Synthesis of TPAI. Compound **2** (1 mmol, 378 mg) was dissolved in acetonitrile (30 mL), followed by the addition of iodomethane (10 mmol, 622 μL). The reaction mixture was then stirred at 70 °C for 5 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the crude product was purified by column chromatography on a silica gel (DCM/methanol = 10:1, v/v) to afford TPAI in 86% yield. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.77 (d, J = 6.2 Hz, 2H), 8.13 (d, J = 6.2 Hz, 2H), 7.93 (d, J = 16.2 Hz, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.35 (t, J = 7.7 Hz, 2H), 7.27 (d, J = 16.2 Hz, 1H), 7.12 (t, J = 7.3 Hz, 5H), 6.99 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.21 (s, 3H), 3.77 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 157.34, 153.39, 150.39, 146.74, 145.17, 141.17, 139.18, 130.19, 130.16, 128.66, 127.52, 125.27, 124.57, 123.26, 120.34, 119.61, 115.79, 55.83, 47.13, 40.46, 40.25, 40.04, 39.83, 39.63. HRMS (ESI, m/z, $C_{27}H_{25}N_2O^+$, [M^+]): calcd., 393.1961; found, 393.1966.

Synthesis of CE-TPA. Compound **3** was synthesized by referring to a previously published paper.[2] Compound **2** (0.3 mmol, 113 mg) and compound **3** (0.3 mmol, 151 mg) were dissolved in acetonitrile, followed by stirring at 35 °C for 10 h. The solvent was then removed under reduced pressure. Next, sodium 2-ethylhexanoate (0.3 mmol, 50 mg), triphenylphosphine (0.03 mmol, 8 mg), and $Pd(PPh_3)_4$ (0.06 mmol, 69 mg) were added to the obtained residue under nitrogen atmosphere, followed by the addition of DCM (8 mL). The reaction mixture was stirred at 25 °C for 2 h. After solvent evaporation under reduced pressure, the crude product was purified by

column chromatography on a silica gel (DCM/methanol = 10:1, v/v) to afford CE-TPA in 46% yield. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.09 (d, J = 7.3 Hz, 1H), 8.90 (d, J = 5.4 Hz, 2H), 8.14 (d, J = 6.0 Hz, 2H), 7.92 (d, J = 16.1 Hz, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.36 (t, J = 6.8 Hz, 3H), 7.26 (d, J = 16.1 Hz, 1H), 7.12 (d, J = 7.8 Hz, 4H), 6.99 (d, J = 8.6 Hz, 2H), 6.95–6.91 (m, 2H), 6.86 (d, J = 8.4 Hz, 2H), 6.70 (s, 1H), 5.54 (d, J = 13.3 Hz, 1H), 5.22 (dd, J = 17.9, 11.1 Hz, 4H), 4.08 (s, 1H), 3.77 (s, 3H), 3.74 (s, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 170.37, 162.62, 157.34, 154.13, 150.48, 146.70, 144.51, 141.71, 139.15, 137.42, 130.29, 130.19, 128.66, 127.50, 127.04, 126.77, 125.42, 125.32, 124.61, 123.43, 122.75, 121.03, 120.39, 119.54, 115.77, 63.24, 60.61, 55.79, 53.67, 36.19. HRMS (ESI, m/z, $C_{40}H_{35}N_4O_5S_2^+$, [M + H^+]): calcd., 715.2043; found, 715.2048.

Characterizations. All absorption and fluorescence spectra were measured by a UV-vis spectrometer (UV-2600, Shimadzu) and a fluorescence spectrometer (F-4700, HITACHI), respectively. All fluorescence images were obtained by a confocal laser scanning microscope (CLSM, A1+, NIKON). The fluorescence quantum yields in different solvents were measured by a fluorescence spectrometer with an integrating sphere (FS5, Edinburgh).

Theoretical calculation. Theoretical calculation was carried out using the Gaussian 09 software. Geometry optimization was performed using density functional theory (DFT) at B3LYP/6-31G* level of theory. The electronic distribution of the frontier molecular orbitals (FMOs) was drawn using Gaussview 5.0.9.

Type-II ROS measurements and singlet oxygen quantum yield calculation. ABDA was used as the indicator of singlet oxygen, in which RB was employed as the reference photosensitizer. Briefly, ABDA stock solution (10 mM, 10 μL) was added to PBS (2 mL) with RB (10, 20, and 40 μM), CE-TPA (10, 20, and 40 μM), and TPAI (10, 20, and 40 μM), respectively. After irradiation with white light (380−800 nm) at a power density of 25 mW/cm^2, the absorption spectra of ABDA were

recorded at 1-min intervals, and the absorbance at 378 nm was used as the variable parameter to calculate the decomposition rate constant of ABDA. The ABDA solution was used as a control. According to a previous report, the singlet oxygen quantum yields (Φ_Δ) of CE-TPA and TPAI at different concentrations were calculated using the following equation,

$$\Phi_\Delta = \Phi_{RB} \frac{k_{compound}}{A_{compound}} \frac{A_{RB}}{k_{RB}}$$

where *k* represents the decomposition rate constant of ABDA by CE-TPA, TPAI, or RB, *A* stands for the light absorbed by CE-TPA, TPAI, or RB, and Φ_{RB} is the singlet oxygen quantum yield of RB (Φ_{RB} = 75% in water).[3]

Type-I ROS measurements. DHR-123 was used as the indicator for type-I ROS by converting into the fluorescent rhodamine 123. Briefly, DHR-123 stock solution (10 mM, 10 μL) was added to PBS (2 mL) with CE-TPA or TPAI at a final concentration of 20 μM. After irradiation with white light at a power density of 25 mW/cm^2, the emission spectra of DHR-123 (Ex = 488 nm) were recorded at 1-min intervals, and the emission intensity at 525 nm was used as the variable parameter to calculate the conversion rate of DHR-123. In terms of quenching type-I ROS, Vc was added to the system at a final concentration of 50 μM prior to white light irradiation. The DHR-123 solution was used as a control.

Total reactive oxygen species (ROS) measurements. Prior to the measurements of total ROS, the chemical probe DCFH-DA was chemically activated to its deacetylated form 2',7'-dichlorofluorescin (DCFH) according to a previous study with the final concentration of DCFH at 40 μM.[4] To the DCFH solution was added CE-TPA or TPAI at a final concentration of 20 μM. Next, the fluorescence spectra (Ex = 488 nm) were recorded at 10-second intervals under white light irradiation (380–800 nm) at a power density of 10 mW/cm^2, in which the DCFH solution was used as a control.

Bacterial culture. Methicillin-resistant *Staphylococcus aureus* (MRSA) and ampicillin-resistant

Escherichia coli (Amp^r *E. coli*) were provided by Prof. Jianfeng Liu (Institute of Radiation Medicine, Chinese Academy of Medical Sciences and Peking Union Medical College) and Prof. Qiong Yang (College of Life Sciences, Beijing Normal University), respectively. A single colony of bacterial strains on a solid agar plate was transferred to 5 mL of medium with antibiotics and grown at 37 °C overnight in a shaking incubator at 170 rpm. For bacterial culture, MRSA was cultured in TSB medium with 10 μg/mL tetracycline hydrochloride and Amp^r *E. coli* was cultured in LB medium with 100 μg/mL ampicillin sodium. After culturing overnight, the bacterial cells were obtained by centrifugation (3500 *g*, 3 min), followed by washing with PBS. The supernatant was discarded and the remaining bacterial cells were resuspended in PBS, which were then diluted to an optical density of 1.0 at 600 nm (OD_{600} = 1.0) for subsequent use.

Bacterial staining and imaging. The bacterial suspensions (OD_{600} = 1.0, 1 mL) were mixed with CE-TPA or TPAI at a final concentration of 10 μM, followed by incubation in the dark at 37 °C for 30 min. The bacterial cells were then harvested by centrifugation (3500 *g*, 3 min) and washed with PBS, which were employed for the measurements of emission spectra (Ex = 465 nm). For CLSM characterization, the bacterial suspensions (10 μL) were added to glass slide, which were gently covered by a clean coverslip prior to image acquisition.

Cell culture. NIH-3T3 cells, a fibroblast cell line of mouse, were cultured in DMEM containing 10% fetal bovine serum (FBS) and 1% antibiotics (100 units/mL penicillin and 100 g/mL streptomycin) in a 5% CO_2 humidity incubator at 37 °C. The culture medium was changed every other day.

Cellular uptake of CE-TPA and TPAI. NIH-3T3 cells were seeded in 35-mm petri dishes at a density of 3–4 × 10^5 cells and cultured in a 5% CO_2 humidity incubator at 37 °C overnight. The cells were incubated with CE-TPA or TPAI (10 μM) at 37 °C for 1 h, respectively, in which the cells treated with culture medium only was used as a control. After washing with PBS, the cells

were supplemented with fresh PBS for CLSM characterization.

Cell viability assay. The cell viability of NIH-3T3 cells incubated with different concentrations of CE-TPA or TPAI was evaluated by the MTT assay. Specifically, NIH-3T3 cells were seeded in a 96-well plate at a density of 8000−10000 cells per well and cultured overnight. Subsequently, CE-TPA or TPAI with different concentrations (0, 2.5, 5, 10, 20, and 40 μM) were added into the wells, followed by incubation at 37 °C for 3 h. After washing with PBS, the cells were replenished with fresh culture medium and incubated for another 12 h. Next, the MTT solution (0.5 mg/mL in medium, 100 μL per well) was added to the wells followed by incubation at 37 °C for 4 h. After removing the supernatant, DMSO (100 μL per well) was then added to dissolve the produced formazan, and the absorbance values at 490 nm was recorded by a microplate reader (Tecan, Infinite M Nano). The cell viability was defined as the percentage of surviving cells versus untreated cells (n = 3 for each group).

In vitro antibacterial experiments of CE-TPA and TPAI. The bacterial suspensions (OD_{600} = 1.0, 500 μL) were mixed with CE-TPA or TPAI with varying concentrations (0, 2.5, 5, 10, 20, and 40 μM), followed by adding into a 24-well plate and incubating in the dark at 37 °C for 30 min. Next, the bacteria incubated with CE-TPA or TPAI at different concentrations were irradiated by white light (380−800 nm) at a power density of 90 mW/cm^2 for 20 min or placed in the dark for 20 min. The treated bacterial suspensions were then diluted by PBS (5×10^4 fold for MRSA; 5×10^3 fold for Amp^r *E. coli*), and the diluted bacterial suspensions (100 μL) were spread on agar plates (TSB agar plates for MRSA; LB agar plates for Amp^r *E. coli*) for overnight culture (37 °C). The colony-forming units (CFU) of each plate were counted for quantitative antibacterial analysis (n = 3 for each group).

