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Light-controllable cell-membrane disturbance for intracellular delivery

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1. Materials and Instruments

1.1 Materials

All chemicals and biological materials were obtained from commercial suppliers. Dichloromethane (DCM) and potassium carbonate (K_2CO_3) were purchased from Kishida Chemical Co., Ltd. (Japan). Heparin sodium salt, acetonitrile (MeCN), 1-bromooctane, anhydrous magnesium sulfate ($MgSO_4$), 4,4'-dimethoxybenzophenone, zinc powder, titanium tetrachloride, hexamethylenetetramine, trifluoroacetic acid (TFA), 4 Å molecular sieves, super dehydrated THF, sodium azide (NaN_3), DMEM, RPMI-1640 medium, endothelial cell basal medium, Cell Counting Kit-8 (CCK-8), and sodium borohydride ($NaBH_4$) were purchased from Fujifilm Wako Pure Chemicals Inc. (Japan). *N,N*-Dimethylformamide (DMF), methanol (MeOH), tetrahydrofuran (THF), hexane, and chloroform ($CHCl_3$) were purchased form nacalai tesque (Japan). Celite® 535 was purchased from Sigma-Aldrich (USA). 4,4'-Dihydroxybenzophenone was purchased from Tokyo Chemical Industry (TCI) Co., Ltd. (Japan). Silica gel (SiO_2, 230-400 mesh) for column chromatography was purchased from Silicycle (Canada). DMF and MeOH were distillated under N_2 atmosphere by using CaH_2 or Mg as drying agents before use. **Cy-5**[1] and R8-PAD [RRRRRRRR-GG- d(KLAKLAK)2-amide][2] were prepared as reported. FITC-R8 was synthesized by reacting FITC with N-terminus of GABA-R8. Antisense oligonucleotides (ASOs) were purchased from Ajinomoto Co., Inc. (Ajinomoto Bio-Pharma Services, Japan). The DNA primers for real-time PCR (RT-PCR) were purchased from Thermo Fisher Scientific Inc. (Invitrogen™, USA). Super Prep™ Cell Lysis & RT-Kit for qPCR was purchased from TOYOBO Co., Ltd. (Japan).

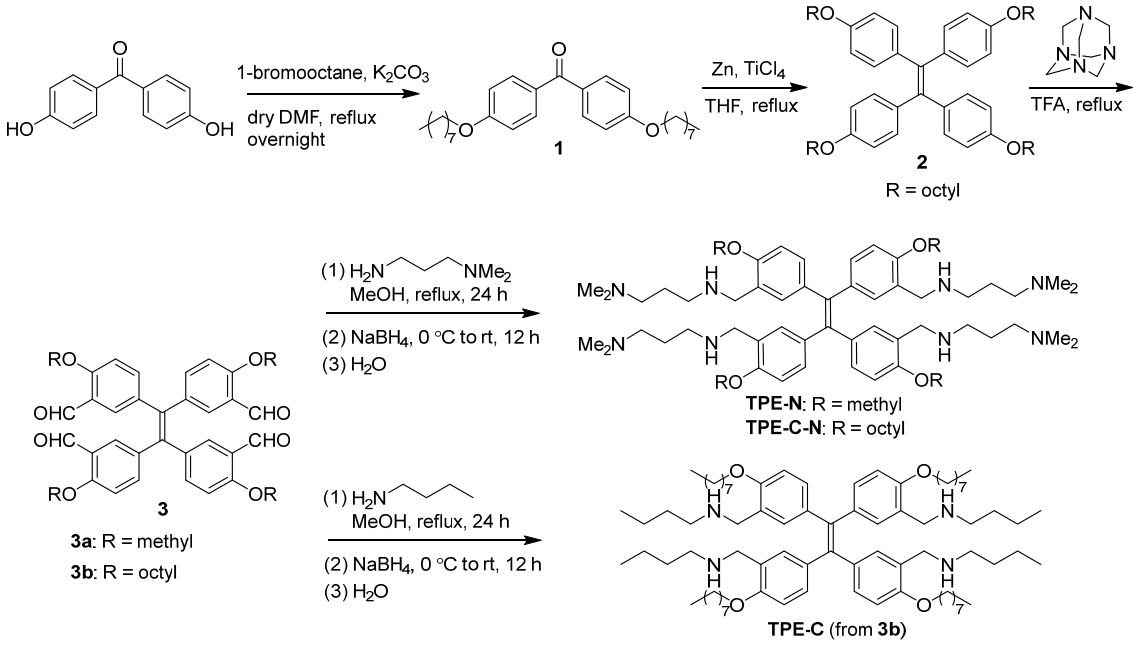
1.2 Instruments

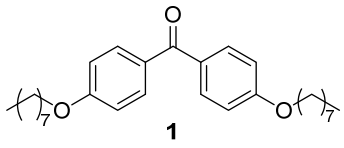
UV-vis absorption spectra of dyes were measured by UV-vis-NIR spectrophotometer (UH5300, Hitachi High-Technologies Co., Japan). Emission spectra of dyes were measured by fluorescence spectrophotometer (RF-6000, Shimadzu Co., Japan). The integrating sphere (ISR-100, Shimadzu Co., Japan) was used for the determination of quantum efficiency. High resolution mass spectra were measured by EXACTICVE (ESI, Thermo Fisher Scientific Inc., USA). NMR spectra were recorded on JEOL ECZ-400 spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR). The FL lifetime measurement was performed on a Horiba DeltaFlex spectrofluorometer system; excitation was conducted using UV diode lasers (DeltaDiode 375 nm, DD375L). Fluorescence images of living cells were taken by a fluorescence microscope (BZ-X810, Keyence Co. Ltd., Japan). Confocal laser scanning microscope (CLSM) images of living cells were taken by a confocal laser scanning microscope system (LSM 710, Carl Zeiss Co. Ltd., Germany). Flow

cytometry analysis was using FACS Attune (Thermo Fisher Scientific Inc., USA). LED light source CL-1501 with timer unit CL-TCN1 (Asahi Spectra Co., Ltd., Japan) is used for irradiation of cell penetration experiments. Reverse transcription was performed using a thermal cycler (Mastercycler® X50s, Eppendorf, Germany). RT-PCR was performed using a thermal cycler (ABI StepOne Plus™ Real-Time PCR System, Thermo Fisher Scientific Inc., USA).

2. Synthesis of TPEs

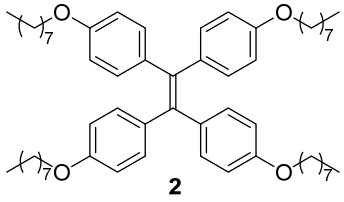
Scheme S1. Synthesis of **TPE**s





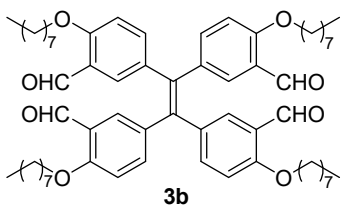
Compound 1: Under nitrogen atmosphere, 4,4'-dihydroxybenzophenone (1.1 g, 5.0 mmol), 1-bromooctane (3.9 g, 20 mmol), and K_2CO_3 (6.9 g, 50 mmol) were added to dry DMF (80 mL) and the resulting mixture was stirred at 80 °C for 12 h. Cold water (Milli-Q, 80 mL) was added to the reaction mixture and the resulting mixture was stirred for 2 h. The reaction mixture was extracted with DCM (3 × 20 mL), then washed by brine (2 × 30 mL). The organic layer was dried over anhydrous $MgSO_4$. After removal of solvent, the residue was purified by recrystallization from hexane to give 2.3 g (4.9 mmol, yield: 98%) of white crystal **1**. mp: 99.0–100.1 °C. IR (ATR) 630, 763, 852, 1025, 1171, 1251, 1603, 1634, 2854, 2922 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.89 (t, J = 6.9 Hz, 6H), 1.30–1.38 (m, 16H),

1.44–1.51 (m, 4H), 1.78–1.85 (m, 4H), 4.03 (t, J = 6.7 Hz, 4H), 6.94 (d, J = 8.7 Hz, 4H), 7.77 (d, J = 9.2 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.5, 23.1, 26.4, 29.5, 29.6, 29.7, 32.2, 68.6, 114.3, 130.9, 132.6, 162.8, 194.8. HRMS (ESI) calcd for $C_{29}H_{42}O_3Na$ ($[M+Na]^+$): 461.3026, found: 461.3024.



2

Compound 2: Under nitrogen atmosphere, to a solution of **1** (1.9 g, 4.1 mmol) in dry THF (40 mL) was added Zn (powder, 1.4 g, 21 mmol) at 0 °C and the resulting mixture was stirred for 20 min. To this solution was added dropwise $TiCl_4$ (3.9 g, 21 mmol) at 0 °C. The solution was held at reflux and stirred overnight. The mixture was allowed to cool to room temperature. Saturated K_2CO_3 aqueous solution (40 mL) was added to the reaction mixture and the resulting mixture was stirred for 30 min, then filtered through a Celite pad. The filtrate was concentrated under vacuum to remove THF and the residue was dissolved in ethyl acetate (20 mL). The organic layer was washed with brine (2 × 30 mL) and dried over anhydrous $MgSO_4$. After removal of solvent, the residue was purified by silica gel column chromatography (hexane-AcOEt, 20:1–10:1) to give 1.3 g (1.6 mmol, yield: 78%) of white waxy solid **2**. IR (ATR) 601, 822, 1109, 1029, 1174, 1243, 1299, 1391, 1469, 1508, 1608, 2855, 2924 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.88 (t, J = 6.4 Hz, 12H), 1.28–1.34 (m, 32H), 1.38–1.46 (m, 8H), 1.70–1.77 (m, 8H), 3.87 (t, J = 6.4 Hz, 8H), 6.62 (d, J = 8.2 Hz, 8H), 6.90 (d, J = 8.2 Hz, 8H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.3, 22.8, 26.2, 29.4, 29.5, 29.6, 32.0, 67.9, 113.6, 132.7, 136.9, 138.4, 157.4. HRMS (ESI) calcd for $C_{58}H_{84}O_4Na$ ($[M+Na]^+$): 867.6262, found: 867.6252.

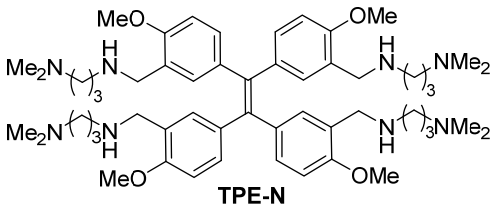


3b

Compound 3a: Compound **3a** was synthesized following the same protocol as reported.[3]

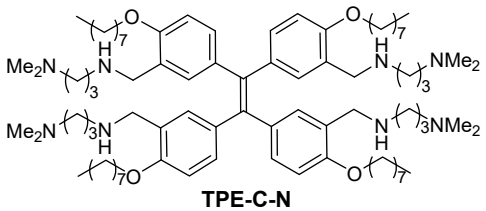
Compound 3b: Under nitrogen atmosphere, **2** (0.46 g, 0.54 mmol) and hexamethylenetetramine (6.0 g, 43 mmol) were added to TFA (50 mL) and the resulting mixture was held at reflux and stirred for 18 h. Cold water (Milli-Q, 80 mL) was added to the reaction mixture and the resulting mixture was stirred for 1 h. The reaction mixture was extracted with DCM (3 × 20 mL), then washed by brine (2 × 30 mL). The organic layer was dried over anhydrous $MgSO_4$. After removal of solvent, the residue was purified by silica gel column chromatography (hexane-AcOEt, 10:1) to give 0.40 g (0.42 mmol, yield: 77%) of pale-yellow waxy solid **3b**. IR (ATR) 653, 813, 910, 1112, 1250, 1386, 1468, 1493, 1601, 1683, 2856, 2925 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C):

δ = 0.89 (t, *J* = 6.9, 12H), 1.26–1.37 (m, 32H), 1.42–1.49 (m, 8H), 1.77–1.84 (m, 8H), 4.00 (t, *J* = 6.4 Hz, 8H), 6.70 (d, *J* = 8.7 Hz, 4H), 7.15 (dd, *J* = 8.7, 2.3 Hz, 4H), 7.43 (d, *J* = 2.3 Hz, 4H), 10.35 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.8, 22.4, 25.8, 28.8, 28.9, 29.0, 31.5, 68.3, 111.9, 124.2, 130.5, 134.9, 138.1, 138.6, 160.1, 189.2. HRMS (ESI) calcd for $C_{62}H_{84}O_8Na$ ($[M+Na]^+$): 979.6058, found: 979.6058.



TPE-N

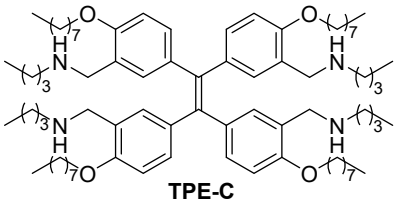
TPE-N: Under a nitrogen atmosphere, **3a** (0.11 g, 0.19 mmol), *N,N*-dimethyl-1,3-propanediamine (0.080 g, 0.78 mmol) and molecular sieves (4 Å) were mixed in dry MeOH (20 mL) and held at reflux for 24 h. The molecular sieves were removed by filtration, and the intermediate imine in MeOH was cooled to 0 °C and treated with solid $NaBH_4$ (0.029 g, 0.78 mmol). The mixture was stirred at rt overnight. Then 5 mL H_2O was added. After neutralization of the reaction mixture with 10% HClaq., pH of the resulting mixture was adjusted to 9 by K_2CO_3. The mixture was then concentrated under vacuum to remove MeOH. Water was removed by lyophilization, and the remaining solid was dissolved in anhydrous DCM, then filtered through a celite pad. The filtrate was concentrated under vacuum to give 0.076 g (0.084 mmol, yield: 44%) of pale-yellow sticky-solid **TPE-N**. IR (ATR) 756, 810, 1024, 1131, 1241, 1463, 1497, 1603, 1685, 2856, 2931 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 1.62–1.67 (m, 8H), 2.25 (s, 24H), 2.37 (t, *J* = 7.3 Hz, 8H), 2.52 (t, *J* = 6.9 Hz, 8H), 3.67 (s, 8H), 3.82 (s, 12H), 6.79 (d, *J* = 8.2 Hz, 4H), 6.94–7.00 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 25.9, 45.2, 47.2, 48.1, 55.1, 58.1, 109.4, 124.5, 131.8, 133.5, 136.2, 138.3, 155.7. HRMS (ESI) calcd for $C_{54}H_{85}N_8O_4$ ($[M+H]^+$): 909.6688, found: 909.6699.



