Supporting Information

Intramolecular π-π Stacking-Regulated ROS Amplification in Water-Soluble GalNAc-Functionalized Tetraphenylethylene Photosensitizers for Hepatocellular Carcinoma

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1. Synthesis

1.1 Materials and Instruments

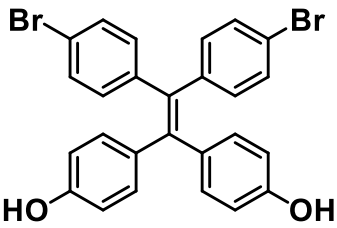
All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions unless otherwise noted. Dry DMF, DCM, and THF were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns, while anhydrous ACN and MeOH were purchased from commercial suppliers and stored under argon. All reagents were of ACS grade and used as received from Acros, Sigma-Aldrich, or Merck without further purification unless otherwise specified. Reactions were monitored by thin-layer chromatography (TLC) on Merck silica gel plates (F-254) under UV light, visualized with ethanolic phosphomolybdic acid, basic $KMnO_4$, or ethanolic ninhydrin solutions. Flash column chromatography was performed on Merck silica gel (60, particle size 0.040-0.063 mm) using a pump-assisted system.

Deuterated solvents were purchased from Cambridge Isotope Laboratories. NMR spectra were recorded on a Bruker AVIII 400 spectrometer (^1H at 400 MHz, ^{13}C at 100 MHz). Chemical shifts (δ) are reported in ppm relative to TMS, with residual solvent signals used as internal references at 298 K: δ_H = 7.26 ($CDCl_3$), 3.31 (CD_3OD), 2.50 (DMSO-d_6), 2.05 (acetone-d_6); δ_C = 77.00 ($CDCl_3$), 49.00 (CD_3OD), 39.52 (DMSO-d_6), 29.84 (acetone-d_6). Spin multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or combinations thereof, with coupling constants (*J*) reported in Hz.

Liquid chromatography-mass spectrometry (LC-MS) was performed on a Bruker microTOF QII coupled with a Dionex U2000 or Agilent 1200 HPLC system. Runs were carried out at a flow rate of 0.5 mL/min with an isocratic gradient of 30% water in acetonitrile over 5 min; the aqueous phase contained 0.1% formic acid. Samples were filtered through 0.22 μm PVDF syringe filters prior to injection.

High-performance liquid chromatography (HPLC) analyses were performed on a Shimadzu LC-20AP system equipped with an SPD-M20A UV detector, using Waters C18 reverse-phase columns. Mobile phases consisted of water containing 0.1% formic acid or trifluoroacetic acid, with flow rates of 1-5 mL/min depending on the run conditions.

1.2 Synthesis of compound **1**



4,4'-(2,2-bis(4-bromophenyl)ethene-1,1-diyl)diphenol (1)

To a 500 mL two-neck round-bottom flask charged with 4,4'-dibromobenzophenone (4.03 g, 18.83 mmol, 1.00 equiv.), 4,4'-dihydroxybenzophenone (6.25 g, 18.38 mmol, 0.98 equiv.), and zinc dust (24.16 g, 369.53 mmol, 19.62 equiv.) in 200 mL of dry THF, $TiCl_4$ (10.0 mL, 91.19 mmol, 4.84 equiv.) was added dropwise under an argon atmosphere at 0 °C using an ice-water bath. After complete addition, the reaction mixture was stirred for 45 min at 0 °C, warmed to room temperature, and refluxed using a standard reflux condenser in an oil bath for 18 h. The reaction progress was monitored by TLC (hexanes/EtOAc = 9/1). Upon completion, the mixture was cooled to room temperature and poured into a 1 L Erlenmeyer flask containing 300 mL of water. The aqueous layer was extracted with EtOAc (200 mL × 3). The combined organic extracts were washed successively with saturated brine (100 mL) and water (100 mL × 2), dried over Na_2SO_4, gravity filtered, and concentrated using a rotary evaporator. The crude product was purified by silica-gel column chromatography (hexanes/EtOAc = 9/1) to afford the desired compound

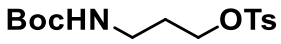
(5.70 g, 10.92 mmol, 58%).

Physical state: off-white foam.

TLC: R_f = 0.30 (Hexs/EtOAc = 9/1).

^{1}H NMR (400 MHz, Acetone-d_6) δ 8.37 (brs, 1H, OH), 7.28 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 4H), 6.84 (d, *J* = 8.6 Hz, 4H), 6.65 (d, *J* = 8.6 Hz, 2H). **^{13}C NMR (100 MHz, Acetone-d_6)** δ 157.3, 144.3, 143.4, 136.7, 135.3, 134.0, 133.3, 131.7, 120.5, 115.5. **HRMS (ESI-TOF)** Calcd for $C_{26}H_{17}Br_2O_2$ $[M-H]^-$: 520.9580. Found: 520.9579.

1.3 Synthesis of compound **2**



3-((*tert*-butoxycarbonyl)amino)propyl 4-methylbenzenesulfonate (2)

A 250 mL two-neck round-bottom flask was charged with 3-aminopropanol (1.6 mL, 21.09 mmol, 1.00 equiv.) and Et_3N (8.4 mL, 60.26 mmol, 2.86 equiv.) in 100 mL of dry DCM. Under an argon atmosphere, the solution was cooled to 0 °C in an ice bath, and Boc_2O (6.0 mL, 26.12 mmol, 1.24 equiv.) was added dropwise. The mixture was stirred at 25 °C for 18 h, and the reaction progress was monitored by TLC. The solvent was removed under reduced pressure using a rotary evaporator, and the residue was extracted with water (25 mL) and DCM (25 mL × 3). The combined organic layers were washed with saturated brine (25 mL) and water (25 mL), dried over Na_2SO_4, gravity filtered, and concentrated. The residue was redissolved in 40 mL of DCM, transferred to a 150 mL two-neck round-bottom flask, cooled to 0 °C in an ice bath, and sequentially treated with Et_3N (8.4 mL, 60.26 mmol, 2.86 equiv.) and TsCl (5.7213 g, 30.00 mmol, 1.42 equiv.). The mixture was stirred at 25 °C for 6 h, and the reaction progress was monitored by TLC (Hexs/EtOAc = 8/2). After removal of solvent by rotary evaporation, the residue was extracted with DCM (100 mL × 3) and water (100