Live/dead staining assay. Live/Dead®Baclight™ bacterial viability kit was used to indicate the viability of bacteria. Specifically, the bacterial suspensions (OD_{600} = 1.0, 500 μL) were mixed with

CE-TPA or TPAI at a final concentration of 20 μM, followed by adding into a 24-well plate and incubating in the dark at 37 °C for 30 min. For the irradiated group, the bacterial suspension was exposed to white light irradiation at a power density of 90 mW/cm^2 for 20 min. For comparison purposes, the bacteria treated with PBS with and without light irradiation as well as the bacteria treated with CE-TPA or TPAI (20 μM) without light irradiation were used as the control groups. The bacteria were then collected by centrifugation at 3500 *g* for 3 min and washed with PBS, followed by staining with SYTO 9 (3.34 μM) and propidium iodide (PI, 30 μM) for 15 min in the dark. The bacterial suspensions (10 μL) were dropped on a glass slide and gently covered with a coverslip. The fluorescence images were collected by CLSM (SYTO 9, Ex = 488 nm, Em = 490−540 nm; PI, Ex = 488 nm, Em = 630−680 nm).

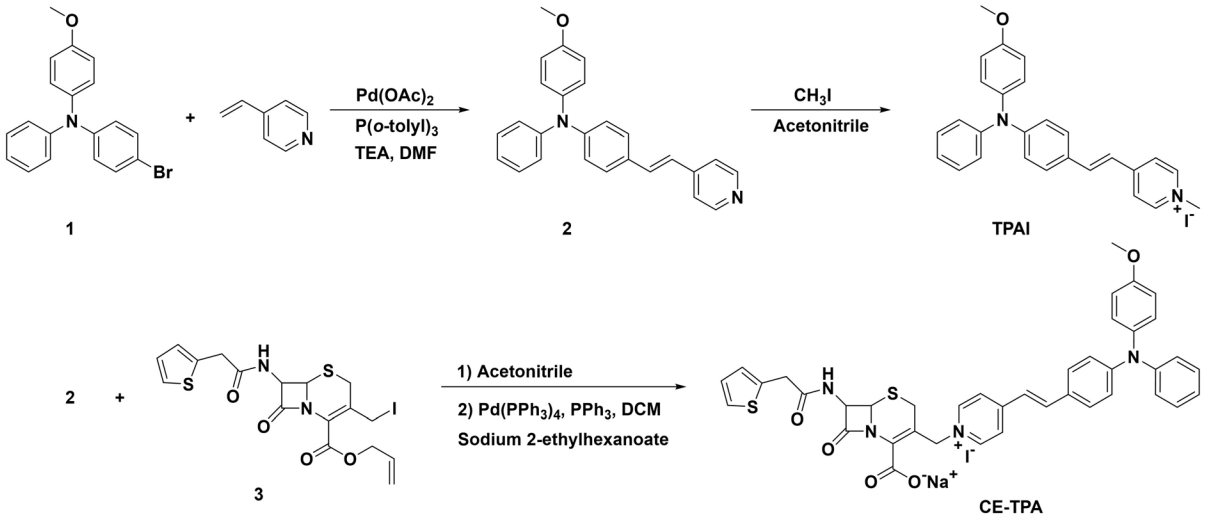
Scanning electron microscopy (SEM) analysis. Once the incubation was completed as described in "*Live/dead staining assay*", the bacteria were collected by centrifugation at 3500 *g* for 3 min, washed with PBS, and fixed with 2.5% glutaraldehyde at room temperature for 30 min. The mixture was then centrifuged at 3500 *g* for 10 min, washed with PBS, and resuspended in water (20 μL). The bacterial suspensions (5 μL) were placed on clean silicon wafers, followed by air drying. Immediately after the samples became dried, the silicon wafers were immersed in 2.5% glutaraldehyde and fixed at room temperature overnight. Subsequently, the samples were washed with water twice and subjected to gradient ethanol dehydration from 30% to 100% (including 30%, 50%, 70%, 80%, 90%, and 100%, 6 min × 2 times for each concentration). After the samples were fully dried, they were coated with gold before examination under a scanning electron microscope (SEM, MERLIN Compact, ZEISS).

Real-time monitoring of photodynamic therapy outcome. The bacterial cells (OD_{600} = 1.0, 1 mL) were harvested by centrifugation (3500 *g*, 3 min), followed by the addition of CE-TPA or TPAI at a final concentration of 20 μM and incubation at 37 °C for 30 min. After irradiation with white light irradiation (380−800 nm) at a power density of 90 mW/cm^2 for different periods of time (0,

5, 10, 20, and 30 min), the emission spectra (Ex = 465 nm) of the bacterial suspensions were measured, in which the ones placed in the dark were used as the control groups.

References

1. J. Liu, L. Chen, S. Shao, Z. Xie, Y. Cheng, Y. Geng, L. Wang, X. Jing and F. Wang, *J. Mater. Chem.*, 2008, **18**, 319–327.
2. X. Tang, T. Cai and P. Wang, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1687−1690.
3. M. Lan, S. Zhao, Y. Xie, J. Zhao, L. Guo, G. Niu, Y. Li, H. Sun, H. Zhang, W. Liu, J. Zhang, P. Wang and W. Zhang, *ACS Appl. Mater. Interfaces*, 2017, **9**, 14590−14595.
4. L. Bourré, S. Thibaut, A. Briffaud, N. Rousset, S. Eléouet, Y. Lajat, T. Patrice, *J. Photochem. Photobiol. B*, 2002, **67**, 23–31.



Scheme S1. Synthetic routes to TPAI and CE-TPA.

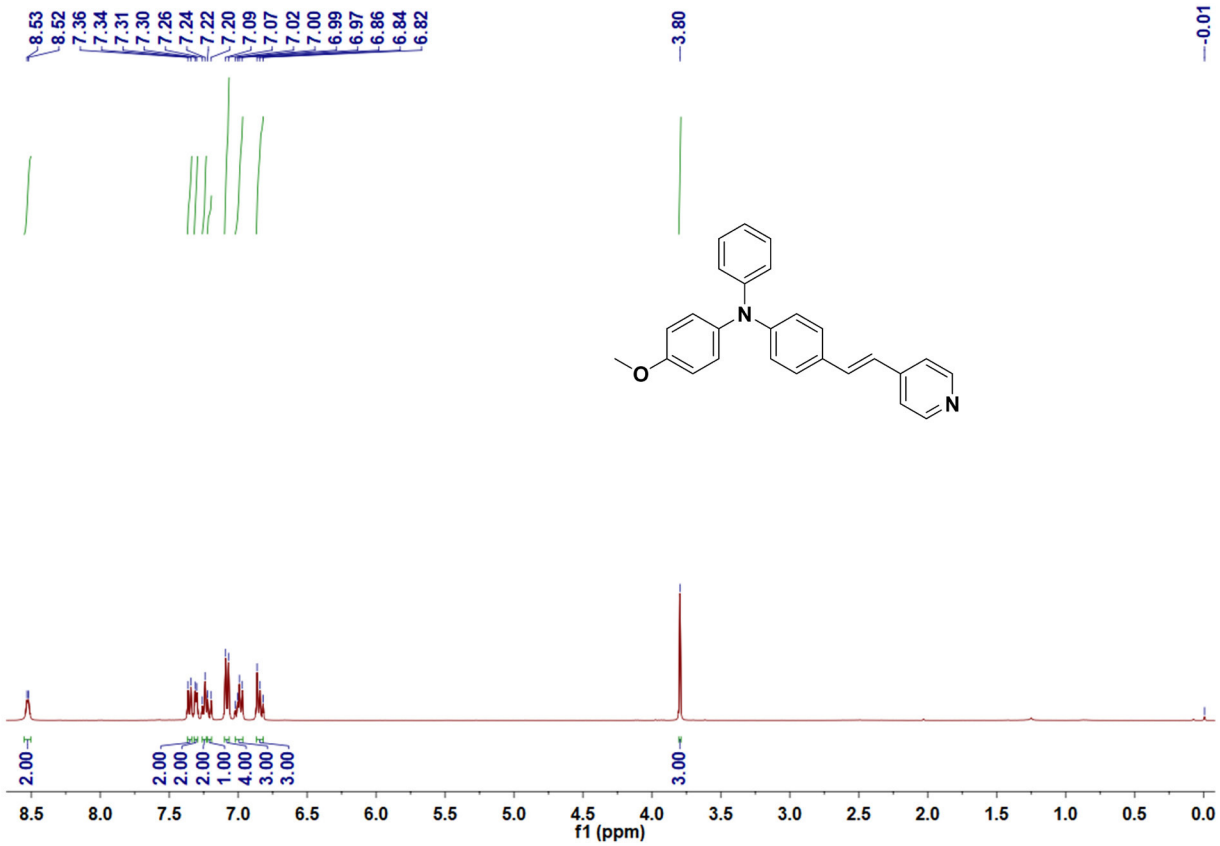


Fig. S1 ^{1}H-NMR spectrum of compound **2** in $CDCl_3$.