TPE-C-N

TPE-C-N: Under a nitrogen atmosphere, **3b** (0.11 g, 0.12 mmol), *N,N*-dimethyl-1,3-propanediamine (0.047 g, 0.46 mmol) and molecular sieves (4 Å) were mixed in dry MeOH (15 mL) and held at reflux for 24 h. The molecular sieves were removed by filtration, and the intermediate imine in MeOH was cooled to 0 °C and treated with solid $NaBH_4$ (0.018 g, 0.47 mmol). The mixture was stirred at rt overnight. Then 5 mL H_2O was added. After neutralization of the reaction mixture with 10% HClaq., pH of the resulting mixture was adjusted to 9 by K_2CO_3. The mixture was then concentrated under vacuum to remove MeOH. Water was removed by lyophilization, and the remaining solid was dissolved in anhydrous DCM, then

filtered through a Celite pad. The filtrate was concentrated under vacuum to give 0.078 g (yield: 52%) of pale-yellow oil **TPE-C-N**. IR (ATR) 724, 809, 1041, 1130, 1237, 1467, 1498, 1604, 2462, 2813, 2855, 2926 cm^{-1}. ^1H NMR (400 MHz, CD_3OD, 25 °C): δ = 0.91 (t, *J* = 6.8 Hz, 12H), 1.29–1.39 (m, 32H), 1.45–1.51 (m, 8H), 1.56–1.64 (m, 8H), 1.75–1.82 (m, 8H), 2.21 (s, 24H), 2.28 (t, *J* = 7.3 Hz, 8H), 2.38 (t, *J* = 6.9 Hz, 8H), 3.56 (s, 8H), 3.96 (t, *J* = 6.4 Hz, 8H), 6.71 (d, *J* = 8.2 Hz, 4H), 6.87–6.91 (m, 4H), 6.89 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.2, 22.8, 26.4, 28.2, 29.4, 29.5, 31.9, 45.7, 47.2, 49.4, 58.2, 67.9, 110.2, 127.3, 131.3, 133.2, 136.5, 138.6, 155.5. Elemental analysis, calcd for $C_{82}H_{140}O_4N_8 \cdot 3H_2O$: H = 10.85%, C = 72.63%, O = 8.26%; found: H = 10.57%, C = 72.64%, O = 8.02%. HRMS (ESI) calcd for $C_{82}H_{141}O_4N_8$ ($[M+H]^+$): 1302.1070, found: 1302.1081.



TPE-C: Under a nitrogen atmosphere, **3b** (0.15 g, 0.16 mmol), *n*-butylamine (0.047 g, 0.64 mmol) and molecular sieves (4 Å) were mixed in dry MeOH (20 mL) and held at reflux for 24 h. The molecular sieves were removed by filtration, and the intermediate imine in MeOH was cooled to 0 °C and treated with solid $NaBH_4$ (0.048 g, 1.3 mmol). The mixture was stirred at rt overnight. Then 5 mL H_2O was added. The filtrate was concentrated under vacuum to remove MeOH and the residue was dissolved in chloroform (20 mL). The organic layer was washed with brine (2 × 30 mL) and dried over anhydrous $MgSO_4$. The filtrate was concentrated under vacuum to give 0.097 g (0.082 mmol, yield: 51%) of pale-yellow oil **TPE-OR-C**. IR (ATR) 660, 753, 809, 1026, 1108, 1239, 1468, 1498, 1604, 2856, 2924 cm^{-1}. ^1H NMR (400 MHz, CD_3OD, 25 °C): δ = 0.89–0.92 (m, 24H), 1.25–1.9 (m, 56H), 1.74–1.79 (m, 8H), 2.31 (t, *J* = 6.9 Hz, 8H), 3.55 (s, 8H), 3.95 (t, *J* = 6.4 Hz, 8H), 6.71 (d, *J* = 8.2 Hz, 4H), 6.86–6.93 (m, 4H), 6.88 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.8, 13.9, 20.3, 22.5, 26.1, 29.1, 29.2, 31.6, 32.0, 48.1, 49.2, 67.5, 77.0, 109.9, 127.1, 130.9, 133.0 136.2, 138.3, 155.2. HRMS (ESI) calcd for $C_{78}H_{129}N_4O_4$ ($[M+H]^+$): 1186.0008, found: 1185.9995.

3. Theoretical Calculation

DFT calculation by using Gaussian 16 package[4] was carried out to anticipate the energy-minimized structure of **TPE-1**. The ground state was estimated at the calculation level of M062X/6-31G(d,p).[5] Time-dependent (TD) DFT calculation was carried out at the M062X/6-31G(d,p) level by using Gaussian 16 package to estimate its excited state. The four octyl groups were replaced to methyl groups, and the dimethylaminopropyl groups were replaced to methyl groups for reducing the calculation cost.

4. Photophysical and Spectroscopic Properties of TPEs

4.1 UV-vis absorbance and fluorescence spectra

For absorbance and fluorescence measurements, the **TPE-C-N** solutions (10 μM) were prepared by mixing a solution of **TPE-C-N** in DMF (15 μL, 2.0 mM) with MeCN containing different amounts of Milli-Q water (2985 μL). For UV-vis absorbance and fluorescence measurements, the **TPE-C** solutions (10 μM) were prepared by mixing a solution of **TPE-C** in DMF (15 μL, 2.0 mM) with MeCN containing different amounts of Milli-Q water (2985 μL). For absorbance and fluorescence measurements, the **TPE-N** solutions (10 μM) were prepared by mixing a solution of **TPE-N** in DMF (15 μL, 2.0 mM) with MeCN containing different amounts of Milli-Q water (2985 μL).

4.2 Photophysical properties of TPE-C, TPE-N, and TPE-C-N

Table S1. Photophysical properties of **TPE-C**, **TPE-N**, and **TPE-C-N** determined at 25 °C.

compound	λ_{max} (nm)	ε (cm^{-1} M^{-1})[a]	λ_{em} (nm)	Φ_{FL}[b]	<τ> (ns)[c]
TPE-C	320	1.43×10^4	491	0.17	4.49
TPE-N	321	1.35×10^4	480	–	–
TPE-C-N	320	1.62×10^4	486	0.13	3.92

a] Determined in MeCN.

[b] Determined in H_2O as an absolute value, λ_{ex} = 330 nm.

[c] Average FL lifetime, determined in H_2O, monitored at 480 nm.

Table S2. Fluorescence decay analysis of **TPEs**.

compound	τ_1 (ns)	A_1	τ_2 (ns)	A_2	τ_3 (ns)	A_3
TPE-C	2.25	0.311	6.12	0.614	0.430	0.0749
TPE-C-N	2.00	0.352	5.62	0.567	0.381	0.0806

τ: lifetime, A: relative amplitude, <τ>: average lifetime.

$\langle\tau\rangle = (A_1\tau_1 + A_2\tau_2 + A_3\tau_3) / (A_1 + A_2 + A_3)$

5. Molecular Dynamics Simulation

The GROMACS 2021.5 package[6] was used to performed MD simulations. The CHARMM36 force field[7] with the TIP3P model[8] were employed for POPC and water molecules, respectively. **TPE-C-N** were modeled using Ligand Reader & Modeler[9] in CHARMM-GUI,[10] though the torsion potentials around the bond connecting phenyl to ethene was modified based on the quantum mechanical calculations from a previous study.[11] In our calculation, all amino groups of **TPE-C-N** were assumed to be protonated. The simulated system consisted of one **TPE-C-N**, a lipid bilayer membrane consisting of 128 POPCs, hydrated with 6199 water molecules. Sodium and chloride ions were added to neutralize the system and to reproduce the physiological salt concentration (150 mM NaCl). The initial configuration was prepared using CHARMM-GUI Membrane Builder,[12] where **TPE-C-N** was placed in the water region. The system temperature was controlled at 310 K using a Nosé-Hoover thermostat.[13,14] Pressure was maintained at 1 bar using a Parrinello-Rahman barostat with semi-isotropic coupling.[15] Electrostatic interaction was calculated using the particle mesh Ewald method.[16] The cutoff distance of Lenard-Jones interactions was set to 1.2 nm with a force switching distance of 1.0 nm. All bonds involving hydrogen atoms were constrained using the LINCS algorithm.[17] The water geometries were maintained constant by adopting the SETTLE algorithm.[18] The time step for the simulation was set to 1 fs. After minimizing the energy with the steepest decent algorithm, a 100 ns steered MD simulation was performed pulling **TPE-C-N** along the *z*-direction (membrane normal direction) toward the bilayer membrane surface at a constant rate of 0.02 nm ns^{-1}. Then, after removing the constraint to **TPE-C-N**, another 500 ns MD simulation were carried out, and the last 300 ns of the simulation were used to calculate the number density distributions.

6. Living cell imaging

6.1 General Cell Culture

Human pancreatic adenocarcinoma cell line (SUIT-2, JCRB No.: JCRB1094) and luciferase-expressing human pancreatic cancer cell line MIA PaCa-2/CMV-Luc (MIA PaCa-2-Luc, JCRB No.: JCRB1681) were purchased from Japanese Collection of Research Bioresources Cell Bank (JCRB cell bank, Japan). Human ovarian endometrioid adenocarcinoma cell line (OVK-18), human lung cancer cell line (A549), and human umbilical vein endothelial cell line (HUVEC) were purchased from Riken cell bank (Japan). Human cervical cancer cell line (HeLa) and human epidermoid carcinoma cell line (A431) were purchased from American Type Culture Collection (USA).

HeLa, A549, OVK-18, and A431 human cancer cells were cultured at 37 °C and 5% CO_2 in

Dulbecco's Modified Eagle's Medium (DMEM, high-glucose) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin (PS). HUVEC cells were cultured in endothelial cell basal medium containing 10% FBS and 1% PS. SUIT-2 cells were cultured in RPMI-1640 with 10% FBS and 1% PS. MIA PaCa-2-Luc cells were cultured at 37 °C and 5% CO_2 in DMEM (low-glucose) supplemented with 10% FBS and 1% PS.

6.2 Co-Localization of TPE-C-N and Cy-5 in A549 Cells

A549 cells were seeded in 8-well slides (μ-Slide 8 Well ibiTreat, Germany) at a density of 3 × 10^4 cells per well. The cells were incubated for 24 h for cell attachment. After the removal of medium, cells were washed with PBS (150 μL/well) twice. **TPE-C-N** (150 μL, 10 μM in PBS) were added per well and incubated with cells in the dark at 25 °C for 5 min. Cells were covered by aluminum film to ensure a dark environment. Then, **Cy-5** (50 μL/well, 40 μM in PBS; final concentration: 10 μM) was added. Cells were then irradiated by 365 nm LED light (10 mW/cm^2) at 25 °C for 5 min. For dark control experiments, cells were covered by aluminum film and incubated at 25 °C for 5 min. Cells were then washed with PBS containing 0.5% (w/v) heparin sodium (150 μL/well) once. During fluorescence imaging, cells were cultured with PBS containing 0.5% (w/v) heparin sodium (150 μL/well). Fluorescence images of living cells were taken by BZ-X800 (Keyence Corporation, Japan) with 40× objective lens. Sectioning module BZ-H4XF was used for obtaining high-contrast images. Excitation wavelength of 600/60 nm (detection: 700/75 nm) were used for obtaining red channel (**Cy-5**) images. Excitation wavelength of 350/50 nm (detection: 500/40 nm) were used for obtaining blue channel (**TPE-C-N**) images.

6.3 Fluorescence Imaging of TPE-C, TPE-N, and TPE-C-N in A549 Cells

A549 cells were seeded in 8-well slides (μ-Slide 8 Well ibiTreat, Germany) at a density of 3 × 10^4 cells per well. The cells were incubated for 24 h for cell attachment. After the removal of medium, cells were washed with PBS (150 μL/well) twice. Next, **TPE-C** (150 μL, 10 μM in PBS) or **TPE-N** (150 μL, 10 μM in PBS) were added per well and incubated with cells in darkness at 25 °C for 5 min. Cells were covered by aluminum film to ensure a dark environment. Then, PBS (50 μL/well) was added.

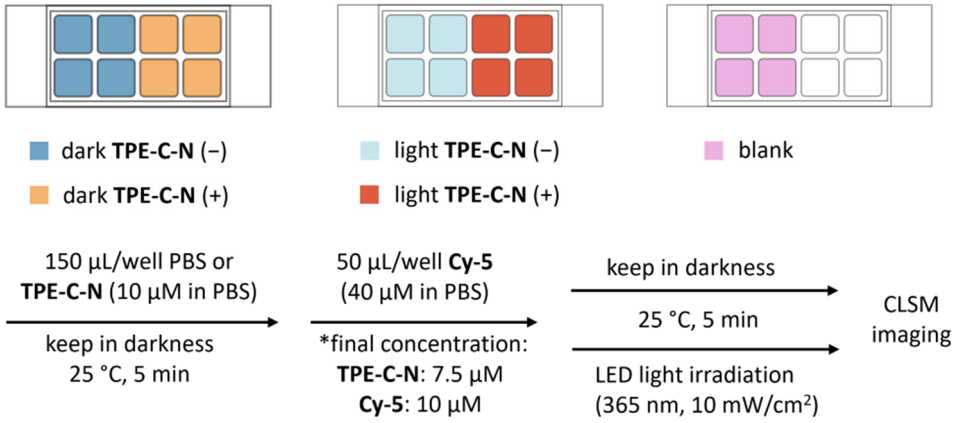
Cells were then irradiated by 365 nm LED light (intensity: 10 mW/cm^2) at 25 °C for 5 min. For dark control experiments, cells were covered by aluminum film and incubated at 25 °C for 5 min. Cells were then washed with PBS containing 0.5% (w/v) heparin sodium (EMD Millipore Corp., USA, 150 μL/well) once. Cells were cultured with PBS containing 0.5% (w/v) heparin sodium

(150 μL/well) during fluorescence imaging. For monitoring the fluorescence signal changes of **TPE-C-N**, A549 cells were incubated in DMEM at 37°C for 1, 3, and 6 h. Cells were washed with PBS containing 0.5% (w/v) heparin sodium (150 μL/well) before fluorescence imaging.

For monitoring the fluorescence signal changes of **TPE-C-N**, A549 cells were

Fluorescence images of living cells were taken by BZ-X800 (Keyence Corporation, Japan) with 40× objective lens. Sectioning module BZ-H4XF was used for obtaining high-contrast images. Excitation wavelength of 350/50 nm (detection: 500/40 nm) were used for obtaining blue channel (**TPE-C** and **TPE-N**) images.

6.4 CLSM Imaging of Cy-5 Treated A549 Cells



A549 cells were seeded in three 8-well slides (μ-Slide 8 Well ibiTreat, Germany) at a density of 3×10^4 cells per well. Cells were incubated for 24 h for cell attachment. After the removal of medium, cells were washed with PBS (150 μL/well) twice. For light irradiation slides, PBS (150 μL) or **TPE-C-N** (150 μL, 10 μM in PBS) was added per well and incubated with cells in the dark at 25 °C for 5 min. Cells were covered by aluminum film to ensure a dark environment. Next, **Cy-5** (50 μL, 40 μM in PBS; final concentration is 10 μM) was added per well. Cells were then irradiated by 365 nm LED light (10 mW/cm^2) at 25 °C for 5 min. For the dark control slide, after the addition of **Cy-5** (50 μL/well, 40 μM in PBS; final concentration is 10 μM), cells were then covered by aluminum film and incubate in the dark at 25 °C for 5 min. For the blank slide, cells were cultured in DMEM (200 μL/well) at 37 °C in a 5% CO_2 humidified incubator for 10 min. All cells were then washed with PBS containing 0.5% (w/v) heparin sodium (150 μL/well) once. During CLSM imaging, cells were cultured with PBS containing 0.5% (w/v) heparin sodium (150 μL/well). CLSM images of A549 cells were acquired by LSM 710 (Carl Zeiss, Germany) with 63× objective lens. Excitation laser of 633 nm (detection: 647–759 nm) was used for obtaining

images. Relative fluorescence intensity of CLSM images was calculated according to the equation shown in supplementary information.