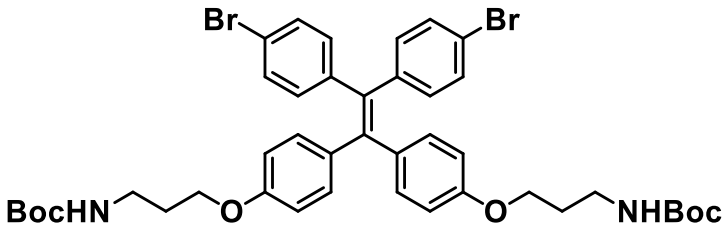
mL). The combined organic layers were washed with saturated brine (50 mL) and water (50 mL × 2), dried over Na_2SO_4, gravity filtered, and concentrated. Purification by silica-gel column chromatography (Hex/EtOAc = 8/2 → 3/1) afforded the product as a liquid (6.87 g, 20.84 mmol, 99%).

Physical state: colorless liquid.

TLC: R_f = 0.30 (Hexs/EtOAc = 8/2).

^{1}H NMR (400 MHz, Acetone-*d*$_6$) δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 7.9 Hz, 2H), 5.96 (brs, 1H, NH), 4.09 (t, *J* = 6.4 Hz, 2H), 3.10 (q, *J* = 4.8 Hz, 2H), 2.46 (s, 1H), 1.86 - 1.79 (m, 2H), 1.37 (s, 9H); **^{13}C NMR (100 MHz, Acetone-*d*$_6$)** δ 145.7, 134.3, 130.8, 128.6, 78.6, 69.4, 66.0, 37.4, 28.6, 21.5. **HRMS (ESI-TOF)** Calcd for $C_{15}H_{23}NNaO_5S$ $[M+Na]^+$: 352.1189. Found 352.1169.

1.4 Synthesis of compound **3**



di-*tert*-butyl((((2,2-bis(4-bromophenyl)ethene-1,1-diyl)bis(4,1-phenylene))bis (oxy))bis(propane-3,1-diyl))dicarbamate (3)

A 100 mL two-neck round-bottom flask was charged with compound **1** (2.11 g, 4.04 mmol, 1.00 equiv.), compound **2** (5.13 g, 15.59 mmol, 3.85 equiv.), and K_2CO_3 (2.01 g, 14.51 mmol, 3.59 equiv.) in 30 mL of acetone. The mixture was refluxed under an argon atmosphere with a reflux condenser in an oil bath for 18 h, and the reaction progress was monitored by TLC (Hexane/EtOAc = 8/2). After cooling, the solvent was removed by rotary evaporation under reduced pressure, and the residue was extracted

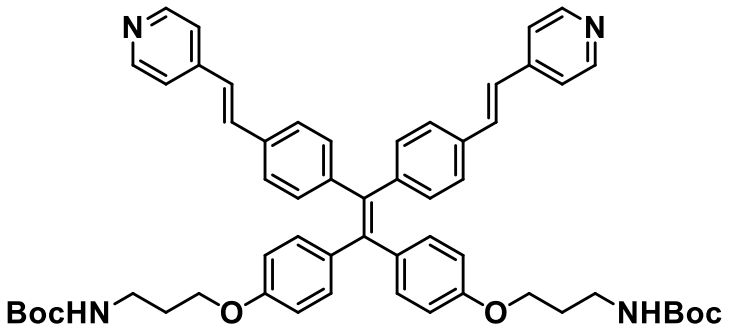
with water (25 mL) and DCM (25 mL × 3). The combined organic layers were washed with saturated brine (25 mL) and water (25 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by silica-gel column chromatography (Hex/EtOAc = 9/1 → 7/3) yielded the desired product as a foam (2.61 g, 3.13 mmol, 77%).

Physical state: off-white foam

TLC: R_f = 0.21 (Hexane/EtOAc = 8/2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.1 Hz, 4H), 6.88 (d, *J* = 8.6 Hz, 4H), 6.85 (d, *J* = 8.4 Hz, 4H), 6.63 (d, *J* = 8.6 Hz, 4H), 4.82 (brs, 2H, NH), 3.94 (t, *J* = 5.7 Hz, 4H), 3.32 - 3.27 (m, 4H), 1.96 - 1.90 (m, 4H), 1.43 (s, 18H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 157.6, 155.9, 142.7, 141.4, 136.4, 135.5, 132.9, 132.4, 130.9, 120.2, 113.7, 78.9, 65.5, 37.8, 29.5, 28.4. **HRMS (ESI-TOF)** Calcd for $C_{42}H_{48}Br_2N_2NaO_6$ $[M+Na]^+$: 857.1771. Found 857.1732.