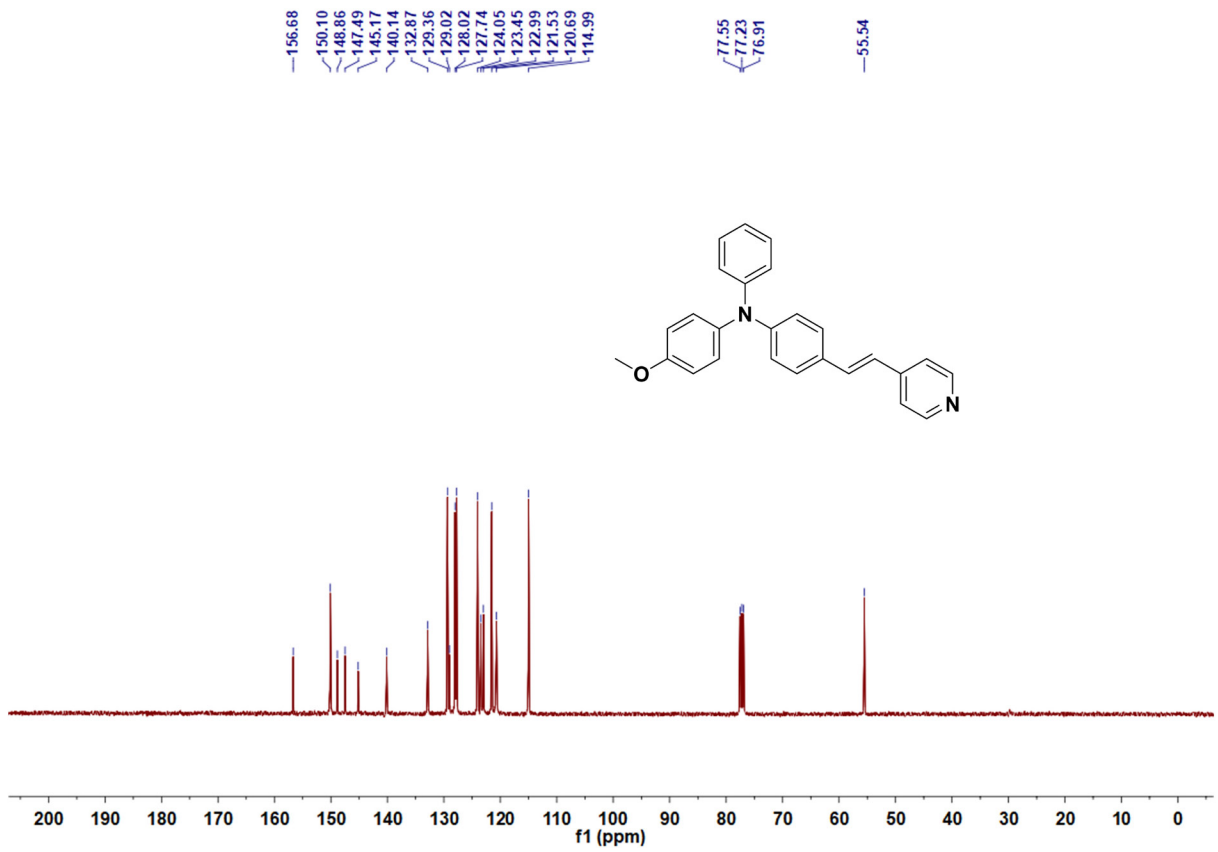


Fig. S2 ^{13}C-NMR spectrum of compound **2** in $CDCl_3$.

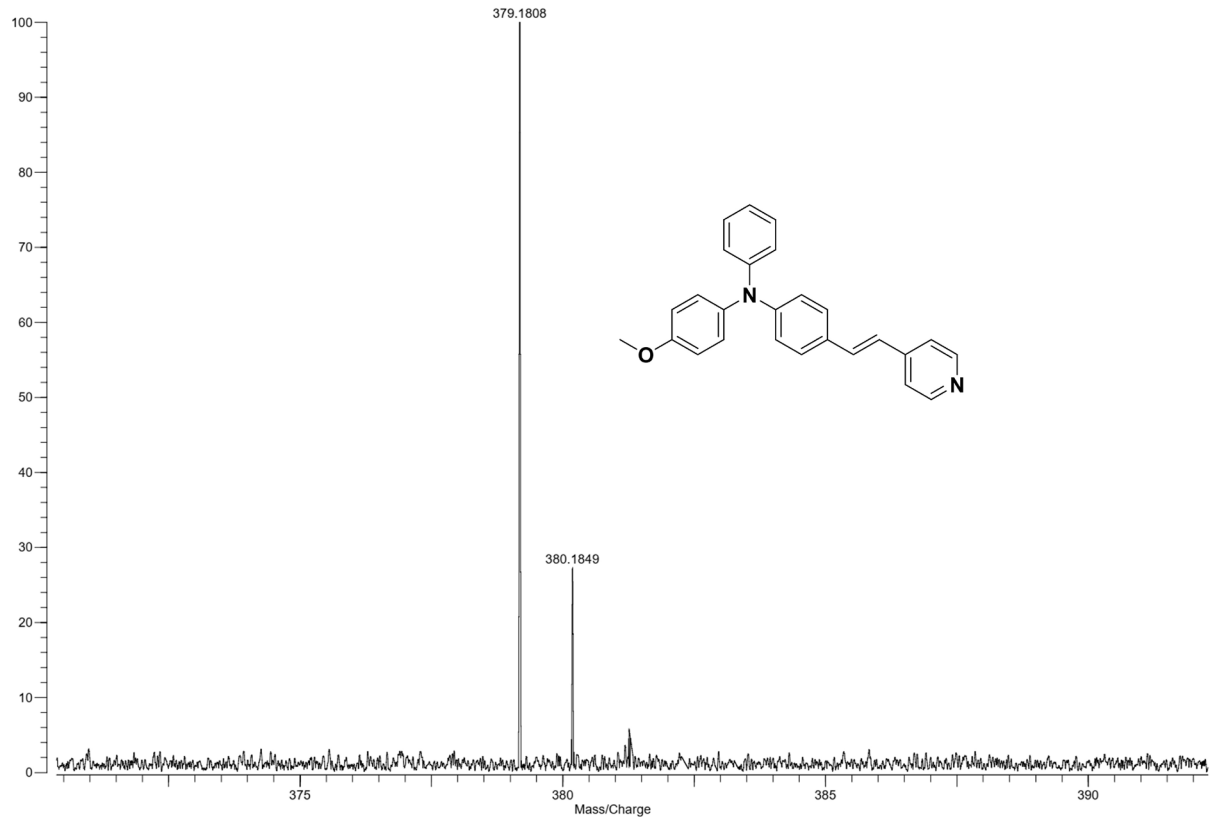


Fig. S3 HRMS spectrum of compound **2**.

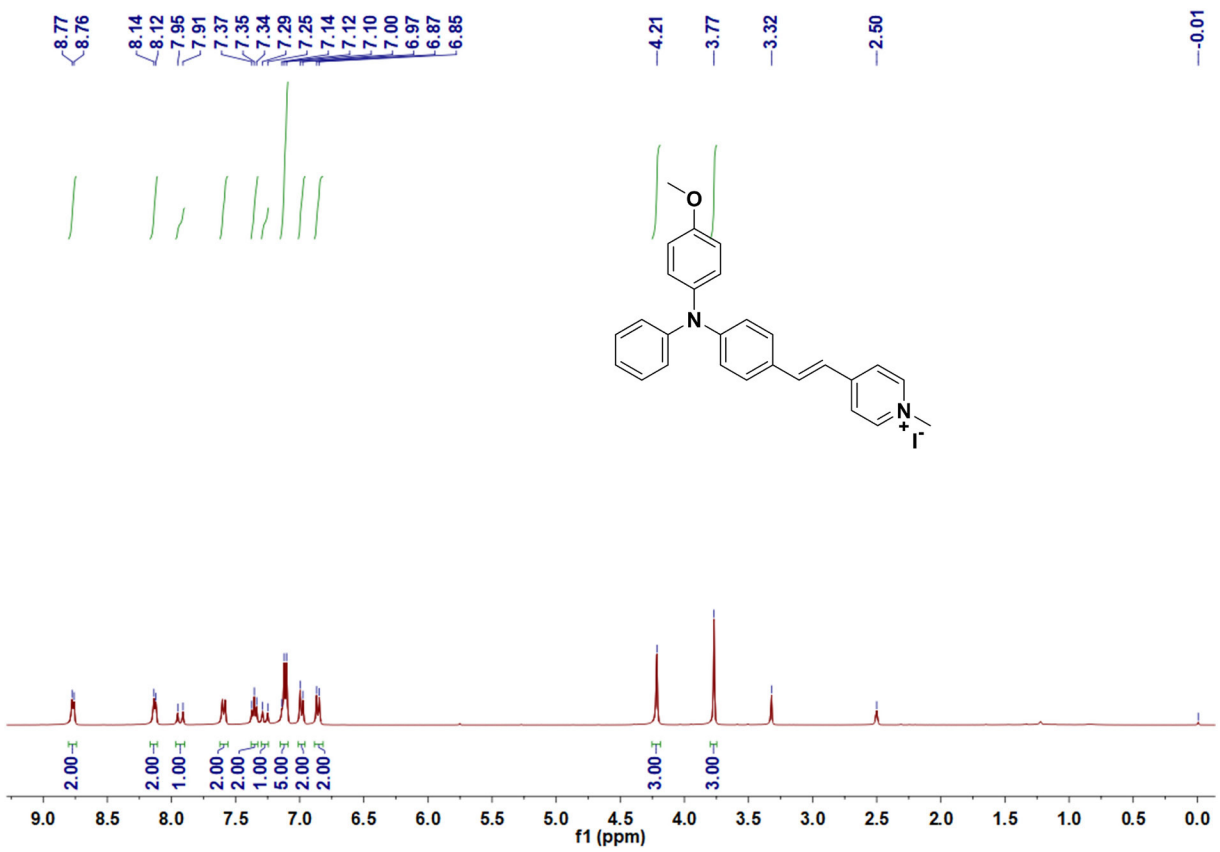


Fig. S4 ^{1}H-NMR spectrum of TPAI in DMSO-d_6.

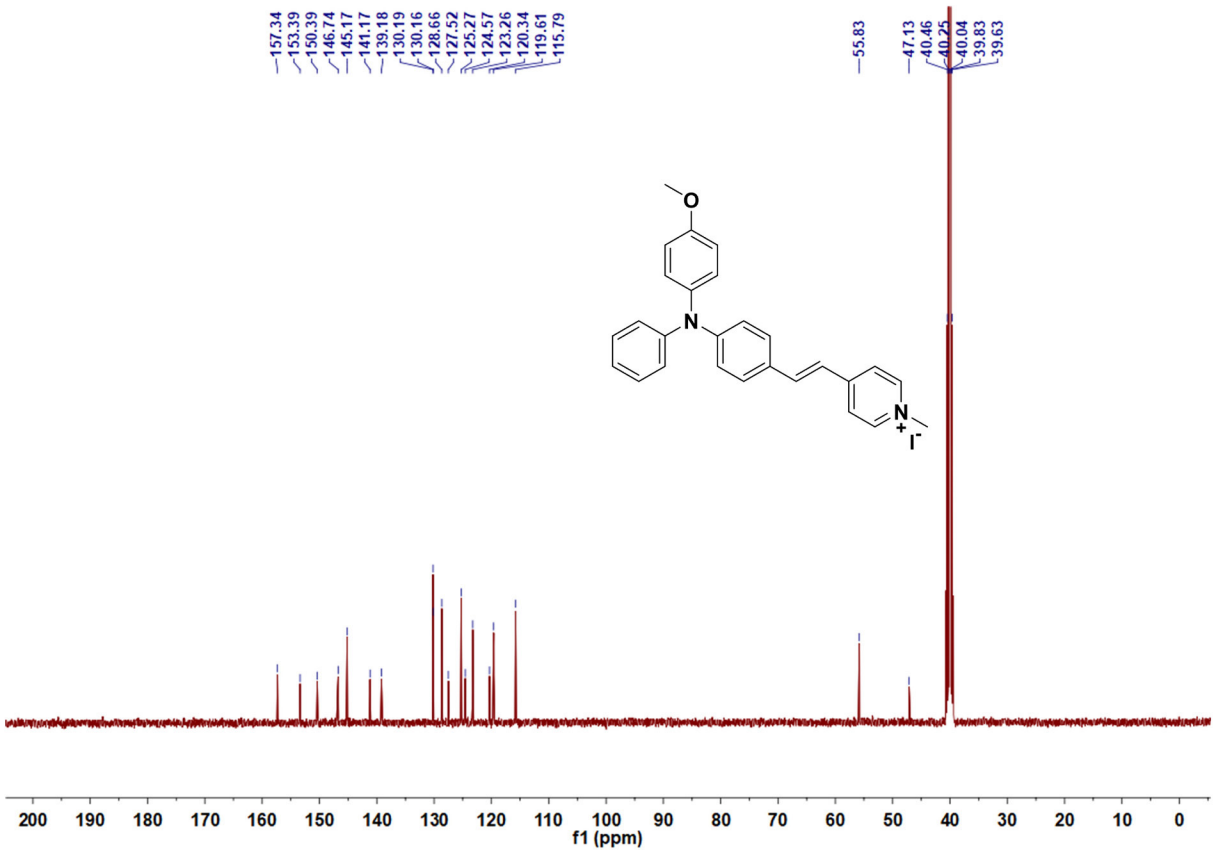


Fig. S5 ^{13}C-NMR spectrum of TPAI in DMSO-d_6.