Relative fluorescence intensity of CLSM images was calculated using the following equation:

Relative FL intensity = $(F_{test} - F_{blank}) / (F_{control} - F_{blank})$

F_{test}: Average fluorescence of cells under different treatments

F_{blank}: Average fluorescence of cells in the blank slide

$F_{control}$: Average fluorescence of cells in the ***dark TPE-C-N (−)*** wells

6.5 PI Penetration CLSM Imaging

The integrity of A549 cells after irradiation in the presence of **TPE-C-N** was investigated by the penetration of PI. A549 cells were seeded in an 8-well slide (μ-Slide 8 Well ibiTreat, Germany) at a density of 3×10^4 cells per well. The cells were incubated for 24 h for cell attachment. After the removal of medium, cells were washed with PBS (150 μL/well) twice. Next, **TPE-C-N** (150 μL, 10 μM in PBS) was added per well and incubated with cells in darkness at 25 °C for 5 min. Cells were covered by aluminum film to ensure a dark environment. PBS (50 μL) was added per well and cells were irradiated by 365 nm LED light (intensity: 10 mW/cm^2) at 25 °C for 5 min. Cells were then washed with PBS containing 0.5% (w/v) heparin sodium once and DMEM (150 μL) was added per well.

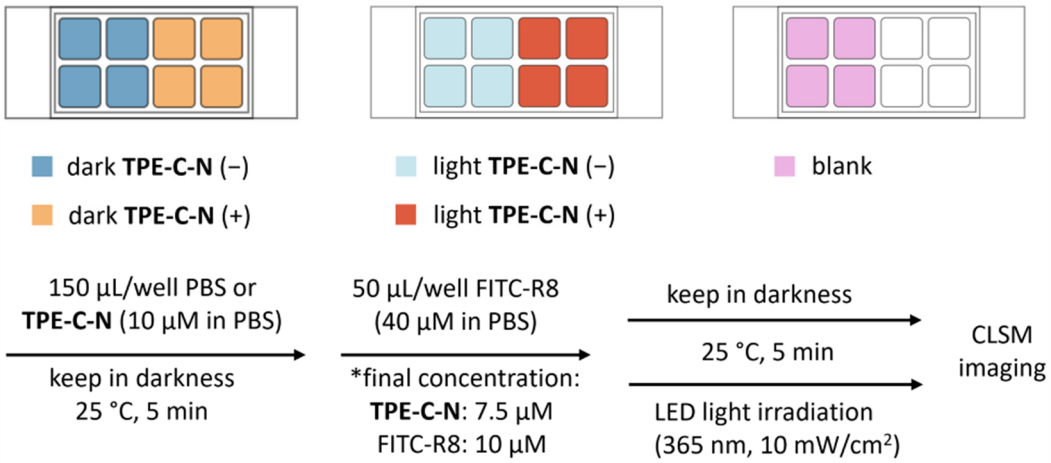
After LED light irradiation, CLSM images of **TPE-C-N** treated A549 cells were obtained by adding PI (10 μg/mL in DMEM) immediately, or after a 15 min waiting period.

For PI treatment test just after irradiation, DMEM was immediately removed and PI (150 μL/well, 10 μg/mL in DMEM) was added.

For PI treatment test 15 min after irradiation, cells are incubated at 25 °C for 15 min. Then, DMEM was removed and PI (150 μL/well, 10 μg/mL in DMEM) in PBS was added.

After 10 min incubation with PI at 25 °C, cells were washed with PBS containing 0.5% (w/v) heparin sodium (150 μL/well) once. Cells were cultured with PBS containing 0.5% (w/v) heparin sodium (150 μL/well) during CLSM imaging. CLSM images of A549 were acquired by LSM 710 (Carl Zeiss, Germany) with 63× objective lens. Excitation lasers of 488 nm (detection: 551–697 nm) were used for obtaining images.

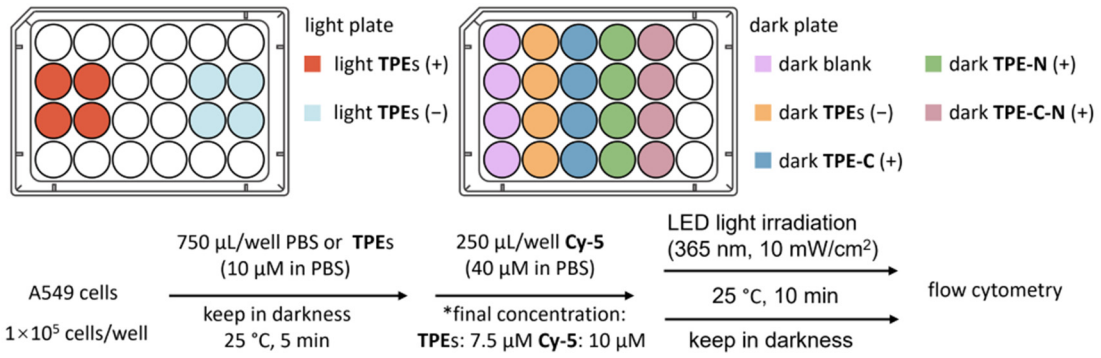
6.6 FITC-R8 Penetration CLSM Imaging



The experimental procedures for **TPE-C-N** treatment and light irradiation are similar to those in the CLSM imaging of **Cy-5** cell membrane permeabilization experiments, with the only difference being the substitution of **Cy-5** with FITC-R8. CLSM images of FITC-R8 treated A549 cells were acquired by LSM 710 (Carl Zeiss, Germany) with 63× objective lens. Excitation laser of 488 nm (detection: 493–630 nm) was used for obtaining images. Relative fluorescence intensity of CLSM images was calculated according to the equation shown in section 6,4.

7. Flow Cytometric Analysis

7.1 Cy-5 Penetration in the Presence of TPE-C, TPE-N, and TPE-C-N



A549 cells were seeded in four 24 well plates (VTC-P24, AS ONE, Japan) at a density of 1 × 10^5 cells per well. Three plates will be irradiated by LED light, one plate will not be irradiated. Four wells in the dark plate will be the blank group.

Cells were incubated for 24 h for cell attachment. After the removal of medium, cells except for the blank group were washed with PBS (750 µL/well) twice. In this experiment, cells in the blank group were incubated with medium only. Then PBS (750 µL) or **TPE-C** (750 µL, 10 µM in PBS) was added per well in the first irradiation plate and incubated with cells at 25 °C in darkness for 5 min. In the second irradiation plate, PBS (750 µL) or **TPE-N** (750 µL, 10 µM in PBS) was added per well and incubated with cells at 25 °C in darkness for 5 min. In the third irradiation plate, PBS (750 µL) or **TPE-C-N** (750 µL, 10 µM in PBS) was added per well and incubated with cells at 25 °C in darkness for 5 min. In the dark plate, PBS (750 µL) or **TPE**s (750 µL, 10 µM in PBS) was added per well. All cells were covered by aluminum film to ensure a dark environment.

Cy-5 (250 µL, 40 µM in PBS) was then added per well. For the three light irradiation plates, cells were irradiated by 365 nm LED light (intensity: 10 mW/cm^2) at 25 °C for 10 min. For the dark control plate, cells were covered by aluminum film and incubate in darkness at 25 °C for 10 min.

After being washed with PBS containing 0.5% (w/v) heparin sodium (750 µL/well, once), cells were harvested with 0.25 w/v% trypsin-1 mM EDTA (0.1 mL/well) and suspended in DMEM (0.5 mL) supplemented with 10% FBS. The cells were collected and washed by PBS (0.2 mL) through centrifugation at 3000 rpm for 5 min. The cells were then resuspended in PBS (0.3 mL). The samples were analyzed by a FACS Attune (Thermo Fisher Scientific) using a yellow laser (561 nm) and a YL3 channel filter (695/40 nm). Each sample was analyzed for 10,000 events.

Relative percentage of **Cy-5**-penetrated cells in all detected cells (relative gate%) was

calculated using the following equation:

Relative gate% = (C_{test} / $C_{control}$) × 100%

C_{test}: Cell count of cells under different treatments

$C_{control}$: Cell count of cells that were incubated with **Cy-5** in darkness without the pretreatment of **TPE-C-N**

7.2 Inhibition of Endocytosis

A549 cells after A549 cells were seeded in two 24 well plates (VTC-P24, AS ONE, Japan) at a density of 1 × 10^5 cells per well. One plate will be irradiated by LED light, another plate will not be irradiated. Cells were incubated for 24 h for cell attachment. Four wells in the dark plate will be the blank group.

Cells were preincubated at 4°C for 15 min. After the removal of medium, cells except for the blank group were washed with PBS (750 μL/well) twice. In this experiment, cells in the blank group were incubated with medium only. Then cold PBS (750 μL) or cold **TPE-C-N** (750 μL, 10 μM in PBS) was added per well and incubated with cells at 4 °C in darkness for 5 min. All cells were covered by aluminum film to ensure a dark environment.

Cold **Cy-5** (250 μL, 40 μM in PBS) was then added per well. For the light irradiation plate, cells were irradiated by 365 nm LED light (intensity: 10 mW/cm^2) at 4 °C for 10 min. For the dark control plate, cells were covered by aluminum film and incubate at 4 °C for 10 min.

After being washed with PBS containing 0.5% (w/v) heparin sodium (750 μL/well, once), cells were harvested with 0.25 w/v% trypsin-1 mM EDTA (0.1 mL/well) and suspended in DMEM (0.5 mL) supplemented with 10% FBS. The cells were collected and washed by PBS (0.2 mL) through centrifugation at 3000 rpm for 5 min. The cells were then resuspended in PBS (0.3 mL). The samples were analyzed by a FACS Attune (Thermo Fisher Scientific) using a yellow laser (561 nm) and a YL3 channel filter (695/40 nm). Each sample was analyzed for 10,000 events.

Relative gate% was similarly calculated according to the equation shown in section 7.1.

7.3 Cy-5 Penetration in the Presence of Singlet Oxygen Quencher NaN_3

A549 cells were seeded in two 24 well plates (VTC-P24, AS ONE, Japan) at a density of 1 × 10^5 cells per well. One plate will be irradiated by LED light, another plate will not be irradiated. Cells were incubated for 24 h for cell attachment. Four wells in the dark plate will be the blank group.

After the removal of medium, cells except for the blank group were washed with PBS (750

μL/well) twice. In this experiment, cells in the blank group were incubated with medium only. Then **TPE-C-N** (750 μL, 10 μM in PBS) or **TPE-C-N** + NaN_3 (750 μL in PBS, **TPE-C-N**: 10 μM, NaN_3: 10 mM) was added per well and incubated with cells at 25 °C in darkness for 5 min. All cells were covered by aluminum film to ensure a dark environment.

Cy-5 (250 μL, 40 μM in PBS) was then added per well. For the light irradiation plate, cells were irradiated by 365 nm LED light (intensity: 10 mW/cm^2) at 25 °C for 10 min. For the dark control plate, cells were covered by aluminum film and incubate at 25 °C for 10 min.

After being washed with PBS containing 0.5% (w/v) heparin sodium (750 μL/well, once), cells were harvested with 0.25 w/v% trypsin-1 mM EDTA (0.1 mL/well) and suspended in DMEM (0.5 mL) supplemented with 10% FBS. The cells were collected and washed by PBS (0.2 mL) through centrifugation at 3000 rpm for 5 min. The cells were then resuspended in PBS (0.3 mL). The samples were analyzed by a FACS Attune (Thermo Fisher Scientific) using a yellow laser (561 nm) and a YL3 channel filter (695/40 nm). Each sample was analyzed for 10,000 events.

Relative gate% was similarly calculated according to the equation shown in section 7.1.

7.4 Cy-5 Penetration in Different Cell Lines

HeLa, SUIT-2, OVK-18, HUVEC, and A431 cells were seeded in 24 well plates (VTC-P24, AS ONE, Japan) at a density of 1×10^5 cells per well, respectively. Every type of cells was separately seeded in two plates. One plate will be irradiated by LED light, another plate will not be irradiated. Four wells in the dark plate will be the blank group.

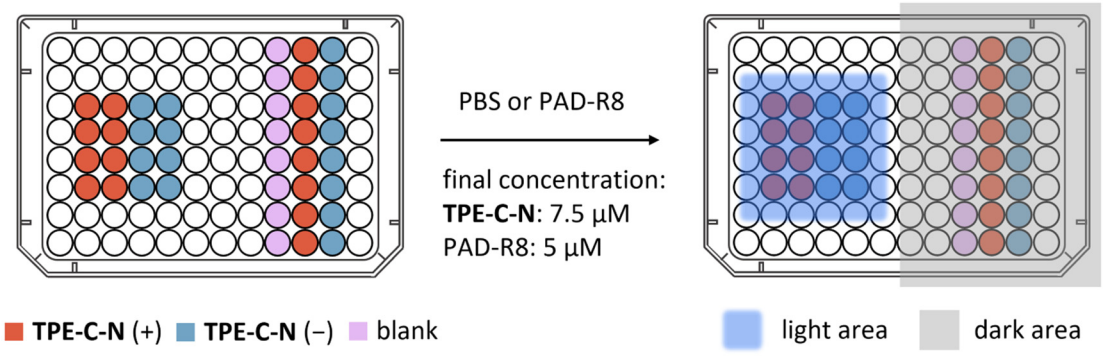
A431 cells were incubated for 48 h, the other cells were incubated for 24 h for cell attachment. After the removal of medium, cells except for the blank group were washed with PBS (750 μL/well) twice. In this experiment, cells in the blank group were incubated with medium only. Then PBS (750 μL) or **TPE-C-N** (750 μL, 10 μM in PBS) was added per well and incubated with cells at 25 °C in darkness for 5 min. Cells were covered by aluminum film to ensure a dark environment. **Cy-5** (250 μL, 40 μM in PBS) was then added per well. For the light irradiation plates, cells were irradiated by 365 nm LED light (intensity: 10 mW/cm^2) at 25 °C for 10 min. For the dark control plates, cells were covered by aluminum film and incubate at 25 °C in darkness for 10 min.

After being washed with PBS containing 0.5% (w/v) heparin sodium (750 μL/well, once), cells were harvested with 0.25 w/v% trypsin-1 mM EDTA (0.1 mL/well) and suspended in medium (0.5 mL) supplemented with 10% FBS. The cells were collected and washed by PBS (0.2 mL) through centrifugation at 3000 rpm for 5 min. The cells were then resuspended in PBS (0.3 mL).

The samples were analyzed by a FACS Attune (Thermo Fisher Scientific) using a yellow laser (561 nm) and a YL3 channel filter (695/40 nm). Each sample was analyzed for 10,000 events.

Relative gate% was similarly calculated according to the equation shown in section 7.1.