1.5 Synthesis of compound **4**



di-*tert*-butyl((((2,2-bis(4-((*E*)-2-(pyridin-4-yl)vinyl)phenyl)ethene-1,1-diyl)bis(4,1-phenylene))bis(oxy))bis(propane-3,1-diyl))dicarbamate (4)

A 25 mL two-neck round-bottom flask was charged with compound **3** (1.31 g, 1.56 mmol, 1.00 equiv.), K_2CO_3 (1.11 g, 8.02 mmol, 5.14 equiv.), tri(*o*-tolyl)phosphine (114 mg, 0.37 mmol, 0.24 equiv.), and $Pd(OAc)_2$ (60.4 mg, 0.27 mmol, 0.17 equiv.) in 10 mL of dry DMF. The reaction mixture was degassed under high vacuum and backfilled

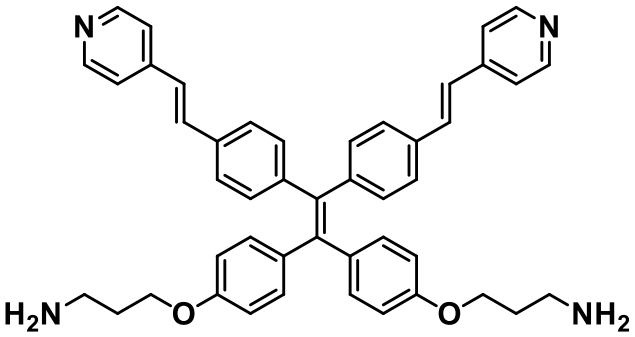
with argon, repeating this cycle three times. Distilled 4-vinylpyridine (1.7 mL, 15.97 mmol, 10.24 equiv.) was then added, followed by an additional three degassing cycles. The mixture was stirred in an oil bath at 100 °C under reflux for 24 h, and the reaction progress was monitored by TLC ($CHCl_3$/MeOH = 95/5). Upon completion, the reaction mixture was extracted with $CHCl_3$ (50 mL) and water (75 mL × 3), and the aqueous layer was further extracted with $CHCl_3$ (30 mL × 3). The combined organic layers were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure using a rotary evaporator, and the residual DMF was thoroughly removed by vacuum distillation. The resulting residue was purified by silica-gel column chromatography ($CHCl_3$/MeOH = 99/1 to 98/2), affording the desired product as a solid (813 mg, 0.94 mmol, 60%).

Physical state: bright yellow foam.

TLC: R_f = 0.31 ($CHCl_3$/MeOH = 95/5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.8 Hz, 4H), 7.30 - 7.26 (m, 8H), 7.20 (d, *J* = 16.4 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 4H), 6.96 - 6.90 (m, 6H), 6.63 (d, *J* = 8.5 Hz, 4H), 4.83 (brs, 2H, NH), 3.93 (t, *J* = 5.6 Hz, 4H), 3.30 - 3.26 (m, 4H), 1.95 - 1.89 (m, 4H), 1.41 (s, 18H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 157.7, 156.1, 150.2, 144.9, 144.8, 141.4, 138.1, 136.2, 134.0, 133.0, 132.8, 132.0, 126.6, 125.6, 120.8, 113.8, 79.3, 65.7, 38.1, 9.7, 28.5. **HRMS (ESI-TOF)** Calcd for $C_{56}H_{61}N_4O_6$, $[M+H]^+$: 885.4586. Found 885.4588.

1.6 Synthesis of compound **5**



3,3'-(((2,2-bis(4-((*E*)-2-(pyridin-4-yl)vinyl)phenyl)ethene-1,1-diyl)bis(4,1-phenylene))bis(oxy))bis(propan-1-amine) (5)

Compound **4** (813.4 mg, 0.92 mmol, 1.00 equiv.) was dissolved in MeOH/THF (9:1, 10.0 mL) in a 25 mL one-neck round-bottom flask, followed by the dropwise addition of 3 N HCl(aq) (3.0 mL). The reaction mixture was stirred in an oil bath at 50 °C for 18 h, and the reaction progress was monitored by TLC (DCM/MeOH = 7/3). Upon completion, the solvents were removed under reduced pressure using a rotary evaporator. The residue was redissolved in MeOH/THF (9:1, 10.0 mL), and Na_2CO_3 was added until gas evolution ceased, neutralizing excess HCl. At this stage, the solution color changed from orange-red to yellow. The solid was removed by gravity filtration, and the filtrate was concentrated under reduced pressure using a rotary evaporator. The residue was redissolved in a small amount of MeOH (2.0 mL), followed by gravity filtration to remove excess white salts. This desalting process was repeated thrice, affording the desired product as a foam (578.2 mg, 0.84 mmol, 91%).

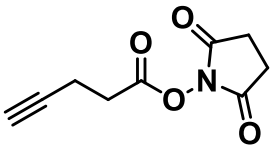
Physical state: yellow foam.

TLC: R_f = 0.10 (DCM/MeOH = 7/3).

^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ 8.37 (s, 4H), 7.38 - 7.25 (m, 10H), 6.96 - 6.87 (m, 10H), 6.61 (d, *J* = 7.1 Hz, 4H), 3.90 - 3.83 (m, 4H), 3.15 - 2.83 (m, 4H), 1.92 - 1.80 (m,

4H). **^{13}C NMR (100 MHz, MeOD-*d*$_4$)** δ 159.2, 150.3, 147.2, 146.3, 143.0, 139.5, 137.4, 135.5, 134.8, 133.8, 133.1, 127.9, 126.3, 122.4, 114.9, 66.7, 39.3, 31.7. **HRMS (ESI-TOF)** Calcd for $C_{46}H_{46}N_4O_2$, $[M+2H]^{2+}$: 343.1805. Found 343.1799.