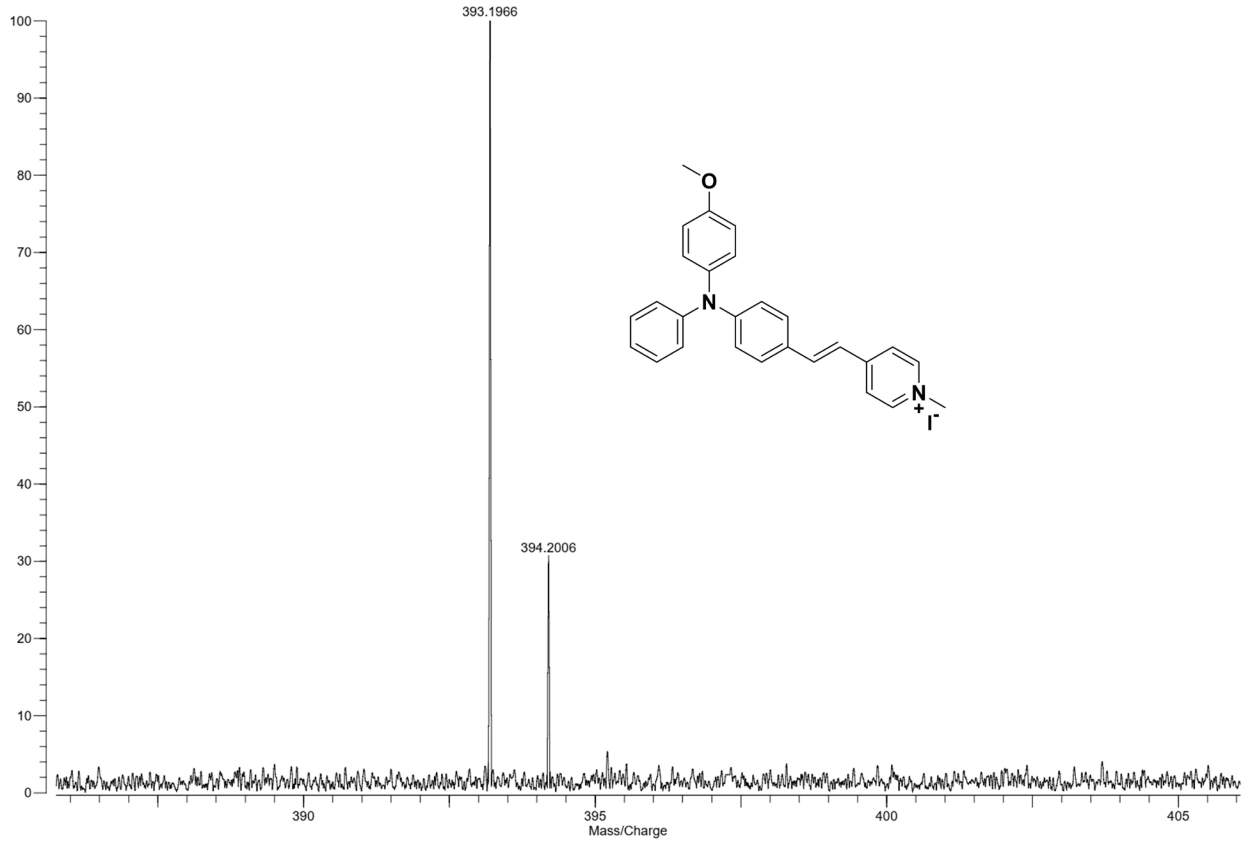


Fig. S6 HRMS spectrum of TPAI.

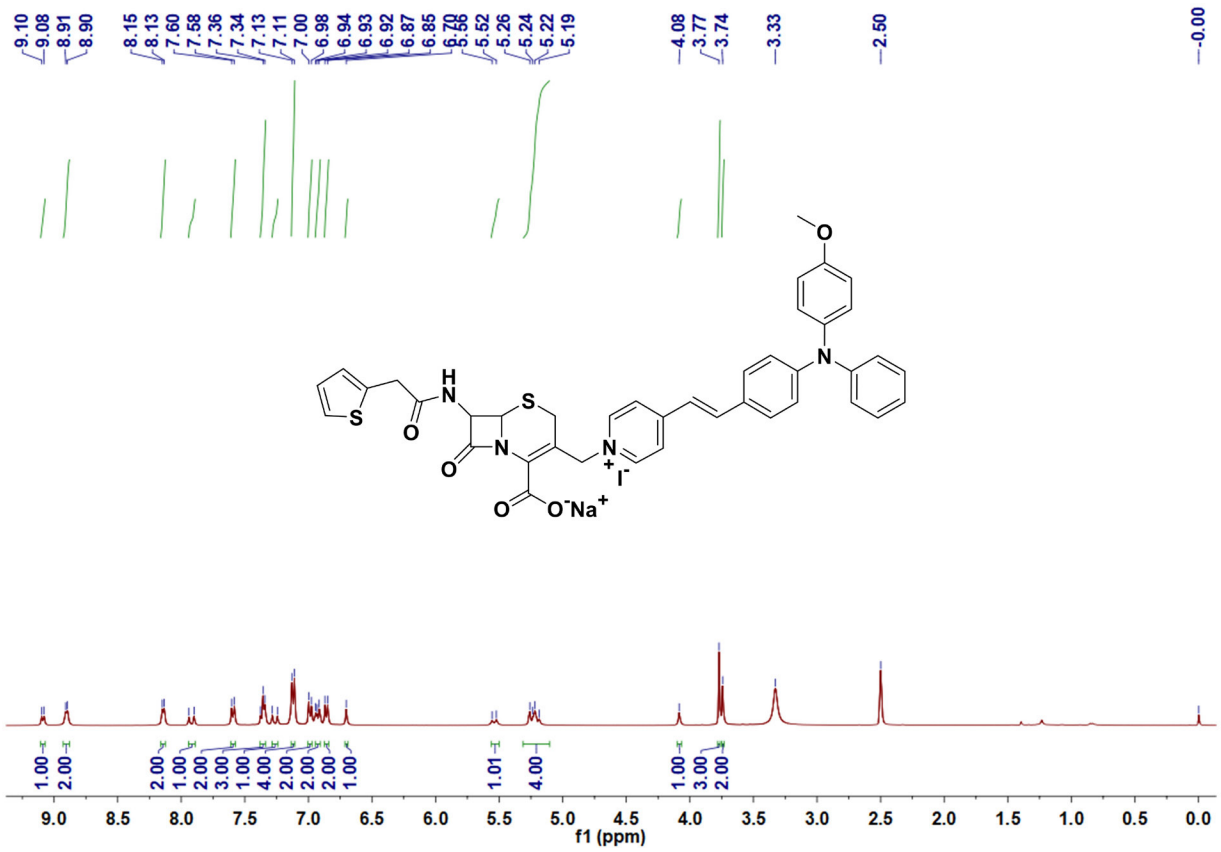


Fig. S7 ^{1}H-NMR spectrum of CE-TPA in DMSO-d_6.

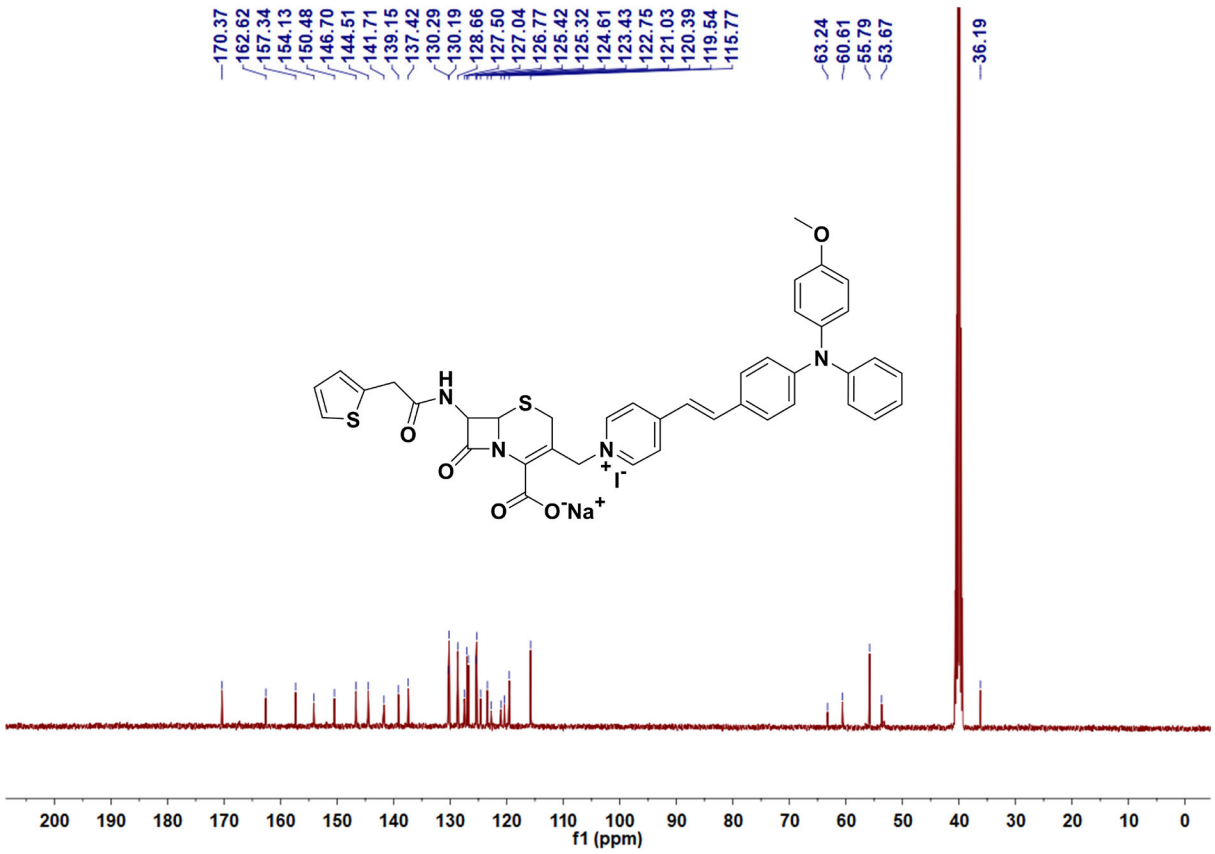


Fig. S8 ^{13}C-NMR spectrum of CE-TPA in DMSO-d_6.