8. Cell Viability



A549 cells were seeded into two 96 well microplates (Falcon® 96-well Clear Flat Bottom TC-treated Culture Microplate, Coning, USA) at a density of 1×10^4 cells per well. Every plate has blank wells in which there is no cells but medium. The cells were incubated for 24 h for cell attachment. After the removal of medium, cells were washed with PBS twice. For the R8-PAD (+) plate, PBS or **TPE-C-N** (75 μL,10 μM in PBS) was added per well and incubated with cells at 25 °C for 5 min. Cells were covered by aluminum film to ensure a dark environment. Then, R8-PAD (25 μL, final concentration: 5 μM in PBS) was added per well. In the light irradiation area, cells were irradiated by 365 nm LED light (10 mW/cm^2) at 25 °C for 5 min. In the dark control area, cells were covered by aluminum film and incubate at 25 °C for 5 min. For the R8-PAD (−) plate, PBS (25 μL) was added per well instead of R8-PAD solution. In the light irradiation area, cells were irradiated by 365 nm LED light (10 mW/cm^2) at 25 °C for 5 min. In the dark control area, cells were covered by aluminum film and incubate at 25 °C for 5 min. All cells were then washed with PBS containing 0.5% (w/v) heparin sodium once. Cells were incubated with DMEM at 37 °C for another 30 min or 24 h in a 5% CO_2 humidified incubator. Subsequently, CCK-8 (10 μL) was added to each well and the cells were incubated at 37 °C in a 5% CO_2 humidified incubator. After 2 h, the absorbance at 450 nm was measured using 800TS Absorbance Microplate Reader (BioTek Instruments, USA).

For phototoxicity experiment, A549 cells were seeded into 96 well microplates at a density of 1×10^4 cells per well. The cells were incubated for 24 h for cell attachment. After the removal of medium, cells were washed with PBS twice. Cells were irradiated by 365 nm LED light (10 mW/cm^2) at 25 °C for 0, 5, 10, 15, 20, and 25 min. Cell viability was evaluated by CCK-8 assay.

Cell viability was calculated using the following equation:

Cell viability (%) = $(A_{test} - A_{blank}) / (A_{control} - A_{blank}) \times 100$

A_{test}: Absorbance of cells under different treatments

A_{blank}: Absorbance of blank wells

$A_{control}$: Absorbance of cells with none of **TPE-C-N**, R8-PAD, and light irradiation

9. ASO cell membrane permeabilization

Two types of DMEM used in this section are following: DMEM-A: low glucose, phenol-red free, without FBS; DMEM-B: low glucose, containing phenol-red and 5% FBS. **TPE-C-N** (2 mM in DMF) was diluted with DMEM-A to a concentration of 40 μM. ASO (50 μM) was diluted with DMEM-A and DMEM-B to a concentration of 1.92 μM, respectively. The ASO sequence are as follows, NEG#11 (NC-ASO): G^A^mC^c^a^a^a^g^c^c^a^t^G^T^g; hMALAT1-6668-LNA(16): G^C^A^t^t^c^t^a^a^t^a^g^c^A^G^C. (Uppercase: LNA (Locked Nucleic Acid); lowercase: DNA; ^: Phosphorothioate linkage; mC: 5-methylcytosine).

MIA PaCa-2-Luc cells were seeded in 96 well plates (Corning® Costar® 96-Well, Flat-Bottom Microplate, lid) at a density of 1.8×10^4 cells per well. Cells were incubated for 24 h for cell attachment. After the removal of medium, cells were washed with PBS twice. Then DMEM-A (50 μL) and **TPE-C-N** (25 μL, 40 μM in DMEM-A) were added per well. For **TPE-C-N** unpretreated cells, DMEM-A (50μL) and DMF (25 μL, 2.0% (v/v) in DMEM-A) were added per well. All cells were covered by aluminum film and incubated at 25 °C for 5 min. ASO (25 μL, 1.92 μM in DMEM-A) was then added per well. For ASO untreated cells, distilled water (25 μL/well, 3.8% (v/v) in DMEM-A) was added. Cells in the light irradiation area were irradiated by 365 nm LED light (10 mW/cm^2) at 25 °C for 10 min. Cells in the dark control area were covered by aluminum film and incubate at 25 °C for 10 min. After being washed with PBS containing 0.5% (w/v) heparin sodium once, DMEM-B (25 μL/well) and ASO (25 μL/well, 1.92 μM in DMEM-B) were incubated with cells at 37 °C in a 5% CO_2 humidified incubator for 30 min. For ASO untreated cells, DMEM-B (25 μL) and distilled water (25 μL, 3.8% (v/v) in DMEM-B) were added per well. All cells were then washed by PBS once. Cells were incubated with DMEM-B at 37 °C in a 5% CO_2 humidified incubator for 3.5 h.

Cell lysis, RNA extraction, and cDNA synthesis were performed by using the Cell Lysis & RT Kit. Solution A was prepared by mixing 24.85 μL of Lysis Solution and 0.15 μL of gDNA Remover per well. Solution B was prepared by mixing 4.75 μL of Stop Solution and 0.25 μL of Nase Inhibitor. Solution C was prepared by mixing 4 μL of 5×RT Master Mix and 12 μL of Nuclease-free water. Solution C was pre-dispensed at 16 μL per well in a PCR plate (VIOLAMO,

96 well PCR Plate (Non-Skirted)). The cells that were treated with ASO were washed once with PBS (120 μL/well). Solution A (25 μL/well) was added, and the mixture was stirred on the shaker (Fisher Scientific, FISHER MICROPLATE VORTEX) for 5 to 10 min. Cell lysis was confirmed under a microscope, followed by the addition of solution B (5 μL/well). The mixture was stirred for 30 s on the shaker and then allowed to stand for 1.5 min. The cell lysate (4 μL/well) was then added to a PCR plate containing solution C (16 μL/well). The plate was covered with a lid (VIOLAMO, 8 strips PCR Tube Cap (Dome)) and centrifuged at 4 °C for 3 min at 3200 rpm. Reverse transcription was performed using a thermal cycler. The temperature cycling conditions were set as follows: 37 °C for 20 min, 50 °C for 5 min, 98 °C for 5 min, and finally ending at 4 °C. Following this, the cDNA and the cell plate were stored at −80 °C. Real-time PCR (RT-PCR) was conducted using the reverse transcribed cDNA to quantify the expression level of *MALAT1* RNA. *GAPDH* mRNA was used as an internal standard, and the analysis was performed using the ΔΔCt method.

The DNA primers sequences are following:
hGAPDH-Fw (GAGTCAACGGATTTGGTCGT);
hGAPDH-Rv (GACAAGCTTCCCGTTCTCAG);
hMALAT1-F4 (GGTCTCCCCACAAGCAACTT);
hMALAT1-R4 (AACCCACCAAAGACCTCGAC).

A total volume of 20 μL was prepared by mixing 2×Master mix (10 μL, ABI PowerUp™ SYBR™ Green Master Mix), primer set (1 μL, final concentration: 200 nM), cDNA (2 μL), and distilled water from Otsuka (7 μL). This mixture was dispensed into the real-time PCR 96-well plate (ABI, MicroAmp™ Fast 96-well Reaction Plate (0.1mL)). Separate wells were prepared for the detection of *GAPDH* mRNA and *MALAT1* RNA. The plate was sealed by adhesive film (ABI, MicroAmp™ Optical Adhesive Film) and centrifuged by the microplate spinner (Labnet, MPS1000) for 10 s. The plate was set in the thermal cycler (ABI StepOne Plus™ Real-Time PCR System), heated at 95 °C for 30 s, followed by a denaturation at 95 °C for 3 s and an extension at 60 °C for 30 s. This denaturation and extension cycle was repeated for a total of 45 cycles.

10. Supplementary Figures

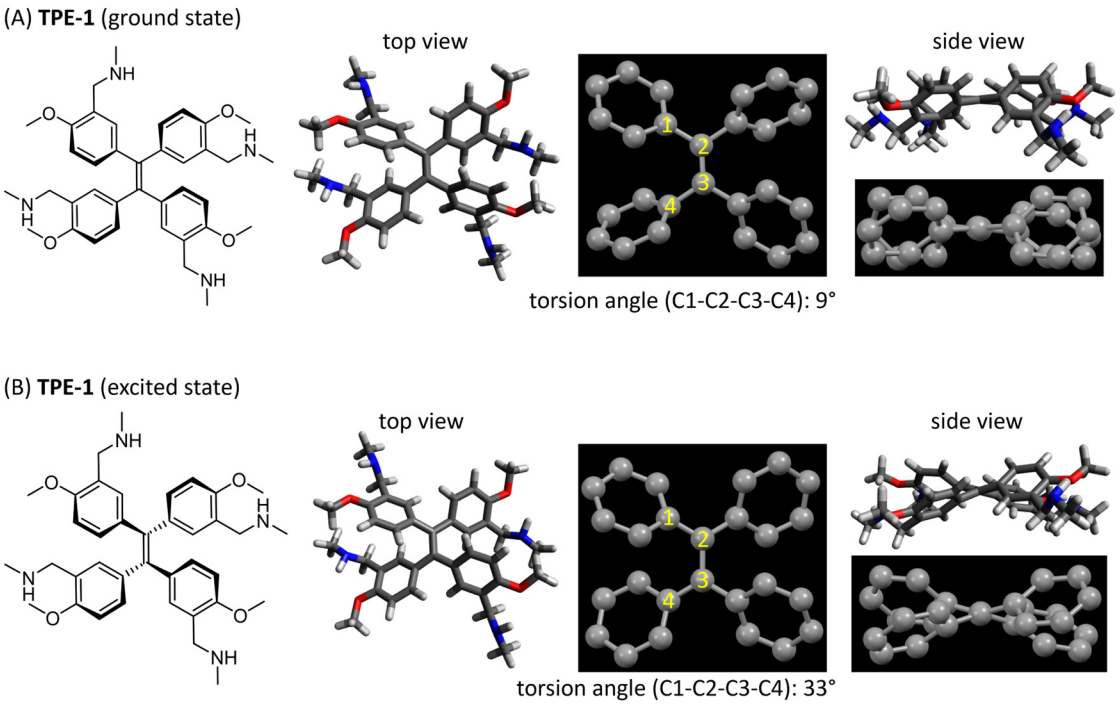


Figure S1. Energy-minimized structures of model compound **TPE-1** in the (A) ground and (B) excited states. Calculation was carried out at M062X/6-31G(d,p) level.

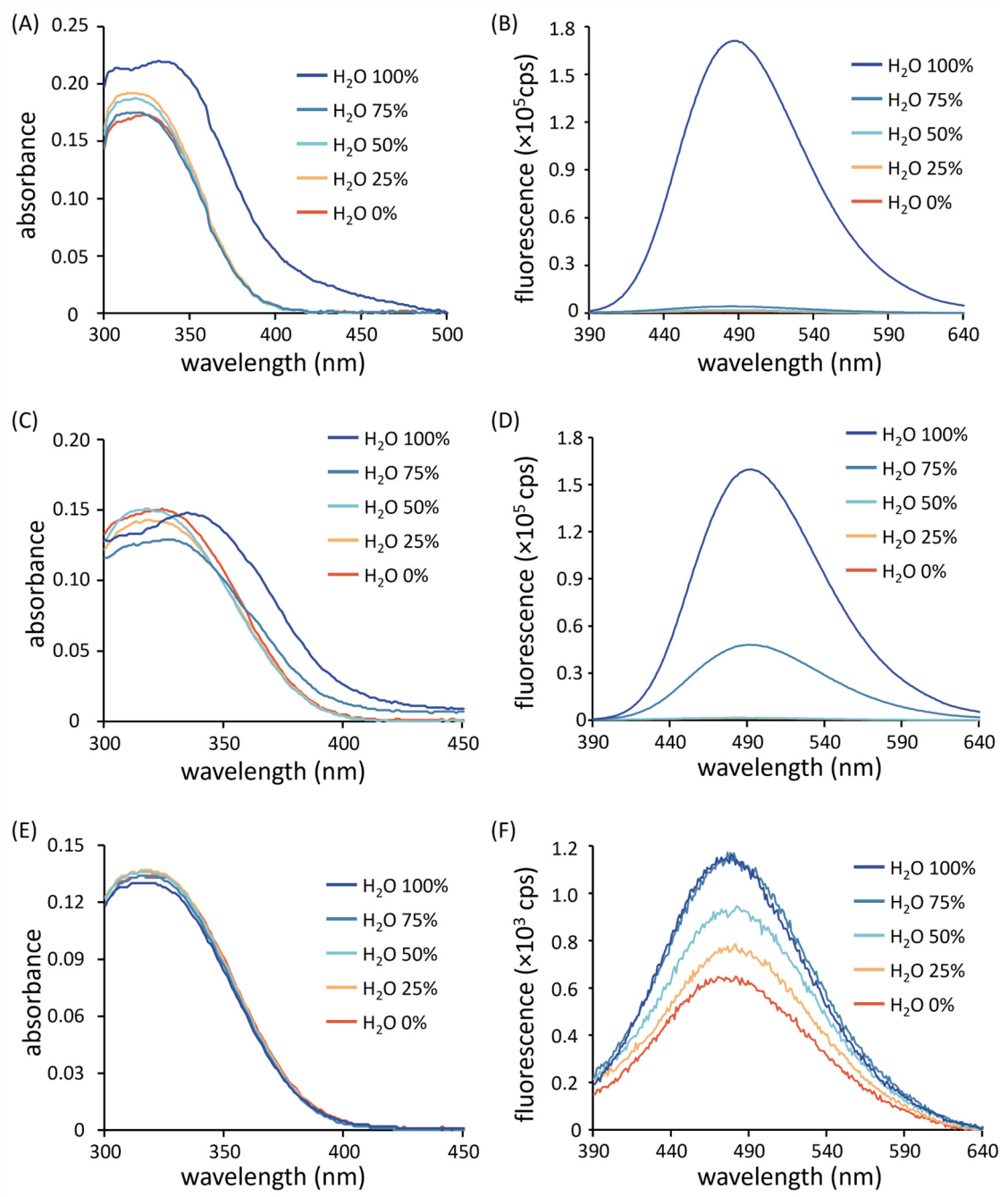


Figure S2. (A) UV-vis absorption and (B) fluorescence spectra of **TPE-C-N** (10 μM) in MeCN with different amounts of Milli-Q water. λ_{ex} = 330 nm. (C) UV-vis absorption and (D) fluorescence spectra of **TPE-C** (10 μM) in MeCN with different amounts of Milli-Q water. λ_{ex} = 330 nm. (E) UV-vis absorption and (F) fluorescence spectra of **TPE-N** (10 μM) in MeCN with different amounts of Milli-Q water. λ_{ex} = 330 nm.

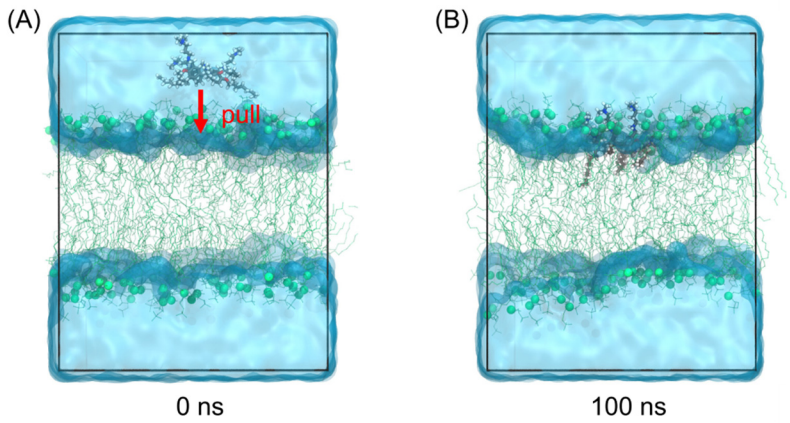


Figure S3. Snapshots of the steered MD simulation at (A) 0 ns and (B) 100 ns. POPC molecules are represented by green lines and spheres (phosphorus atoms). The blue, red, and white colors represent nitrogen, oxygen, and hydrogen atoms constituting **TPE-C-N**. The transparent cyan regions indicate water.