1.7 Synthesis of compound **6**



2,5-dioxopyrrolidin-1-yl pent-4-ynoate (6)

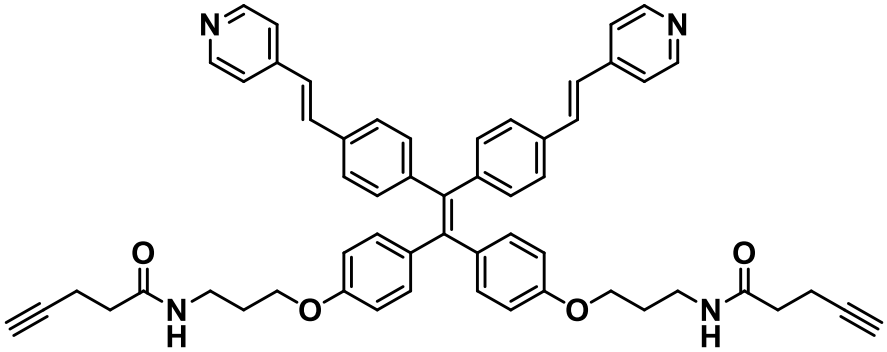
A 250 mL two-neck round-bottom flask was charged with pent-4-ynoic acid (3.0731 g, 36.99 mmol, 1.00 equiv.) and DIPEA (13 mL, 74.63 mmol, 2.02 equiv.) in 100 mL of dry DCM. The solution was cooled to 0 °C in an ice bath, and DSC (8.6150 g, 33.63 mmol, 0.91 equiv.) was added dropwise. The reaction mixture was stirred at room temperature for 18 h, and the reaction progress was monitored by TLC (Hexs/EtOAc = 3/7). Upon completion, the reaction mixture was extracted with DCM (50 mL) and 1 N HCl(aq) (70 mL). The combined organic layers were dried over Na_2SO_4, gravity filtered, and concentrated under reduced pressure using a rotary evaporator to give the desired product as a white solid (6.3537 g, 32.55 mmol, 88%).

Physical state: white solid.

TLC: R_f = 0.66 (Hexs/EtOAc = 3/7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77 (t, *J* = 6.9 Hz, 2H), 2.72 (s, 4H), 2.52 - 2.49 (m, 2H), 2.02 (s, 1H).; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.2, 167.1, 81.0, 77.5, 77.2, 76.8, 70.0, 30.1, 25.4, 13.8. **HRMS (ESI-TOF)** Calcd for $C_9H_{10}NO_4$, $[M+H]^+$: 196.0604. Found 196.0606.

1.8 Synthesis of compound **7**



***N*,*N*'-((((2,2-bis(4-((*E*)-2-(pyridin-4-yl)vinyl)phenyl)ethene-1,1-diyl)bis(4,1-phenylene))bis(oxy))bis(propane-3,1-diyl))bis(pent-4-ynamide) (7)**

Compound **5** (256.8 mg, 0.37 mmol, 1.00 equiv.) was dissolved in MeOH (8.0 mL, solution A) in a 25 mL two-neck round-bottom flask, while compound **6** (294.4 mg, 1.50 mmol, 4.07 equiv.) was dissolved in DCM (4.0 mL, solution B) in a 10 mL one-neck round-bottom flask. Solution B was added dropwise into solution A, and the reaction mixture was stirred at 25 °C for 6 h. The reaction progress was monitored by TLC (DCM/MeOH = 95/5). Upon completion, the mixture was extracted with DCM (25 mL × 3) and water (25 mL). The combined organic layers were washed sequentially with saturated brine (25 mL) and water (25 mL), dried over Na_2SO_4, gravity filtered, and concentrated under reduced pressure using a rotary evaporator. The residue was purified by silica-gel column chromatography (DCM/MeOH = 95:5) to afford the desired product as a foam (295.8 mg, 0.35 mmol, 95%).

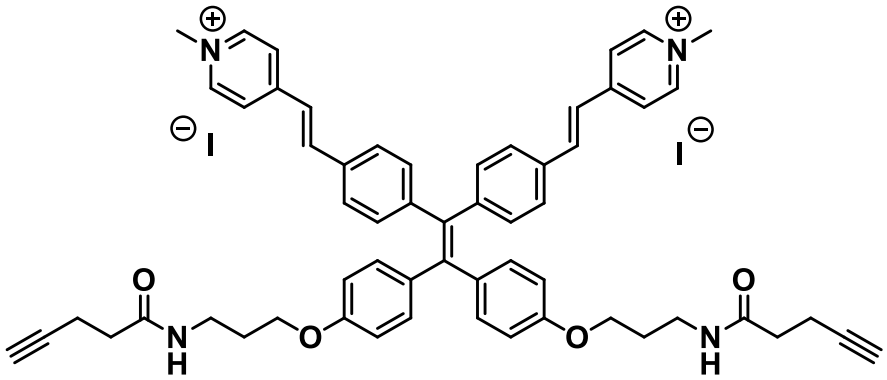
Physical state: yellow foam.

TLC: R_f = 0.23 (DCM/MeOH = 95/5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 6.2 Hz, 4H), 7.32 - 7.29 (m, 8H), 7.21 (d, *J* = 16.3 Hz, 2H), 7.04 (d, *J* = 8.3 Hz, 4H), 6.97 - 6.92 (m, 6H), 6.64 (d, *J* = 8.9 Hz, 4H), 6.00 (brs, 2H, NH), 3.97 (t, *J* = 5.9 Hz, 4H), 3.48 - 3.43 (m, 4H), 2.50 (td, *J* = 6.7, 2.5

Hz, 4H), 2.36 (t, *J* = 7.0 Hz, 4H), 2.00 - 1.94 (m, 4H), 1.92 (t, *J* = 2.6 Hz, 2H),. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 171.1, 157.6, 150.0, 144.8, 141.3, 138.2, 136.3, 134.0, 133.0, 132.7, 132.0, 126.6, 125.6, 120.9, 113.7, 83.1, 69.4, 66.0, 37.3, 35.4, 29.1, 15.0. **HRMS (ESI-TOF)** Calcd for $C_{56}H_{53}N_4O_4$, $[M+H]^+$: 845.4061. Found 845.4099.

1.9 Synthesis of compound **8**



4,4'-((1*E*,1'*E*)-((2,2-bis(4-(3-(pent-4-ynamido)propoxy)phenyl)ethene-1,1-diyl) bis(4,1-phenylene))bis(ethene-2,1-diyl))bis(1-methylpyridin-1-ium) iodide (8)

Compound **7** (592.1 mg, 0.70 mmol, 1.00 equiv.) was dissolved in MeCN/DCM/MeI (5/5/1, 11 mL) in a 25 mL one-neck round-bottom flask. The reaction mixture was stirred in an oil bath at 50 °C for 18 h, and the reaction progress was monitored by TLC (EtOAc/MeOH = 9/1). Upon completion, the solvents were removed under reduced pressure using a rotary evaporator to afford the desired product as a solid (782.6 mg, 0.69 mmol, 99%).