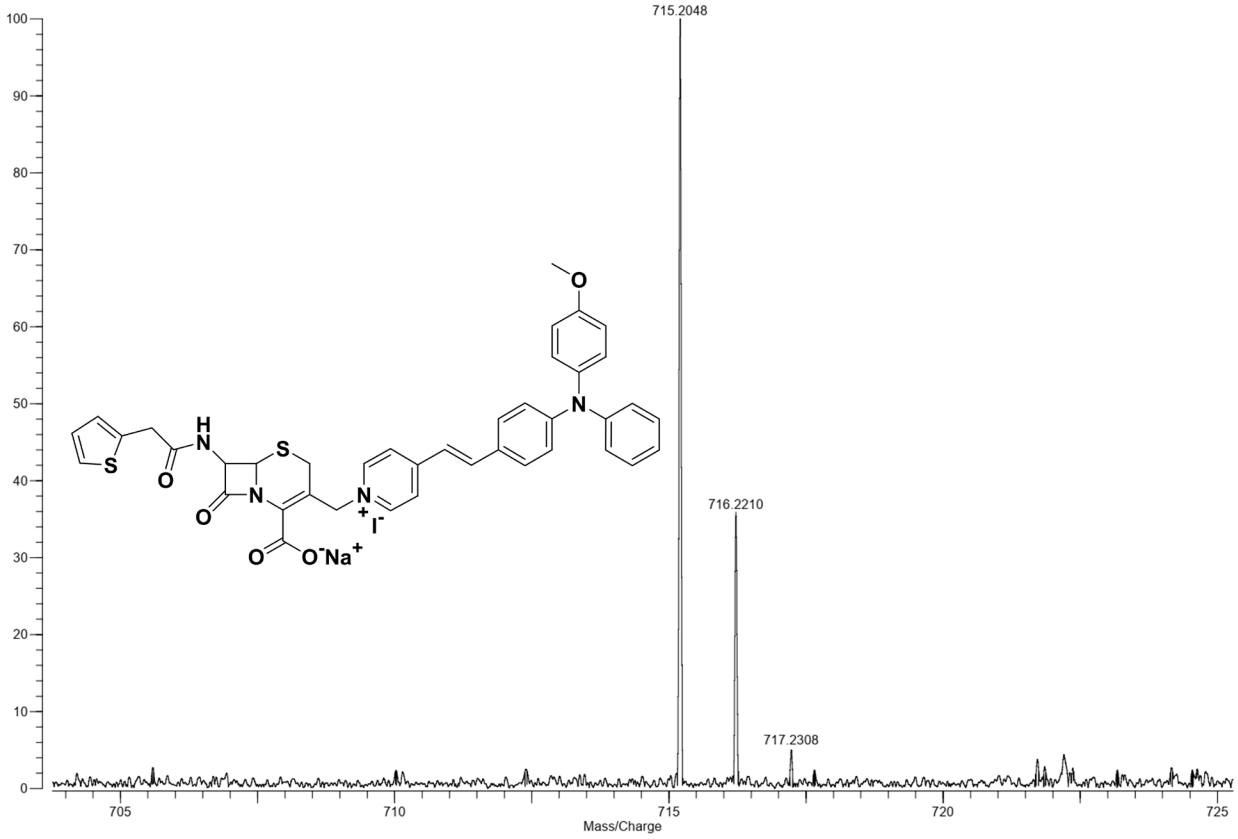


Fig. S9 HRMS spectrum of CE-TPA.

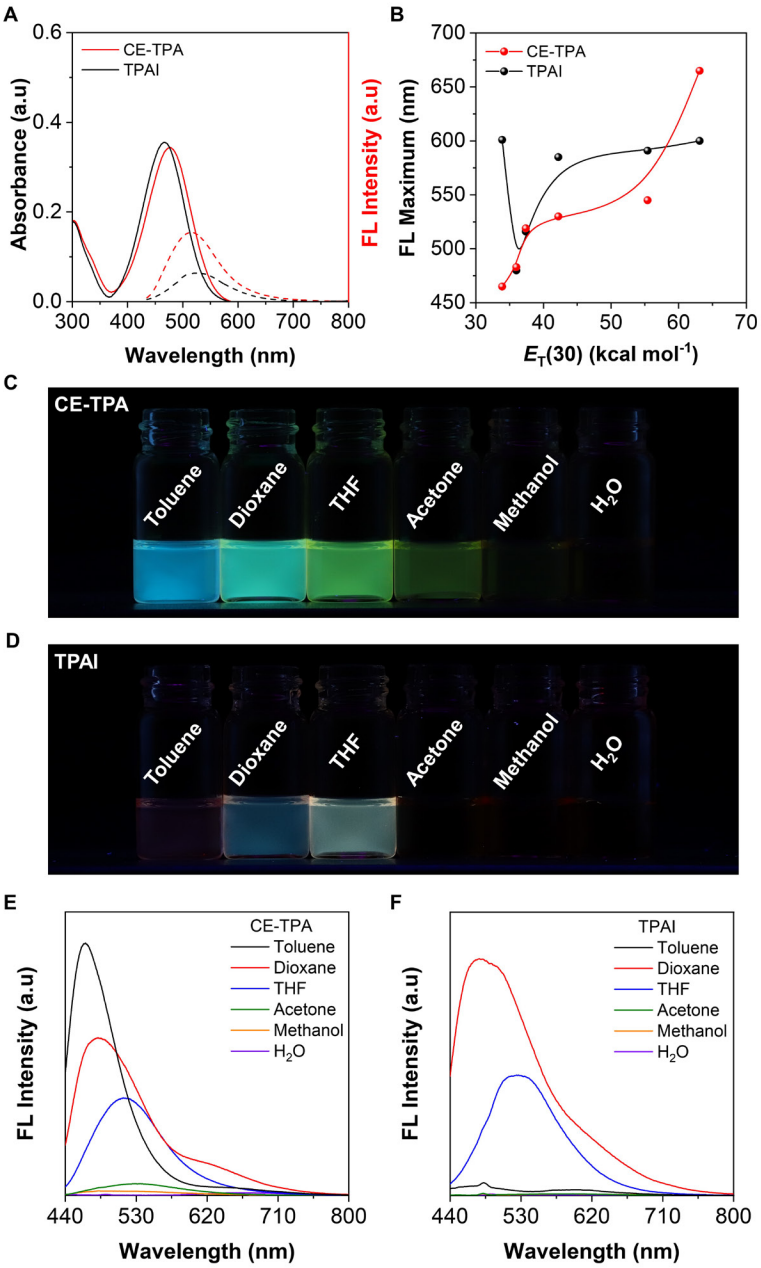


Fig. S10 Photophysical characterizations of CE-TPA and TPAI. (A) UV-vis spectra of CE-TPA and TPAI in DMSO (solid lines) and emission spectra of CE-TPA and TPAI in THF (dashed lines). (B) Emission maxima of CE-TPA and TPAI in different solvents as a function of E_T(30). Note: the red-shifted emission of TPAI in toluene was attributed to its insolubility in the non-polar solvent. (C,D) Photographs of (C) CE-TPA and (D) TPAI in different solvents taken under a 365 nm UV lamp. (E,F) Emission spectra of (E) CE-TPA and (F) TPAI in different solvents. [CE-TPA] = [TPAI] = 10 μM. Ex = 420 nm.

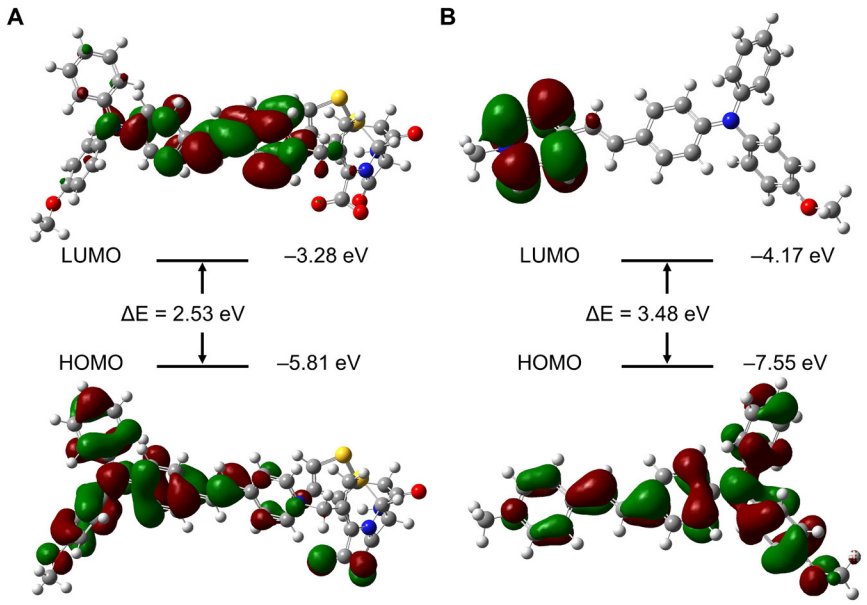


Fig. S11 Calculated FMOs and the corresponding energies. (A) CE-TPA. (B) TPAI.