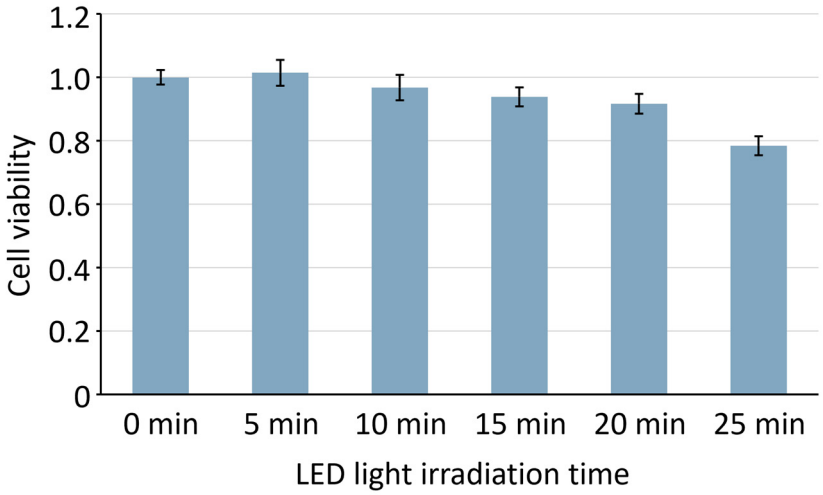


Figure S4. Cell viability of A549 cells under light irradiation for different time. Results are presented as the mean ± standard deviation of eight samples (n = 8). LED light irradiation: 365 nm, 10 mW/cm^2.

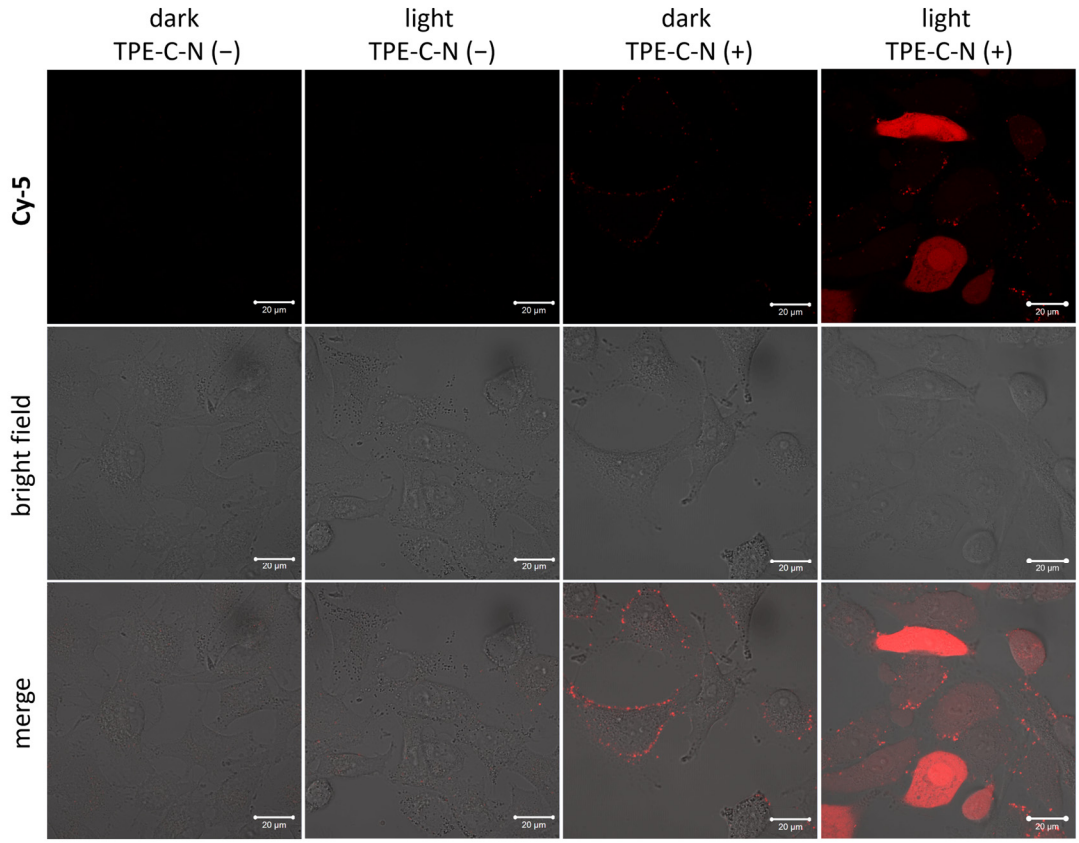


Figure S5. Independent replication experiments of **Cy-5** penetration experiments. CLSM images of A549 cells incubated with **Cy-5** (10 μM) under different treatments. LED light irradiation: 365 nm, 10 mW/cm^2, 5 min. **TPE-C-N**: 10 μM. λ_{ex} = 633 nm, λ_{det} = 647–759 nm. Scale bar for all images is 20 μm.

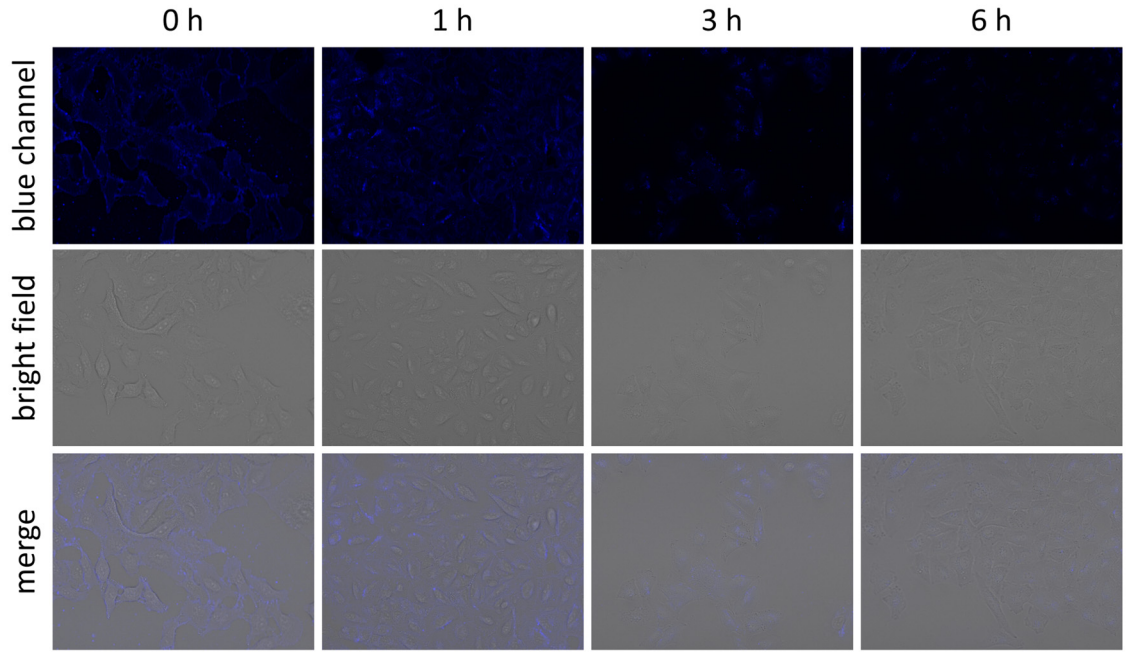


Figure S6. Time-dependent fluorescence images of A549 cells incubated with **TPE-C-N** (10 μM) under LED light irradiation (intensity: 10 mW/cm^2) at 25 °C for 5 min. λ_{ex} = 350/50 nm, λ_{det} = 500/40 nm.

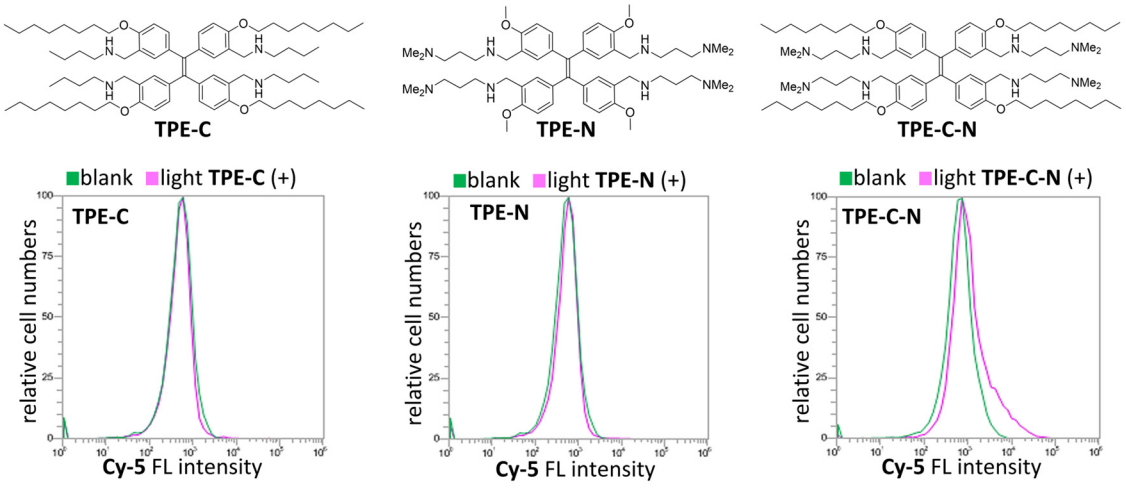


Figure S7. Flow cytometric analysis of A549 cells treated with **Cy-5** (10 μM) in the presence of **TPE**s (**TPE-C**, **TPE-N**, and **TPE-C-N**) and with LED light irradiation. LED light irradiation: 365 nm, 10 mW/cm^2, 10 min. **TPE**s: 10 μM.

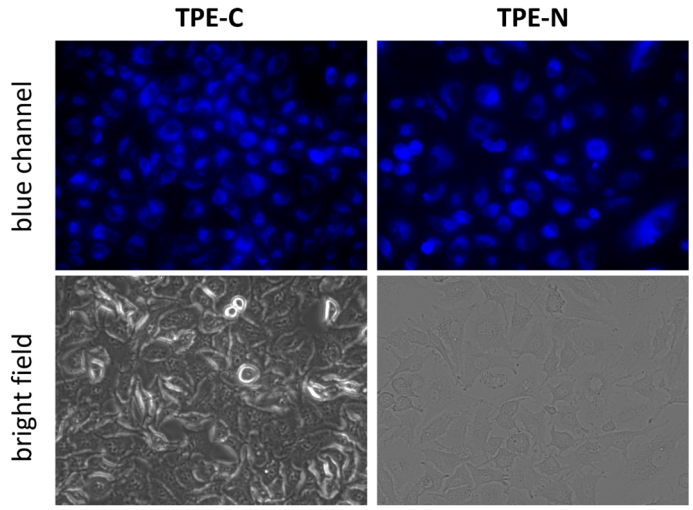


Figure S8. Fluorescence images of A549 cells incubated with **TPE-C** (bright field imaged with phase-contrast microscopy) or **TPE-N** (bright field imaged with traditional microscopy) with LED light irradiation (intensity: 10 mW/cm^2) at 25 °C for 5 min. **TPE**s: 10 μM. λ_{ex} = 350/50 nm, λ_{det} = 500/40 nm.

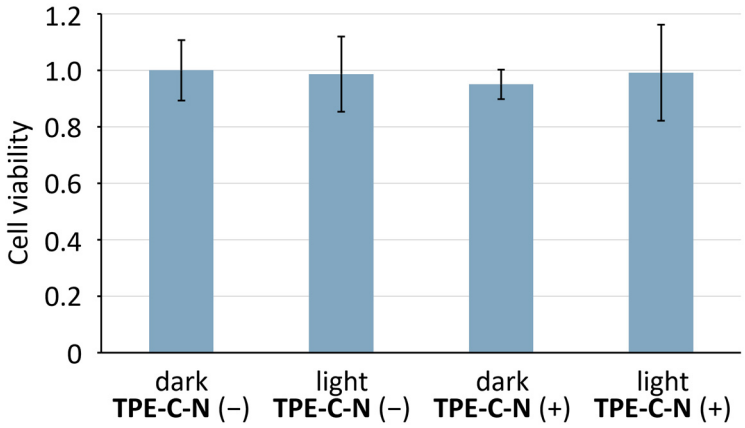


Figure S9. Cell viability of A549 cells under different treatments and then incubated in medium at 37 °C for 30 min. Results are presented as the mean ± standard deviation of eight samples (*n* = 8). LED light irradiation: 365 nm, 10 mW/cm^2, 5 min. **TPE-C-N**: 10 μM. *Data were obtained from Fig. 5C.

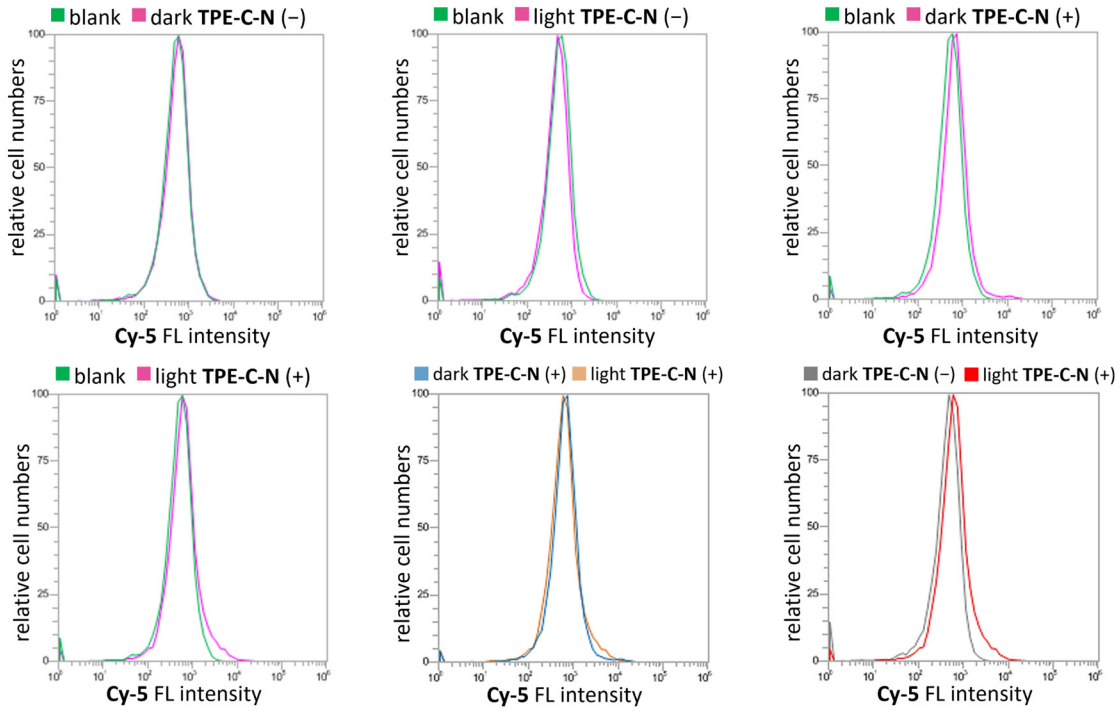


Figure S10. Flow cytometric analysis of A549 cells treated with **Cy-5** (10 μM) at 4 °C under different treatments. LED light irradiation: 365 nm, 10 mW/cm^2, 10 min. **TPE-C-N**: 10 μM.