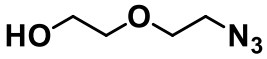
Physical state: Dark-red solid.

TLC: R_f = 0.00 (EtOAc/MeOH = 9/1).

^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ 8.66 (d, *J* = 6.9 Hz, 4H), 8.09 (d, *J* = 7.0 Hz, 4H), 7.81 (d, *J* = 16.2 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 4H), 7.30 (d, *J* = 16.3 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 4H), 6.90 (d, *J* = 8.8 Hz, 4H), 6.65 (d, *J* = 8.9 Hz, 4H), 4.27 (s, 6H), 3.90

(t, J = 6.1 Hz, 4H), 3.28 - 3.26 (m, 4H), 2.42 - 2.37 (m, 4H), 2.34 - 2.30 (m, 4H), 2.16 (t, J = 2.5 Hz, 2H), 1.94 - 1.85 (m, 4H). **^{13}C NMR (100 MHz, MeOD-*d*$_4$)** δ 174.0, 159.6, 155.1, 148.1, 146.0, 144.4, 142.5, 139.1, 137.0, 134.6, 133.8, 133.3, 129.2, 125.0, 123.6, 115.0, 83.6, 70.4, 66.6, 47.9, 37.4, 36.1, 30.2, 15.8. **HRMS (ESI-TOF)** Calcd for $C_{58}H_{58}N_4O_4$, $[M]^{2+}$: 437.2224. Found 437.2223.

1.10 Synthesis of compound **9**



2-(2-azidoethoxy)ethan-1-ol (9)

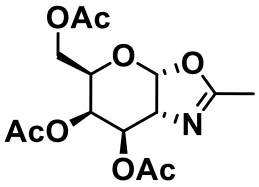
A 150 mL one-neck round-bottom flask was charged with 2,2'-oxybis(ethan-1-ol) (30.0152 g, 282.84 mmol, 7.00 equiv.) and Et_3N (6.2 mL, 44.43 mmol, 1.10 equiv.) in 80 mL of dry DCM. Under an ice bath, TsCl (7.7365 g, 40.56 mmol, 1.00 equiv.) was added. The reaction mixture was stirred at 25 °C for 18 h. Upon completion, the reaction was quenched with 1 N HCl (30 mL) and extracted with DCM (50 mL × 3) and water. The combined organic layers were washed with saturated brine (50 mL) and water (50 mL), dried over Na_2SO_4, gravity filtered, and concentrated under reduced pressure using a rotary evaporator. The residue was dissolved in acetone/water (1:1, 40 mL), followed by the addition of NaN_3 (13.3861 g, 205.91 mmol, 5.09 equiv.). The reaction mixture was stirred at 50 °C for 18 h, and the reaction progress was monitored by TLC (Hexs/EtOAc = 3/1). After completion, acetone was removed under reduced pressure using a rotary evaporator, and the residue was extracted with EtOAc (50 mL × 3) and water (50 mL). The combined organic layers were dried over Na_2SO_4, gravity filtered, and concentrated. The crude product was purified by silica-gel column chromatography (Hex/EtOAc = 3/1) to afford the desired product as a liquid (5.4128 g, 41.27 mmol, 98%).

Physical state: colorless liquid

TLC: R_f = 0.13 (Hexs/EtOAc = 3/1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (t, *J* = 4.7 Hz, 2H), 3.56 (t, *J* = 5.0 Hz, 2H), 3.48 (t, *J* = 4.7 Hz, 2H), 3.29 (t, *J* = 5.0 Hz, 2H), 2.99 (brs, 1H, OH). **^{13}C NMR** (100 MHz, **$CDCl_3$**) δ 72.3, 69.6, 61.3, 50.5. **HRMS (ESI-TOF)** Calcd for $C_4H_9N_3O_2Na$, $[M+Na]^+$: 154.0587. Found 154.0586.

1.11 Synthesis of compound **10**



(3a*R*,5*R*,6*R*,7*R*,7a*R*)-5-(acetoxymethyl)-2-methyl-3a,6,7,7a-tetrahydro-5*H*-pyrano[3,2-d]oxazole-6,7-diyl diacetate (10)

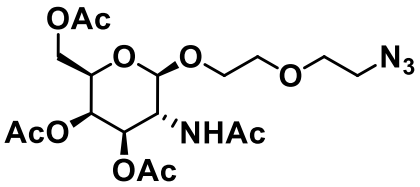
A 250 mL round-bottom flask was charged with 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-*β*-D-galactopyranose (3.1033 g, 8.48 mmol, 1.00 equiv.) in $CHCl_3$ (120 mL). Under an ice bath, TMSOTf (1.6 mL, 8.82 mmol, 1.04 equiv.) was added dropwise. The reaction mixture was stirred for 10 min, then the ice bath was removed, and the solution was gradually warmed to 40 °C in an oil bath and stirred for 1.5 h. The reaction progress was monitored by TLC (DCM/MeOH = 99/1). Upon completion, Et_3N (1.8 mL, 12.93 mmol, 1.52 equiv.) was added to quench the reaction. The solvent and Et_3N were removed under reduced pressure using a rotary evaporator, and the crude product was purified by silica-gel column chromatography (DCM/MeOH = 99/1 to 98/2) to afford the desired product (2.4356 g, 7.40 mmol, 87%). **HRMS (ESI-TOF)** Calcd for $C_{14}H_{20}NO_8$, $[M+H]^+$: 330.1183. Found 330.1180.