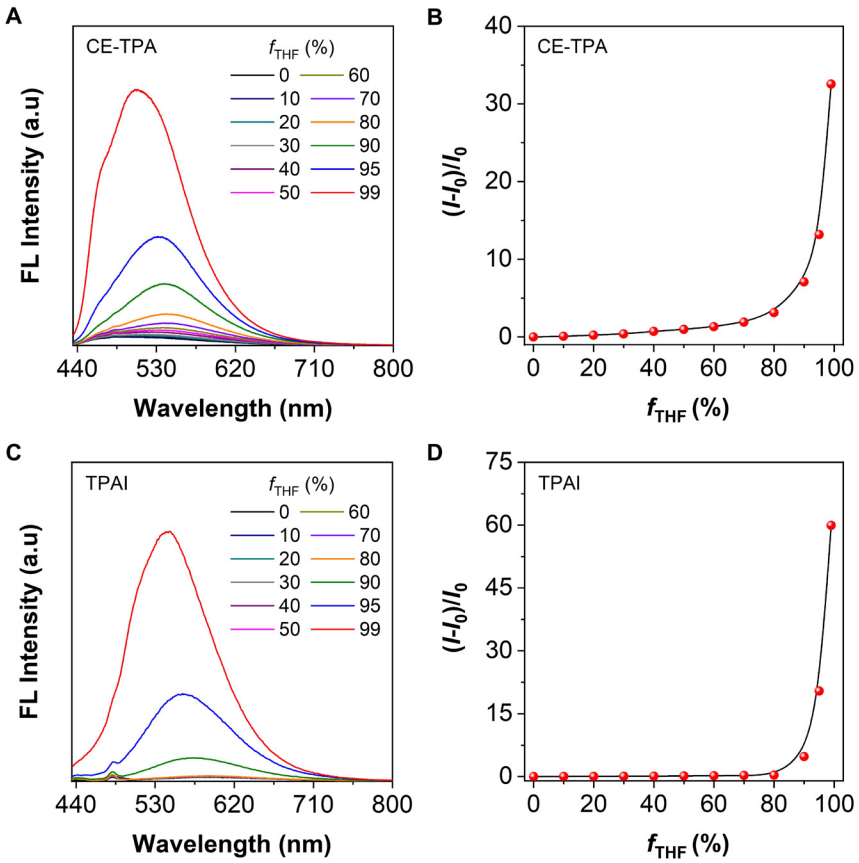


Fig. S12 Characterizations on the AIE properties of CE-TPA and TPAI. (A,C) Emission spectra of (A) CE-TPA and (C) TPAI in methanol with different THF fractions (f_{THF}). Ex = 420 nm. (B,D) Fluorescence enhancement of (B) CE-TPA and (D) TPAI as a function of f_{THF}.

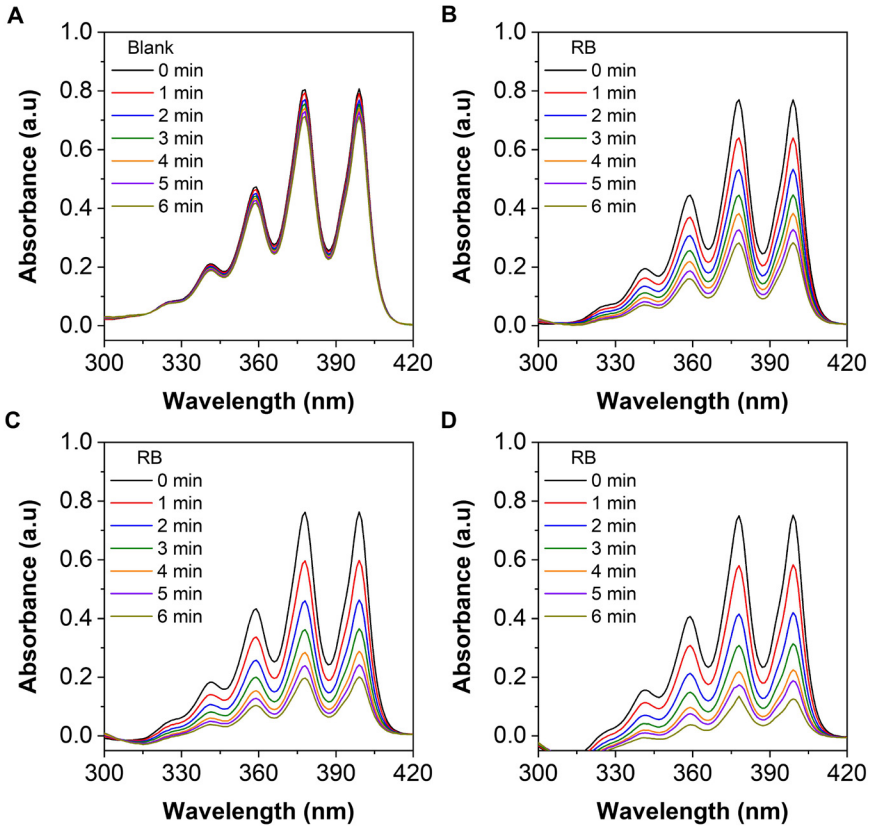


Fig. S13 Absorption spectra of ABDA with different concentrations of RB under white light irradiation. (A) Blank. (B) [RB] = 10 μM. (C) [RB] = 20 μM. (D) [RB] = 40 μM.

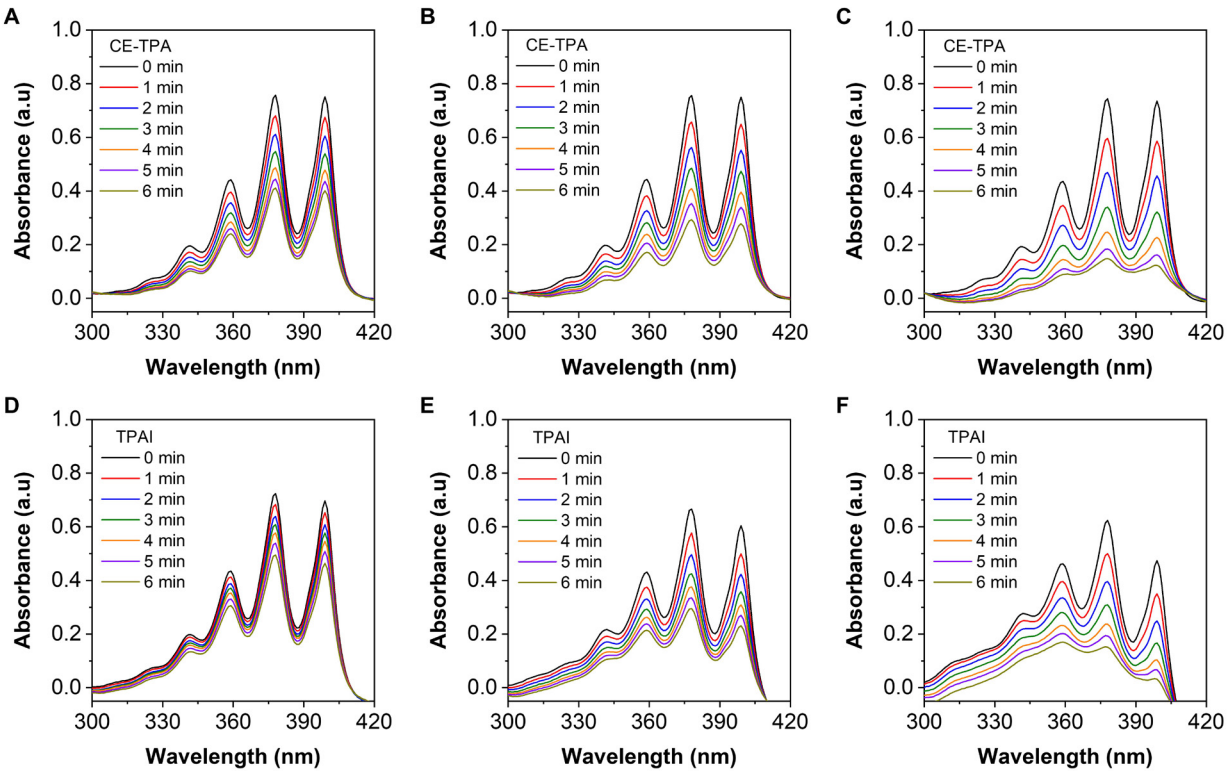


Fig. S14 Absorption spectra of ABDA with different concentrations of CE-TPA and TPAI under white light irradiation. (A) [CE-TPA] = 10 μM. (B) [CE-TPA] = 20 μM. (C) [CE-TPA] = 40 μM. (D) [TPAI] = 10 μM. (E) [TPAI] = 20 μM. (F) [TPAI] = 40 μM.

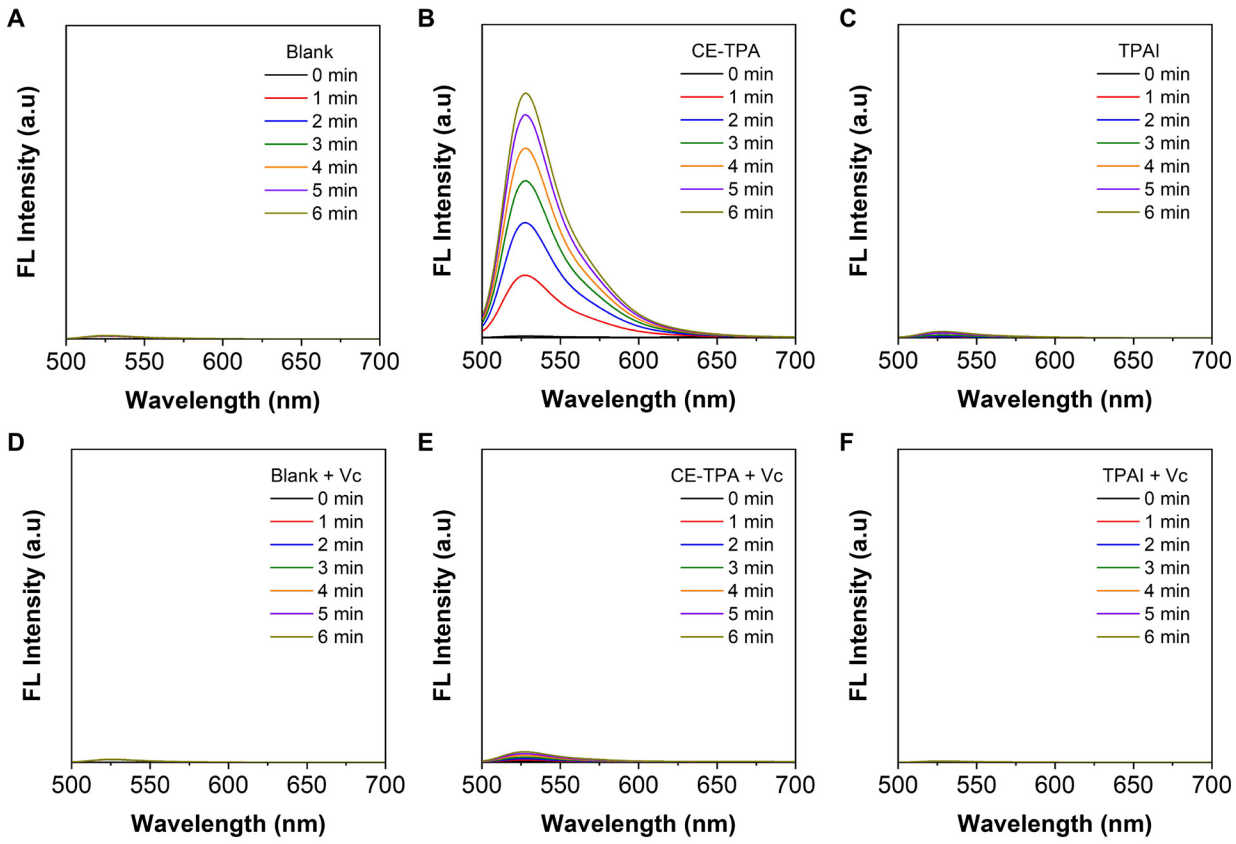


Fig. S15 Emission spectra of DHR-123 in the absence and presence of CE-TPA and TPAI under white light irradiation. (A) Blank. (B) [CE-TPA] = 20 μM. (C) [TPAI] = 20 μM. (D) Blank supplemented with Vc (50 μM). (E) CE-TPA (20 μM) supplemented with Vc (50 μM). (F) TPAI (20 μM) supplemented with Vc (50 μM).