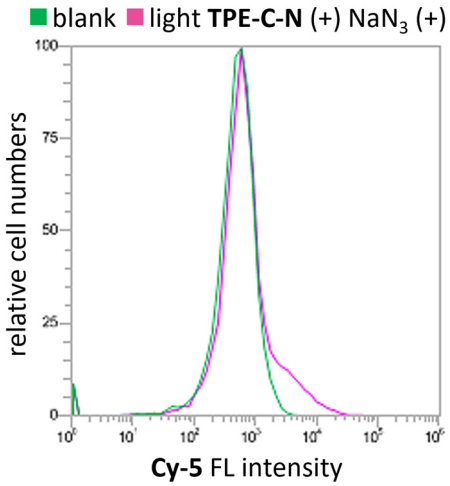


Figure S11. Flow cytometric analysis of A549 cells treated with **Cy-5** (10 μM) in the presence of **TPE-C-N** and NaN_3 (10 mM) with LED light irradiation. LED light irradiation: 365 nm, 10 mW/cm^2, 10 min. **TPE-C-N**: 10 μM.

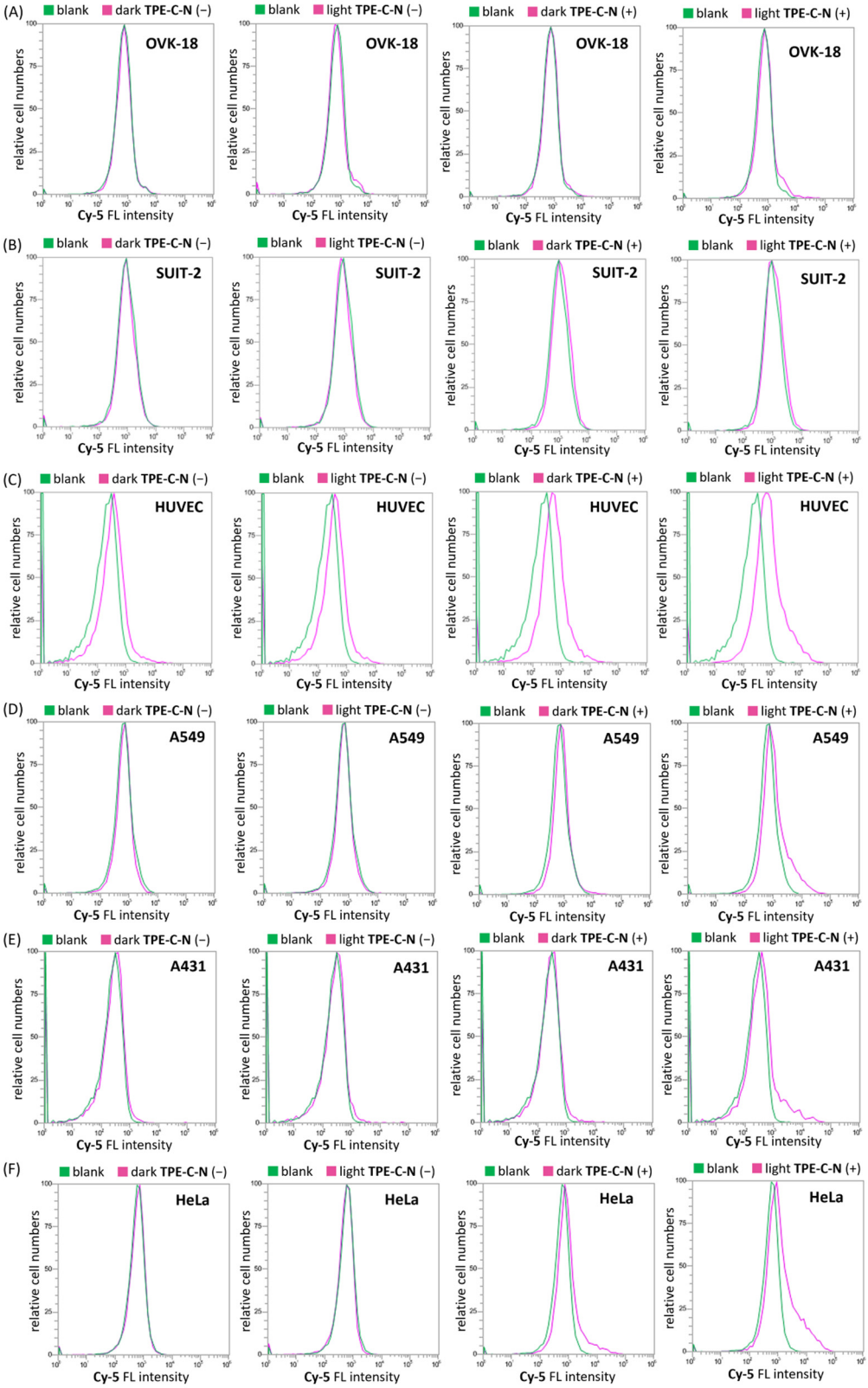


Figure S12. Flow cytometric analysis of (A) OVK-18, (B) SUIT-2, (C) HUVEC, (D) A549 (obtained in Fig. S10), (E) A431, and (F) HeLa cells incubated with **Cy-5** (10 μM) under different treatments. LED light intensity: 10 mW/cm^2, **TPE-C-N**: 10 μM.

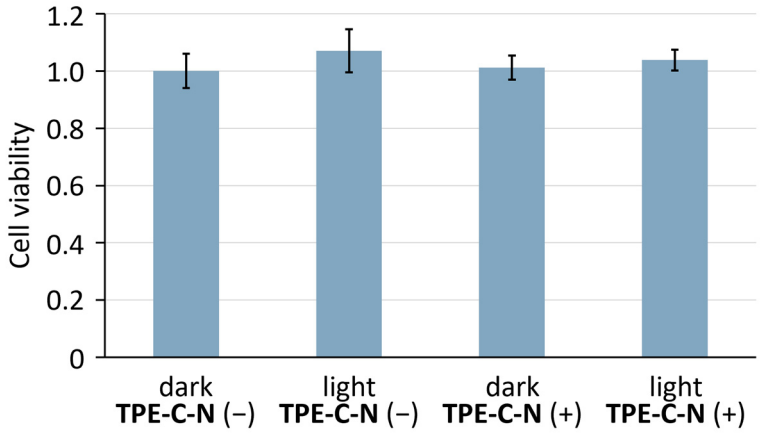


Figure S13. Cell viability of HeLa cells under different treatments and then incubated in medium at 37 °C for 24 h. Results are presented as the mean ± standard deviation of eight samples (n = 8). LED light irradiation: 365 nm, 10 mW/cm^2, 5 min. **TPE-C-N**: 10 μM.

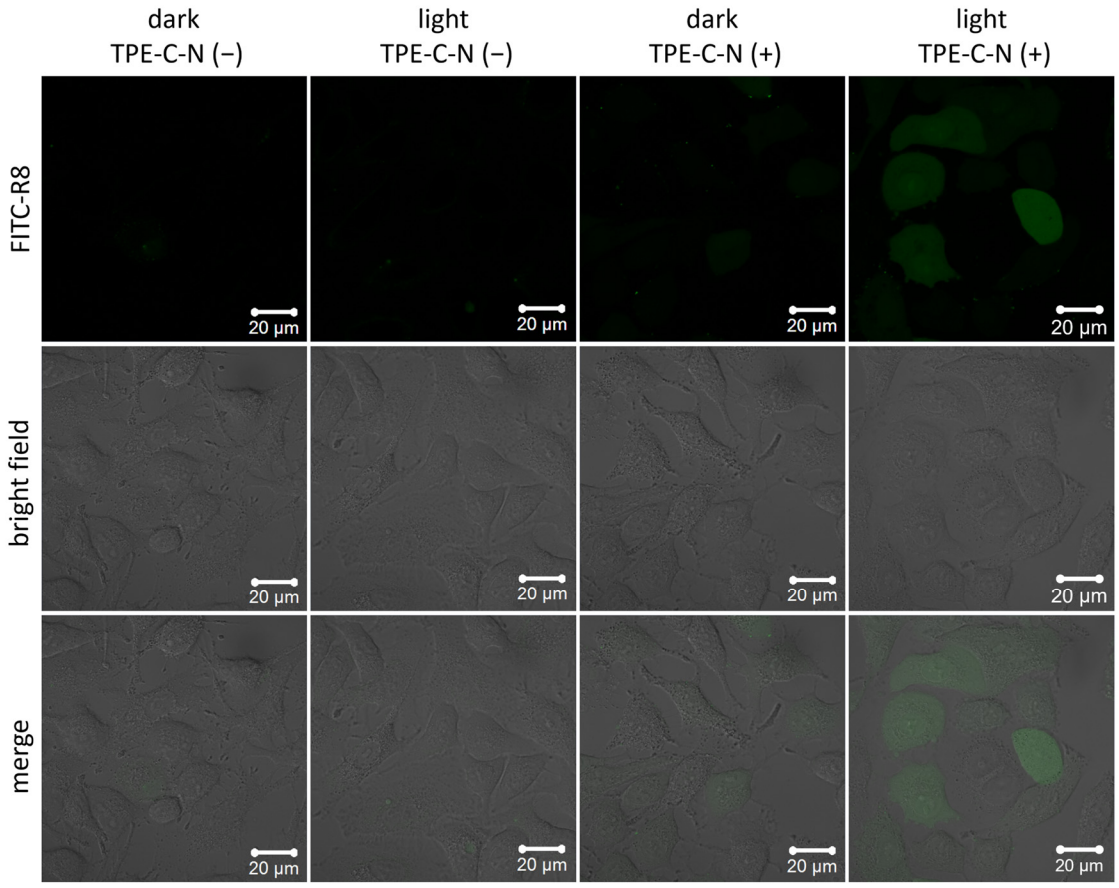


Figure S14. Independent replication experiments of FITC-R8 penetration experiments. CLSM images of A549 cells incubated with FITC-R8 (10 μM) under different treatments. LED light irradiation: 365 nm, 10 mW/cm^2, 5 min. **TPE-C-N**: 10 μM. λ_{ex} = 488 nm, λ_{det} = 493–630 nm.

Scale bar for all images is 20 μm.

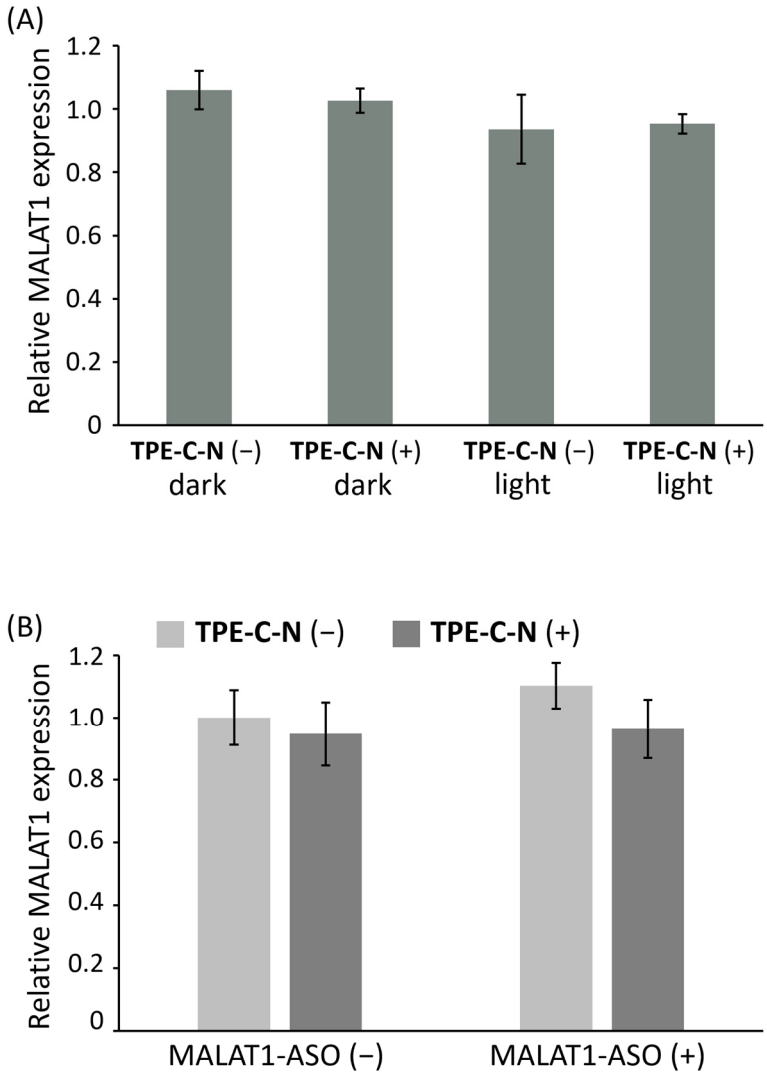


Figure S15. (A) Relative expression level of *MALAT1* in NEG-ASO transfected MIA PaCa-2-Luc cells with different treatments. Results are presented as the mean ± standard deviation of three samples (n = 3). NEG-ASO: 320 nM; **TPE-C-N**: 10 μM. LED light irradiation: 365 nm, 10 mW/cm^2, 10 min. (B) Relative expression level of *MALAT1* in MIA PaCa-2-Luc cells with different treatments under darkness. Results are presented as the mean ± standard deviation of eight samples (n = 8). MALAT1-ASO: 480 nM; **TPE-C-N**: 10 μM.