Physical state: off-white foam

TLC: R_f = 0.32 (DCM/MeOH = 99/1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (d, *J* = 6.8 Hz, 1H), 5.20 (d, *J* = 6.1 Hz, 1H), 4.68 (dd, *J* = 7.3, 3.4 Hz, 1H), 4.03 - 3.86 (m, 3H), 3.76 (td, *J* = 7.0, 1.3 Hz, 1H), 1.88 (s, 3H), 1.82 (s, 6H), 1.80 (m, 3H). **^{13}C NMR** (100 MHz, **$CDCl_3$**) δ 169.9, 169.5, 169.3, 165.8, 101.0, 71.3, 69.0, 64.9, 63.2, 61.2, 20.3, 20.2, 20.1, 13.9. **HRMS (ESI-TOF)** Calcd for $C_{18}H_{28}N_4NaO_{10}$, $[M+Na]^+$: 483.1698. Found 483.1696.

1.12 Synthesis of compound **11**



(2*R*,3*R*,4*R*,5*R*,6*R*)-5-acetamido-2-(acetoxymethyl)-6-(2-(2-azidoethoxy)ethoxy)tetrahydro-2*H*-pyran-3,4-diyl diacetate (11)

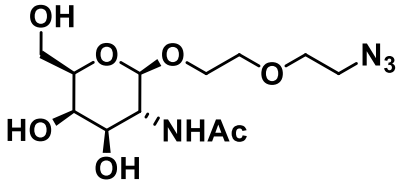
A 25 mL two-neck round-bottom flask was charged with compound **10** (1.5224 g, 4.62 mmol, 1.00 equiv.) and compound **9** (893.5 mg, 6.81 mmol, 1.47 equiv.) in 8 mL of DCE, and the mixture was stirred at 25 °C under an argon atmosphere for 1 h. Subsequently, TMSOTf (415 μL, 2.29 mmol, 0.50 equiv.) was added, and the reaction was allowed to proceed for 18 h. The reaction progress was monitored by TLC (DCM/MeOH = 99/1). Upon completion, the reaction mixture was poured into a 50 mL Erlenmeyer flask containing 20 mL of DCM for dilution, and extracted with water (50 mL) and DCM (50 mL × 3). The combined organic layers were washed sequentially with saturated brine (50 mL) and water (50 mL), dried over Na_2SO_4, gravity filtered, and concentrated under reduced pressure using a rotary evaporator. The crude residue was purified by silica-gel column chromatography (DCM/MeOH = 99/1 → 98/2 → 97/3) to afford the desired product as a foam (1.0532 g, 3.29 mmol, 71%).

Physical state: off-white foam

TLC: R_f = 0.21 (DCM/MeOH = 99/1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (d, *J* = 8.9 Hz, 1H), 5.23 (d, *J* = 3.0 Hz, 1H), 5.11 (dd, *J* = 11.4, 3.3 Hz, 1H), 4.65 (d, *J* = 8.5 Hz, 1H), 4.06 - 3.81 (m, 5H), 3.69 - 3.63 (m, 1H), 3.54 (t, *J* = 4.9 Hz, 4H), 3.32 - 3.27 (m, 2H), 2.02 (s, 3H), 1.92 (s, 3H), 1.86 (s, 3H), 1.84 (m, 3H). **^{13}C NMR** (100 MHz, **$CDCl_3$**) δ 170.5, 170.3, 170.22, 170.17, 101.1, 70.5, 70.4, 70.1, 69.8, 68.4, 66.7, 61.5, 50.8, 50.7, 23.1, 20.5. **HRMS (ESI-TOF)** Calcd for $C_{18}H_{28}N_4NaO_{10}$, $[M+Na]^+$: 483.1698. Found 483.1696.

1.13 Synthesis of compound **12**



***N*-((*2R,3R,4R,5R,6R*)-2-(2-(2-azidoethoxy)ethoxy)-4,5-dihydroxy-6-(hydroxy methyl)tetrahydro-2H-pyran-3-yl)acetamide (12)**

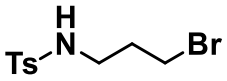
A 10 mL one-neck round-bottom flask was charged with compound **11** (150.3 mg, 0.33 mmol, 1.00 equiv.) and sodium methoxide (89.4 mg, 1.65 mmol, 5.00 equiv.) in MeOH (3 mL). The reaction mixture was stirred at 25 °C under an argon atmosphere for 1 h. The reaction progress was monitored by TLC (EtOAc/MeOH = 9/1). Upon completion, Dowex® 50WX2 (152.3 mg) was added to quench the reaction. The mixture was gravity filtered, and the solvent was removed under reduced pressure using a rotary evaporator to afford the desired product as a colorless oil (544.9 mg, 1.63 mmol, 99%).

Physical state: colorless oil

TLC: R_f = 0.00 (EtOAc/MeOH = 9/1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (d, *J* = 8.7 Hz, 1H), 4.04 - 3.92 (m, 3H), 3.80 - 3.64 (m, 8H), 3.58 (t, *J* = 5.9 Hz, 1H), 3.44 (t, *J* = 4.9 Hz, 2H). **^{13}C NMR** (100 MHz, **$CDCl_3$**) δ 173.3, 101.7, 75.0, 71.4, 69.8, 69.4, 68.6, 68.1, 60.8, 52.4, 50.3, 22.7, 21.8. **HRMS (ESI-TOF)** Calcd for $C_{12}H_{22}N_4NaO_7$, $[M+Na]^+$: 357.1381. Found 357.1383.