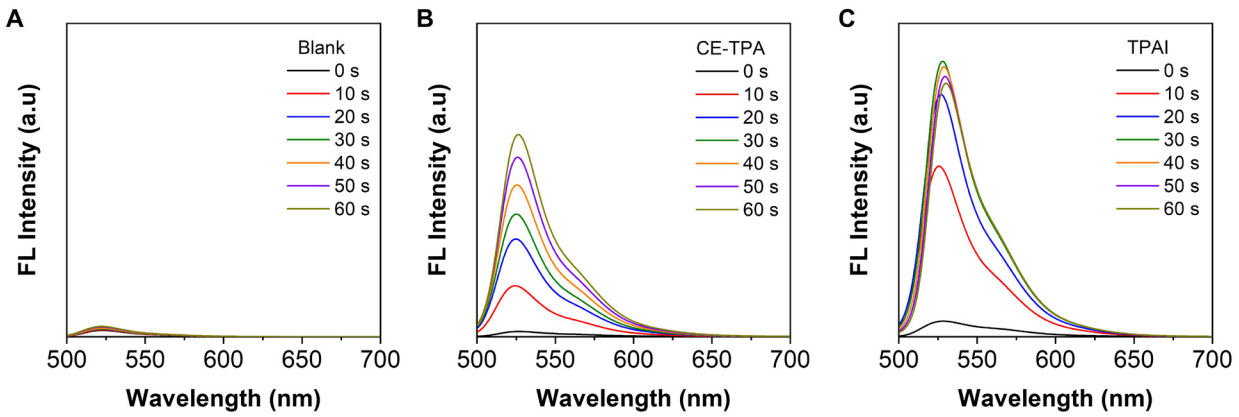


Fig. S16 Emission spectra of DCFH in the absence and presence of CE-TPA and TPAI under white light irradiation. (A) Blank. (B) [CE-TPA] = 20 μM. (C) [TPAI] = 20 μM.

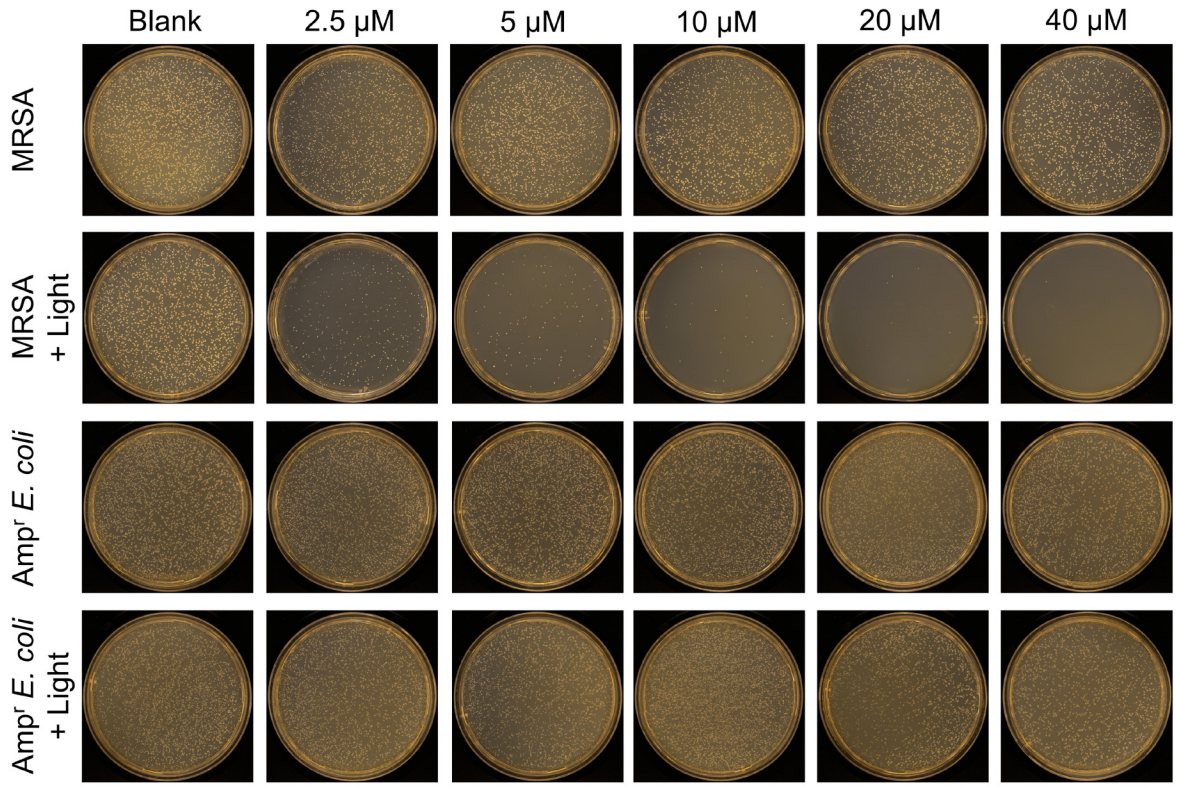


Fig. S17 Photographs of bacterial colonies formed on agar plates after incubation with different concentrations of CE-TPA in the absence and presence of white light irradiation (n = 3).

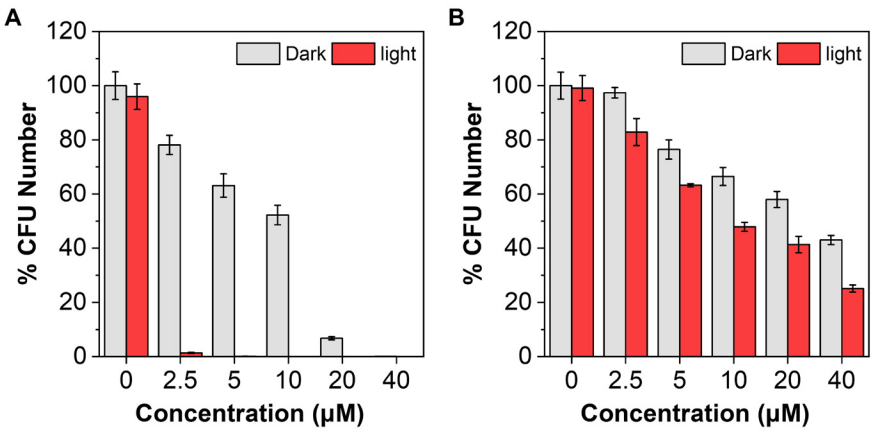


Fig. S18 Bacterial viabilities in the presence of different concentrations of TPAI without and with white light irradiation. (A) MRSA. (B) Amp^{r} *E. coli*.

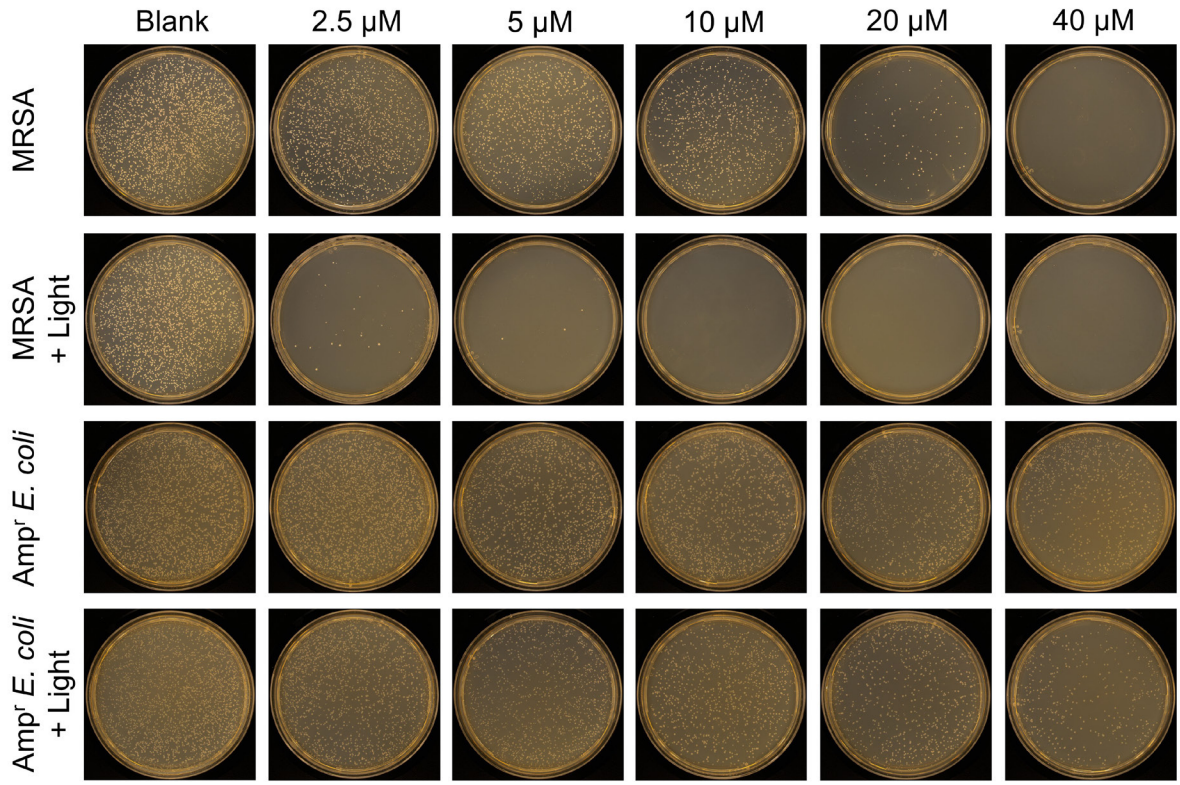


Fig. S19 Photographs of bacterial colonies formed on agar plates after incubation with different concentrations of TPAI in the absence and presence of white light irradiation (n = 3).