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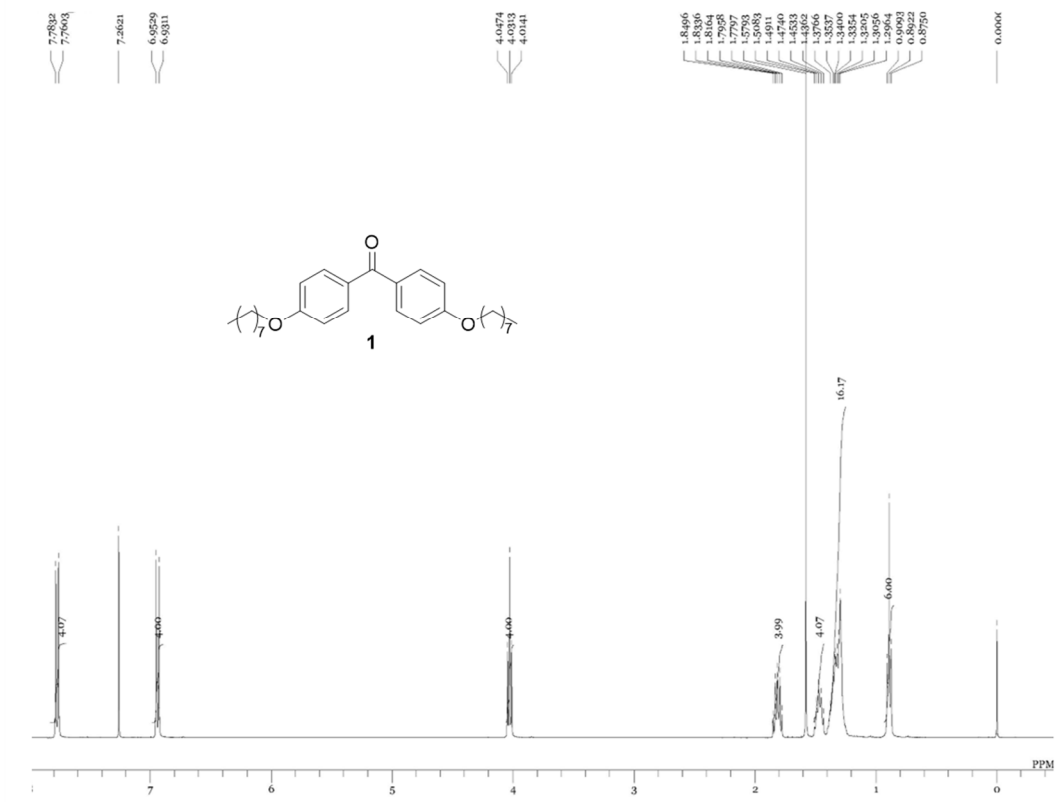
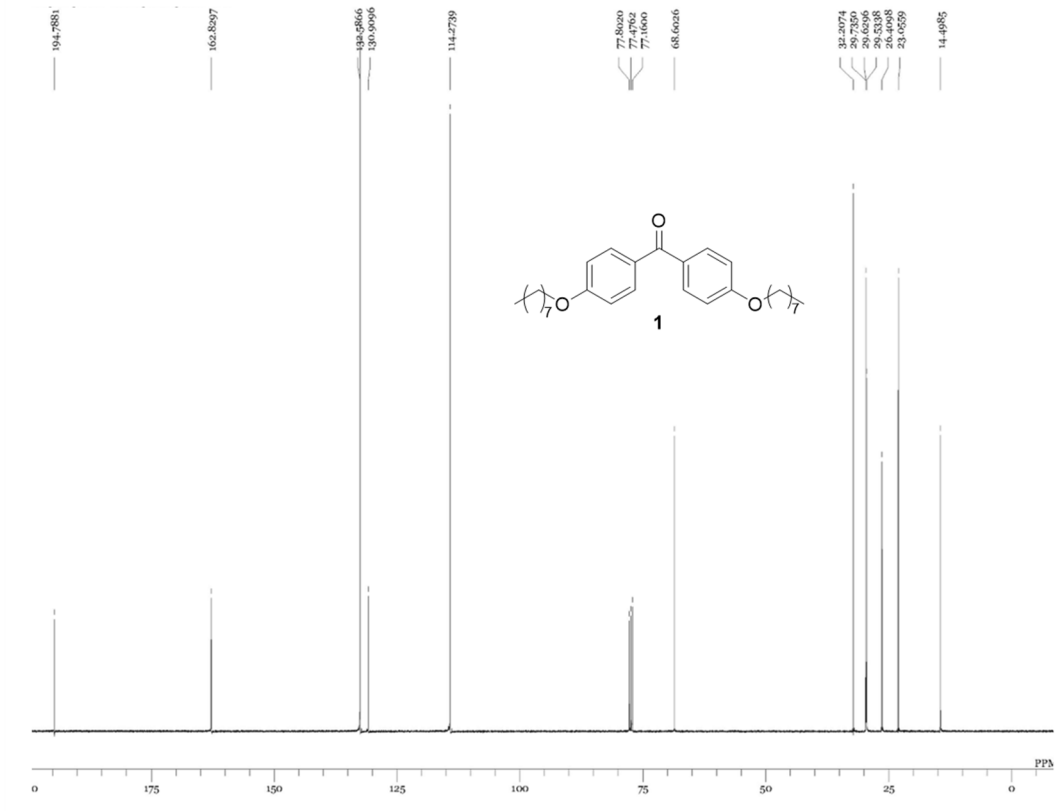
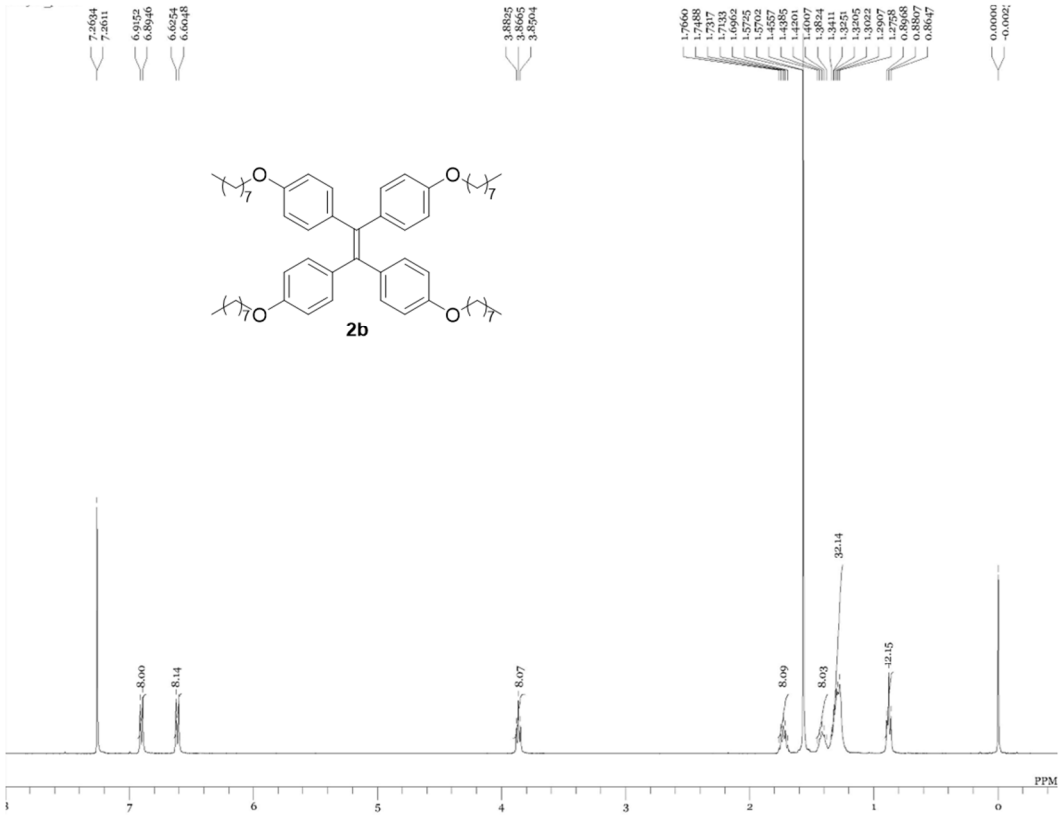
12. NMR Charts