1.14 Synthesis of compound **13**



***N*-(3-bromopropyl)-4-methylbenzenesulfonamide (13)**

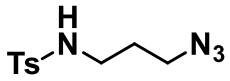
A 100 mL two-neck round-bottom flask was charged with 3-bromopropan-1-aminium bromide (2.5728 g, 11.75 mmol, 1.00 equiv.) and TsCl (2.3173 g, 12.15 mmol, 1.03 equiv.) in 30 mL of DCM. Under an argon atmosphere and cooling in an ice bath at 0 °C, Et_3N (3.4 mL, 24.39 mmol, 2.08 equiv.) was added dropwise. The reaction mixture was stirred at 25 °C for 20 min. The reaction progress was monitored by TLC (Hexs/EtOAc = 8/2). Upon completion, the solvent was removed under reduced pressure using a rotary evaporator. The resulting residue was extracted with 25 mL water and DCM (25 mL × 3). The combined organic layers were washed sequentially with saturated brine (25 mL) and water (25 mL), dried over Na_2SO_4, gravity filtered, and concentrated under reduced pressure using a rotary evaporator. The crude residue was redissolved in 5 mL of DCM in a 100 mL one-neck round-bottom flask, followed by the addition of Hexs (30 mL) with vigorous shaking to form a white precipitate. The solid was collected by gravity filtration and washed thoroughly with Hexs to afford the desired product as a solid (3.0371 g, 10.39 mmol, 88%).

Physical state: white solid

TLC: R_f = 0.21 (Hexs/EtOAc = 8/2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 5.48 (d, *J* = 6.2 Hz, 1H, NH), 3.36 (t, *J* = 6.4 Hz, 2H), 3.03 (q, *J* = 4.9 Hz, 2H), 2.38 (s, 3H), 2.00 - 1.93 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 143.5, 136.5, 129.7, 127.0, 41.3, 32.2, 30.3, 21.5. **HRMS (ESI-TOF)** Calcd for $C_{10}H_{15}BrNO_2S$ $[M+H]^+$: 292.0001. Found 292.0006.

1.15 Synthesis of compound **14**



***N*-(3-azidopropyl)-4-methylbenzenesulfonamide (14)**

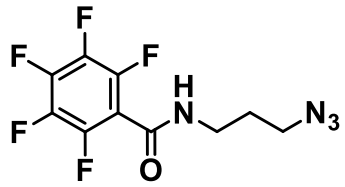
A 25 mL one-neck round-bottom flask was charged with compound **13** (1.5310 g, 5.24 mmol, 1.00 equiv.) and NaN_3 (1.0628 g, 16.35 mmol, 3.12 equiv.) in acetone/water (1/1, 10 mL). The reaction mixture was stirred in an oil bath at 50 °C for 24 h. The reaction progress was monitored by TLC (Hexs/EtOAc = 8/2). Upon completion, the reaction mixture was extracted with DCM (50 mL) and water (50 mL). The combined organic layers were dried over Na_2SO_4, gravity filtered, and concentrated under reduced pressure using a rotary evaporator to afford the desired product as an oil (1.1993 g, 4.72 mmol, 90%).

Physical state: light yellow oil.

TLC: R_f = 0.31 (Hexs/EtOAc = 8/2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 5.56 (brs, 1H, NH), 3.26 (t, *J* = 6.6 Hz, 2H), 2.93 (t, *J* = 6.6 Hz, 2H), 2.35 (s, 3H), 1.68 - 1.62 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 143.4, 136.5, 129.6, 126.9, 48.4, 40.3, 28.6, 21.3. **HRMS (ESI-TOF)** Calcd for $C_{10}H_{14}N_4NaO_2S$, $[M+Na]^+$: 277.0730. Found 277.0727.

1.16 Synthesis of compound **15**



***N*-(3-azidopropyl)-2,3,4,5,6-pentafluorobenzamide (15)**

A 100 mL one-neck round-bottom flask was charged with compound **2** (994.8 mg, 3.02 mmol, 1.00 equiv.) and NaN_3 (601.7 mg, 9.24 mmol, 3.06 equiv.) in water/THF (1/1, 30 mL). The mixture was stirred in an oil bath at 50 °C for 18 h. Upon completion, the solvents were removed under reduced pressure using a rotary evaporator. The residue was extracted with DCM (30 mL × 3) and water (30 mL). The combined organic layers were dried over Na_2SO_4, gravity filtered, and concentrated under reduced pressure using a rotary evaporator.

The crude product was redissolved in 30 mL of DCM in a 100 mL one-neck round-bottom flask, followed by the addition of 2 N HCl in Et_2O (7.5 mL, 15 mmol, 5.00 equiv.). The reaction mixture was stirred at room temperature for 8 h. Upon completion, Na_2CO_3 (3.0388 g) was added to neutralize the reaction. The mixture was gravity filtered, washed with DCM (20 mL), and concentrated using a rotary evaporator.

The residue was then redissolved in 30 mL of DCM in a 100 mL one-neck round-bottom flask, followed by sequential addition of HATU (1.5394 g, 4.05 mmol, 1.34 equiv.), DIPEA (1.6 mL, 9.19 mmol, 3.04 equiv.), and commercially available 2,3,4,5,6-pentafluorobenzoic acid (848.2 mg, 3.99 mmol, 1.32 equiv.). The reaction mixture was stirred at room temperature for 18 h, and the reaction progress was monitored by TLC (Hexs/EtOAc = 8/2). Upon completion, the mixture was extracted with DCM (30 mL × 3) and water (30 mL). The combined organic layers were dried over Na_2SO_4, gravity filtered, and concentrated under reduced pressure using a rotary evaporator. The crude product was purified by silica-gel column chromatography

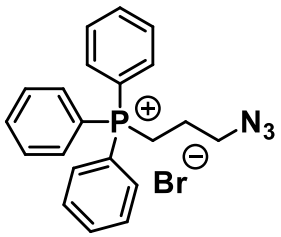
(Hex/EtOAc = 9/1 → 8/2) to afford the desired product as an oil (781.8 mg, 2.66 mmol, 88%).

Physical state: off-white oil.