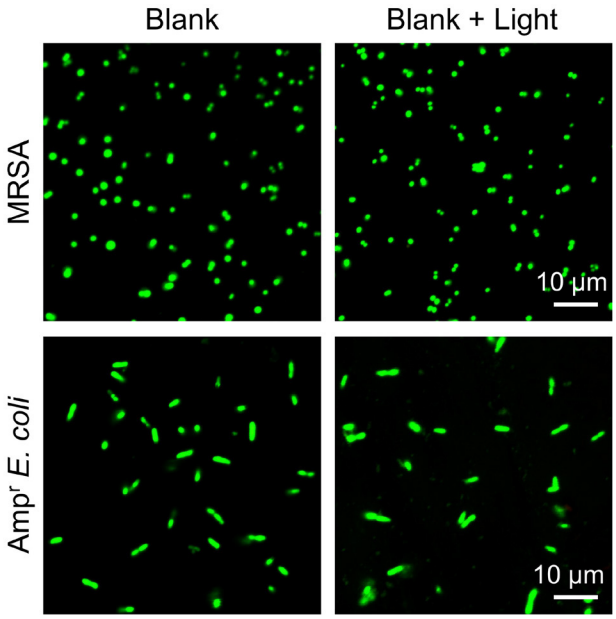


Fig. S20 Live/dead staining of bacteria for the blank groups, where live and dead bacteria are shown in green and red, respectively.

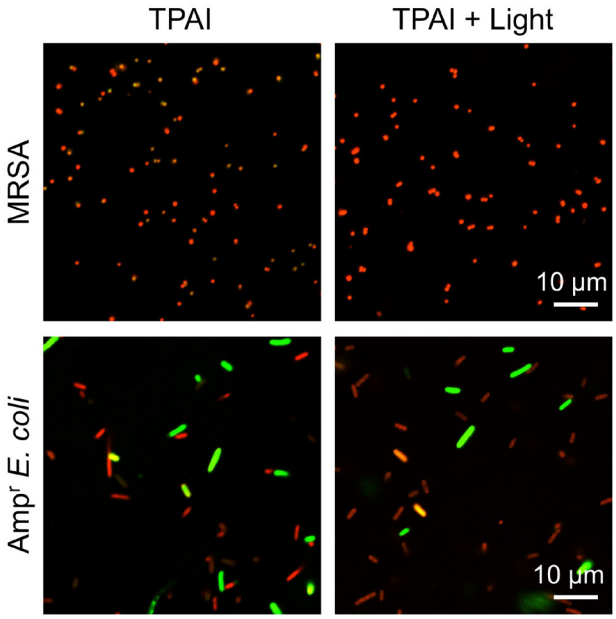


Fig. S21 Live/dead staining of bacteria for the TPAI-treated groups, where live and dead bacteria are shown in green and red, respectively.

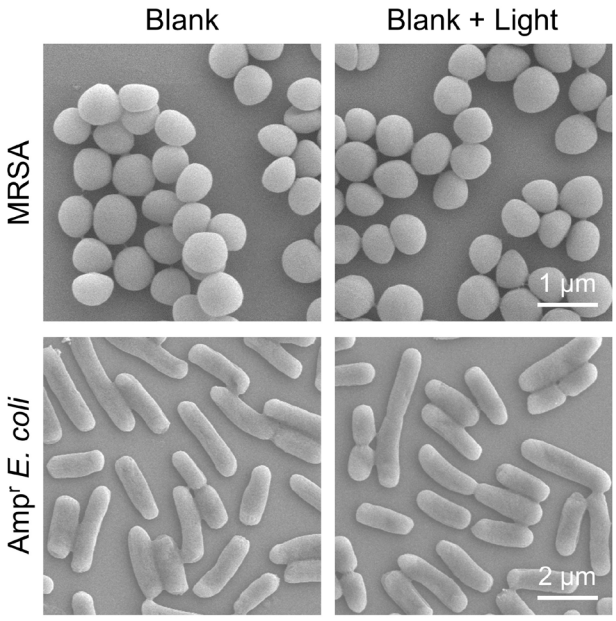


Fig. S22 SEM images of bacteria for the blank groups in the absence and presence of white light irradiation.

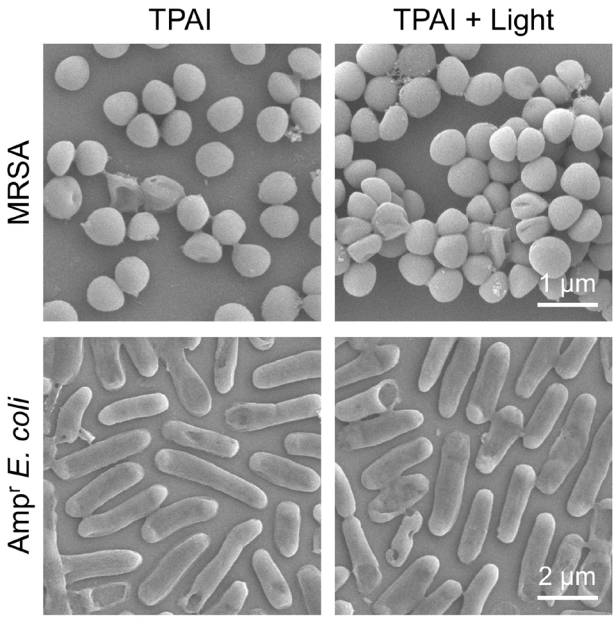


Fig. S23 SEM images of bacteria for the TPAI-treated groups in the absence and presence of white light irradiation.

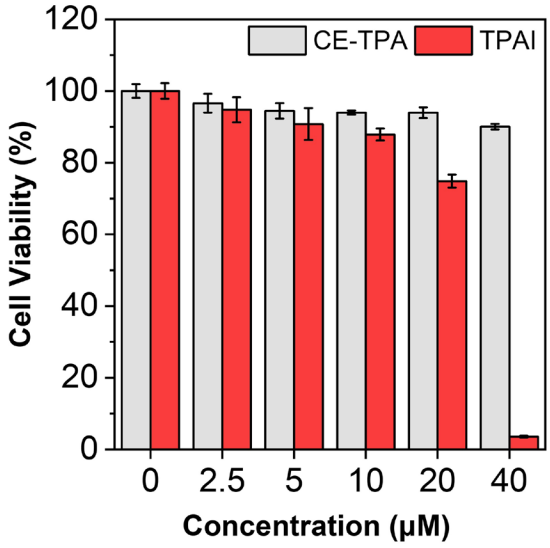


Fig. S24 Cell viability of NIH-3T3 cells incubated with different concentrations of CE-TPA and TPAI in the dark (n = 3).

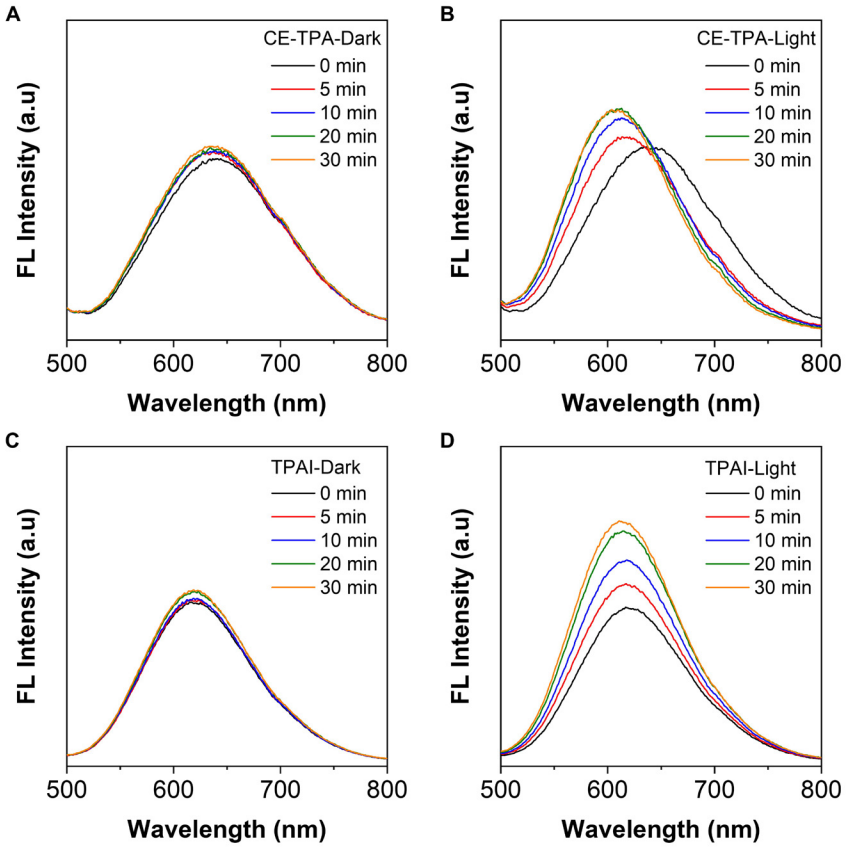


Fig. S25 Real-time monitoring of the PDT outcome of MRSA. (A,B) Emission spectra of MRSA treated with CE-TPA in the (A) absence and (B) presence of white light irradiation. (C,D) Emission spectra of MRSA treated with TPAI in the (C) absence and (D) presence of white light irradiation.

Table S1. Fluorescence quantum yields (Φ_F) of CE-TPA and TPAI in different solvents

Compound	**Φ_F**					
	Toluene	Dioxane	THF	Acetone	Methanol	H_2O
CE-TPA	32.60%	12.76%	10.42%	0.07%	0.04%	0.05%
TPAI	2.14%	2.79%	2.73%	0.07%	0.02%	0.03%

Table S2. Singlet oxygen quantum yields (Φ_Δ) of CE-TPA and TPAI at different concentrations

Compound	**Φ_Δ**		
	10 μM	20 μM	40 μM
CE-TPA	48.6%	49.8%	55.9%
TPAI	36.6%	61.5%	63.9%