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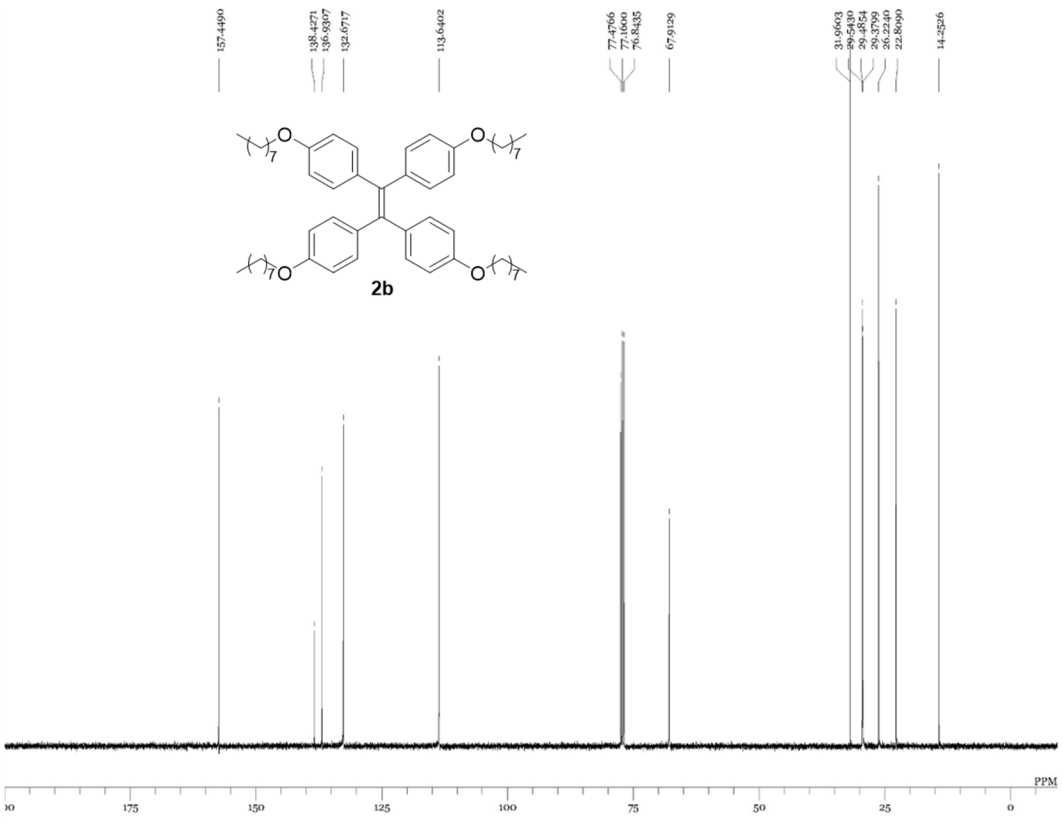
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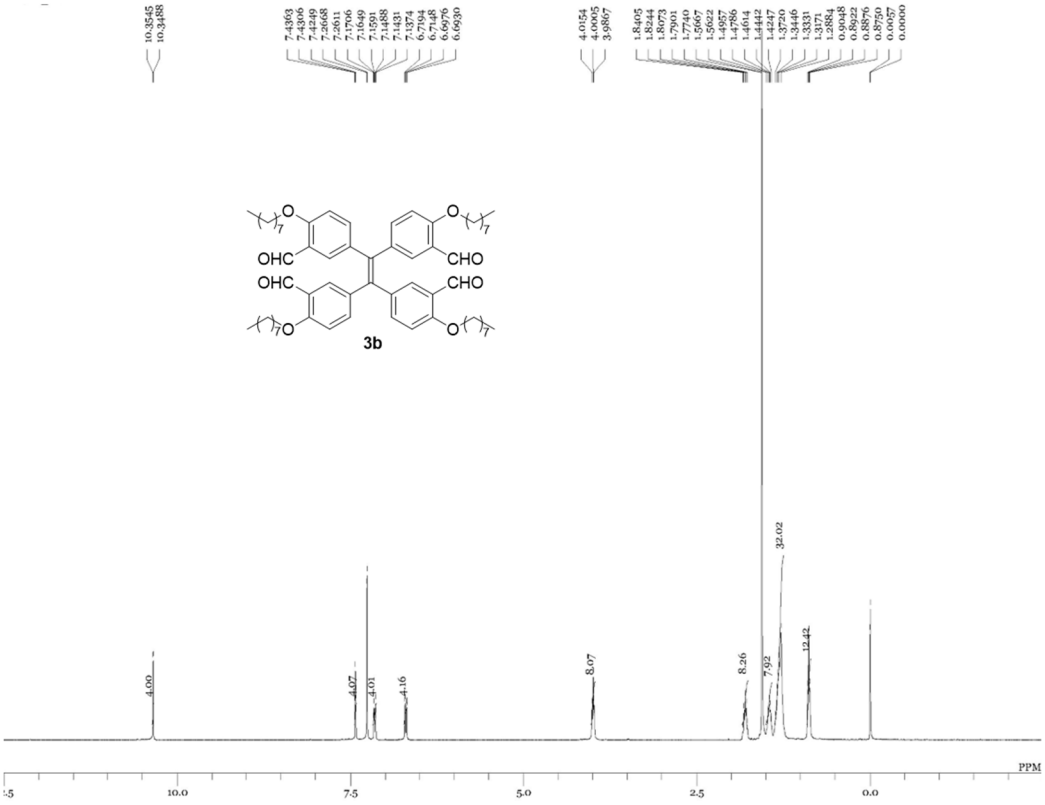
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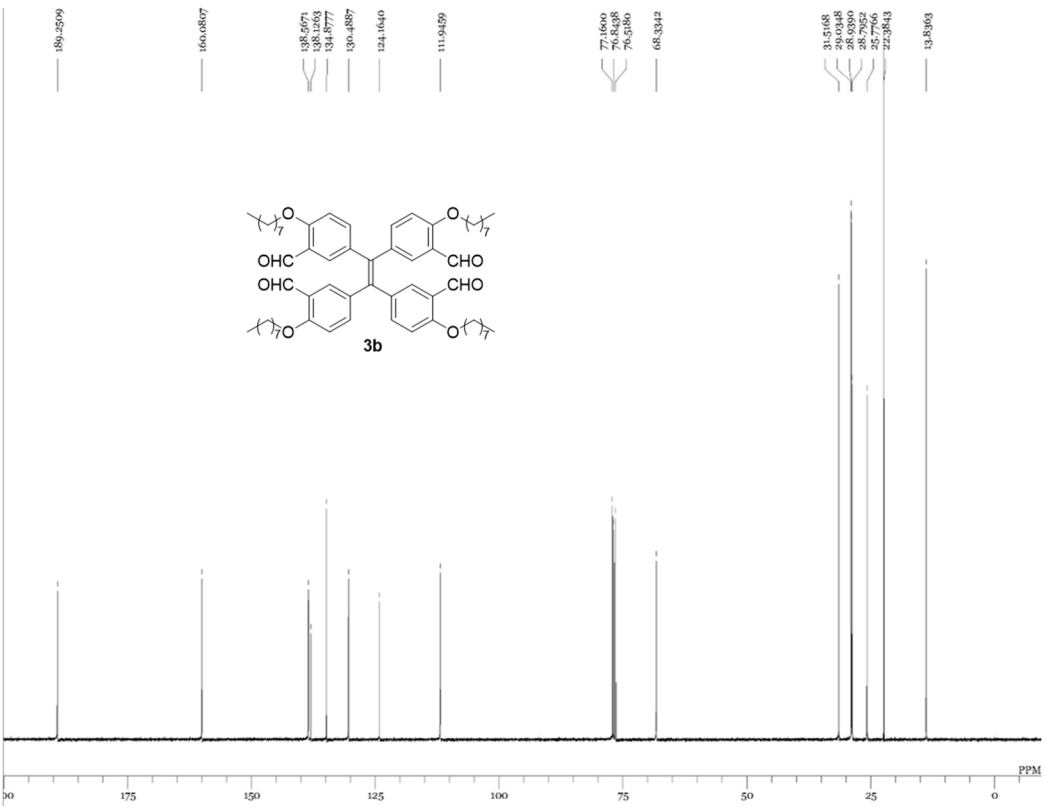
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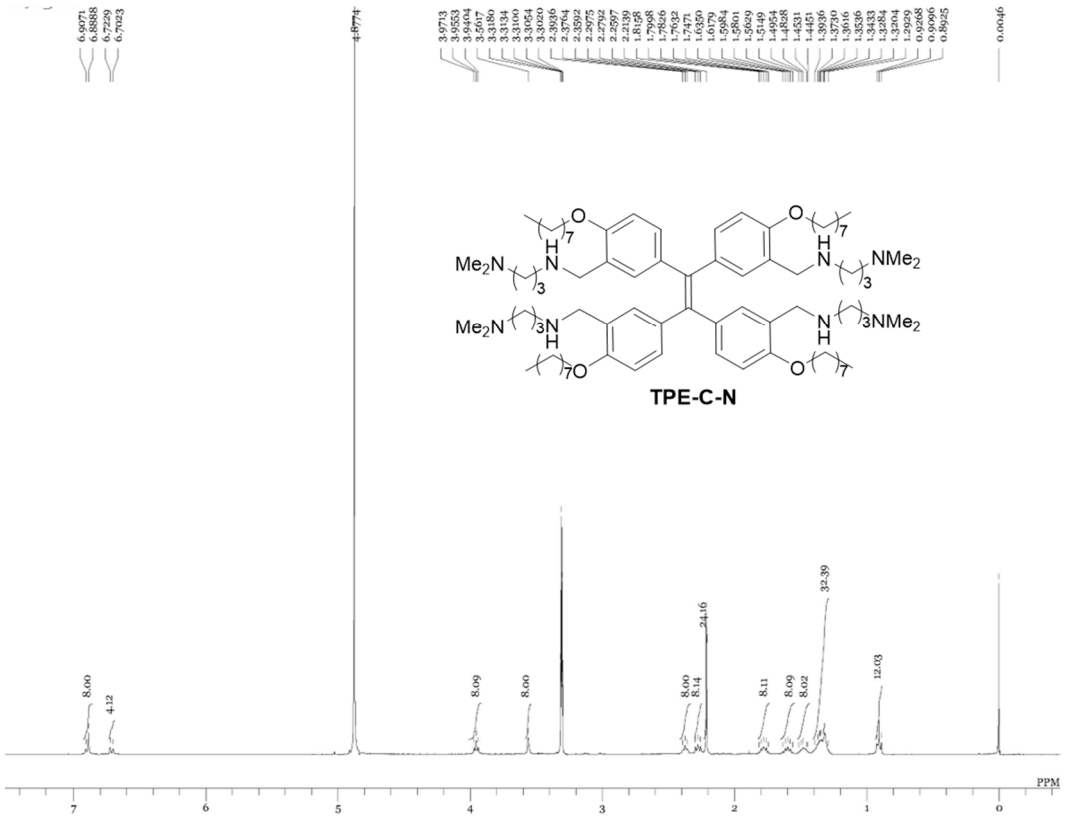
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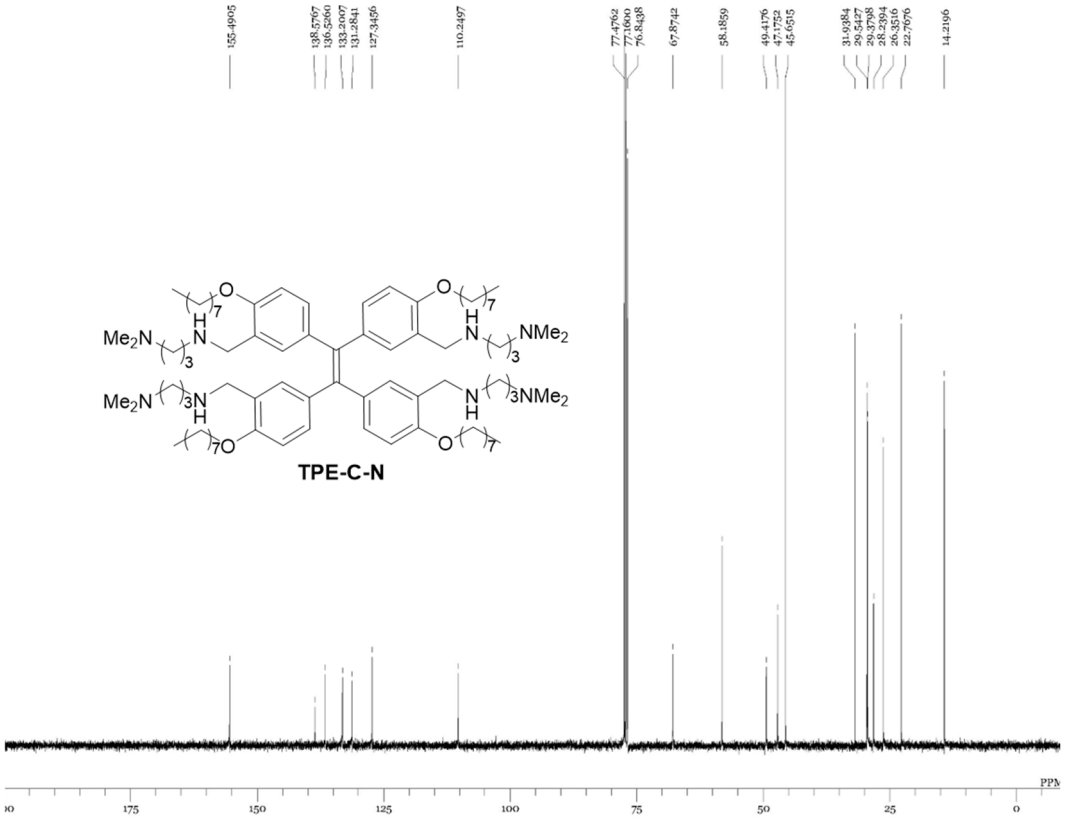
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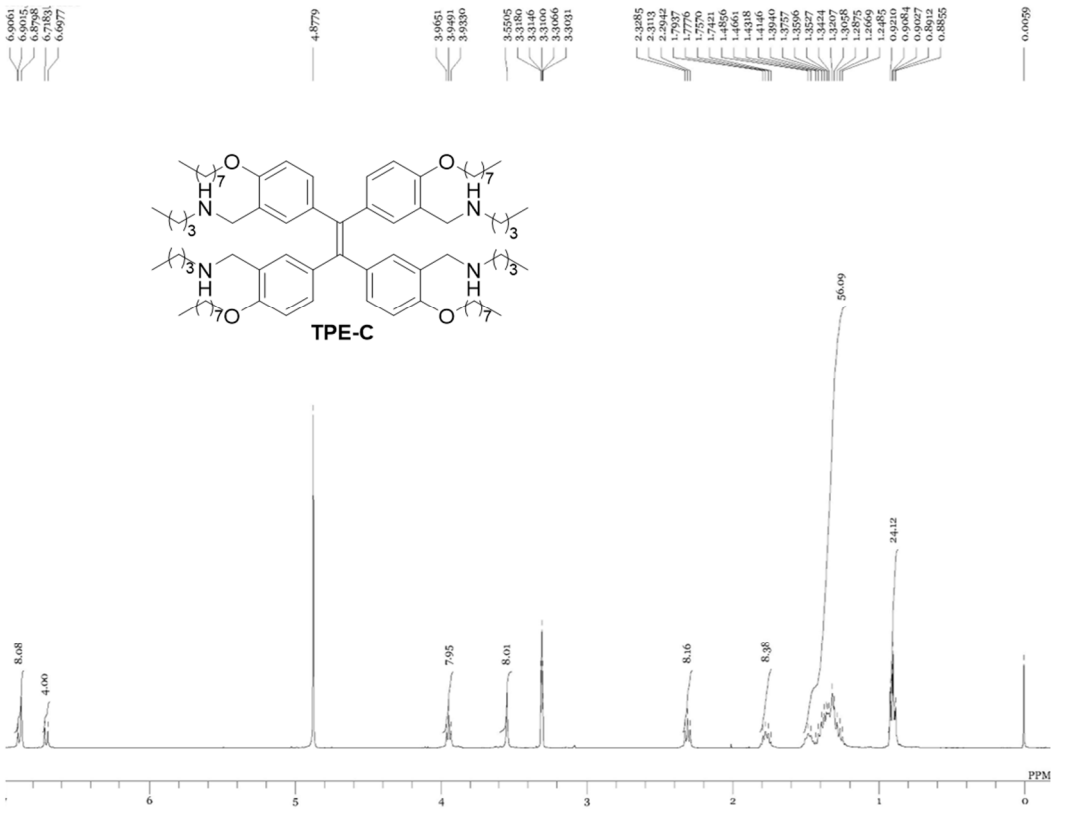
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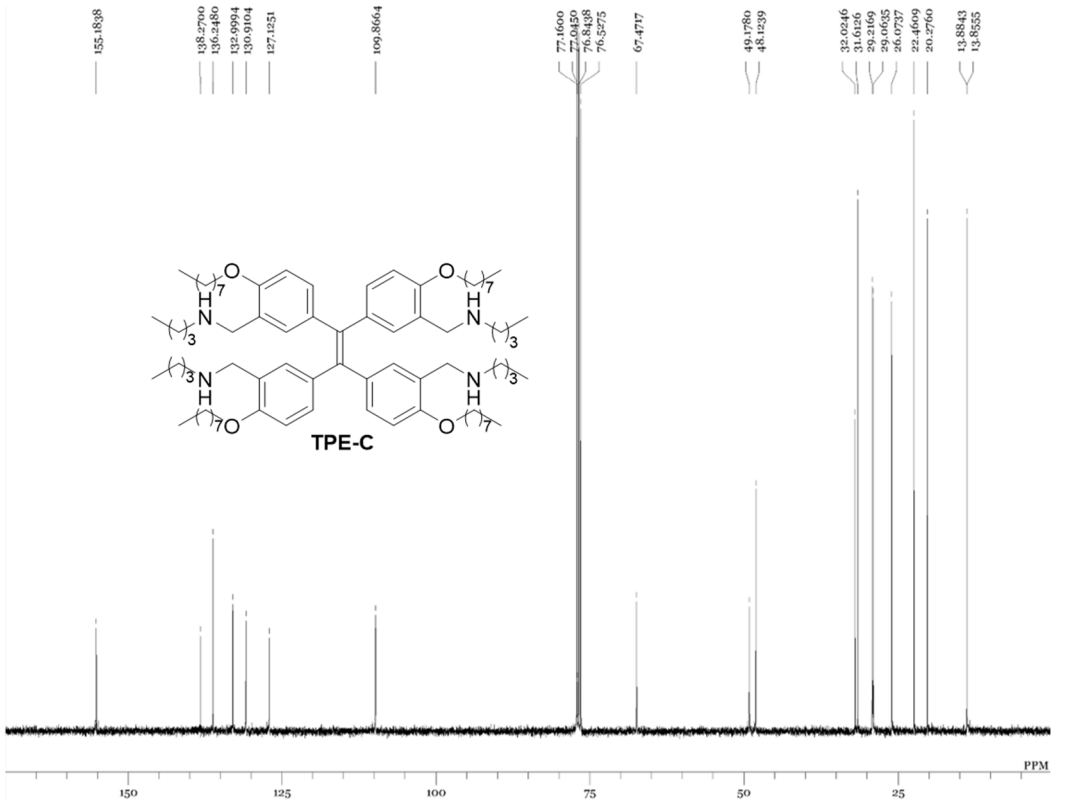
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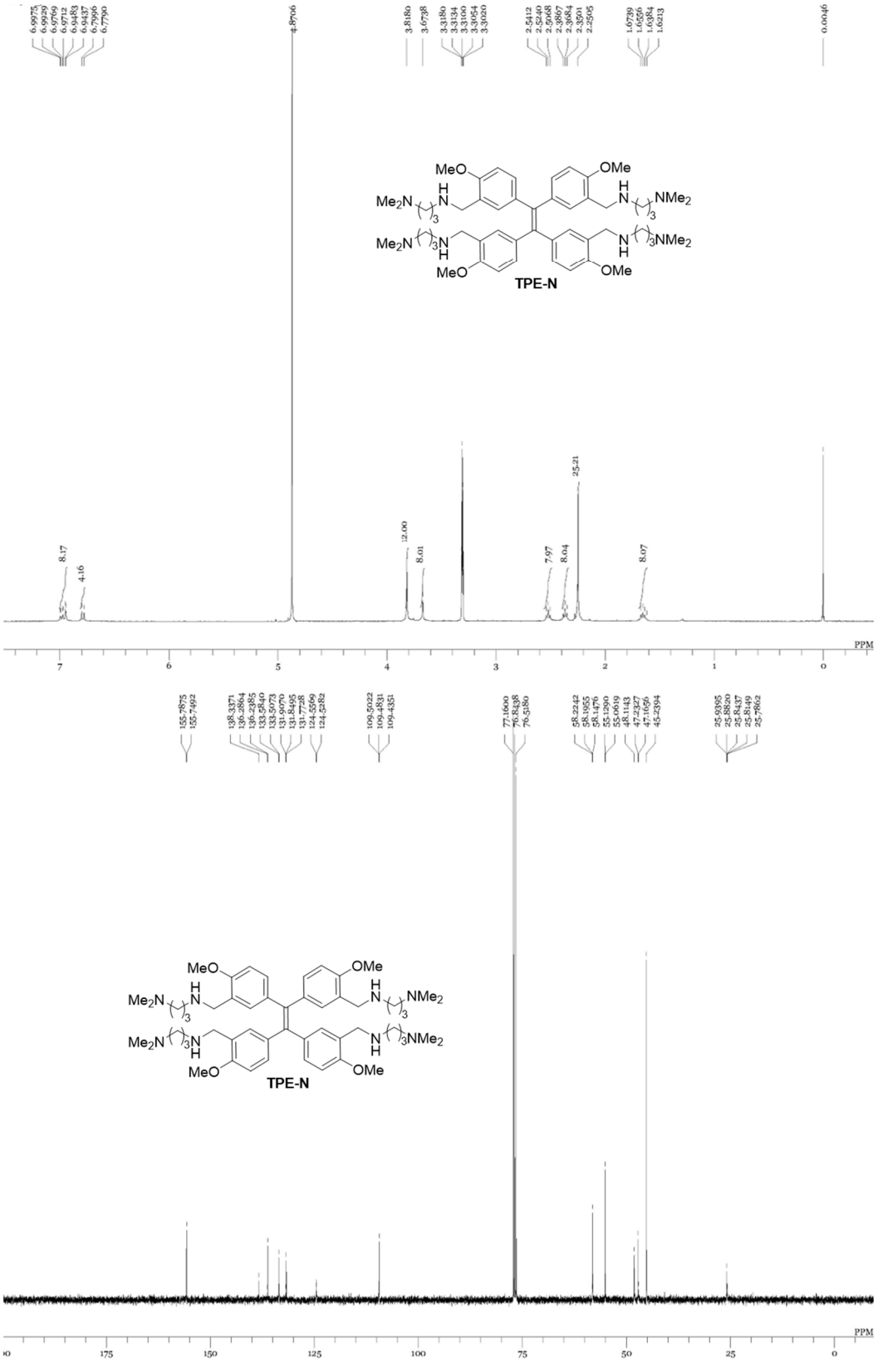
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