TLC: R_f = 0.28 (Hexs/EtOAc = 8/2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (brs, 1H, NH), 3.41 - 3.34 (m, 4H), 1.82 - 1.75 (m, 2H),. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 157.9, 145.1, 143.4, 142.6, 140.9, 138.8, 136.2, 111.6, 48.9, 37.7, 28.2.; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -141.6 (d, *J* = 15.0 Hz, 2F), -151.5 (t, 1F, J = 20.2 Hz), -160.7 ~ -160.8 (m, 2F). **HRMS (ESI-TOF)** Calcd for $C_{56}H_{53}N_4O_4$, $[M+H]^+$: 845.4061. Found 845.4099.

1.17 Synthesis of compound **16**



(3-azidopropyl)triphenylphosphonium bromide (16)

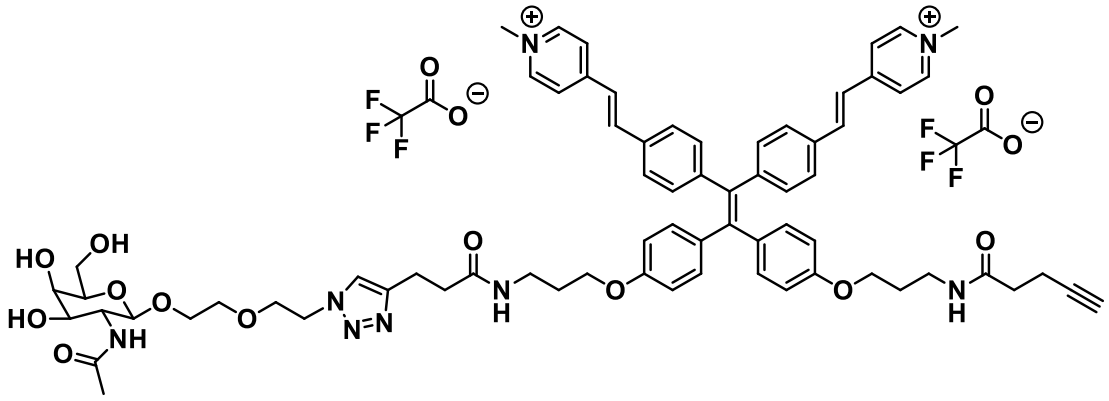
A 100 mL two-neck round-bottom flask was charged with commercially available (3-bromopropyl)triphenylphosphonium bromide (2.3209 g, 5.00 mmol, 1.00 equiv.) and NaN_3 (325.1 mg, 5.00 mmol, 1.00 equiv.) in EtOH/water (1/1, 25 mL). The reaction mixture was refluxed in an oil bath for 18 h, and the reaction progress was monitored by TLC (DCM/MeOH = 9/1). Upon completion, the reaction mixture was extracted with DCM (50 mL × 3) and water (30 mL). The combined organic layers were dried over Na_2SO_4, gravity filtered, and concentrated under reduced pressure using a rotary evaporator. The residue was treated with Et_2O (25 mL) to afford the desired product as a solid (2.0098 g, 4.71 mmol, 94%).

Physical state: white solid.

TLC: R_f = 0.35 (DCM/MeOH = 9/1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 - 7.71 (m, 9H), 7.65 - 7.61 (m, 6H), 3.90 - 38.3 (m, 2H), 3.74 (t, *J* = 3.2 Hz, 2H), 1.86 - 1.77 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 135.2, 133.6, 133.5, 130.6, 130.5, 118.2, 117.4, 50.7, 50.4, 22.6, 20.4, 18.8,; **^{31}P NMR (162 MHz, $CDCl_3$)** δ 24.2 (1P). **HRMS (ESI-TOF)** Calcd for $C_{21}H_{21}N_3P$, $[M]^+$: 346.1468. Found 346.1438.

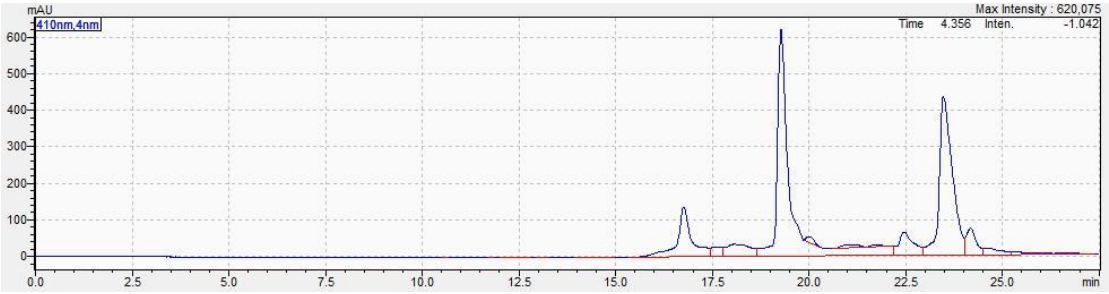
1.18 Synthesis of compound **17**



GPAMG (17)

A 10 mL one-neck round-bottom flask was charged with compound **8** (401 mg, 0.35 mmol, 1.00 equiv.) in DMF (1.8 mL), followed by the addition of a solution of compound 12 (180 mg, 0.53 mmol, 1.5 equiv.) in water (2.7 mL). Subsequently, 0.3 M aqueous $CuSO_4$ (160 μL) and 1.0 M aqueous sodium L-ascorbate (480 μL) were added sequentially. The reaction mixture was stirred in an oil bath at 40 °C for 18 h. Upon completion, the mixture was gravity filtered and purified by preparative high-performance liquid chromatography (prep-HPLC) on a phenyl column (3 cm i.d.) using a linear gradient elution: 0.01 min, 75% H_2O (0.1% TFA); to 5.00 min, 63% H_2O (0.1% TFA)/37% CH_3CN; to 17.50 min, 10% H_2O (0.1% TFA)/90% CH_3CN; to 17.51 min, 100% CH_3CN; held to 27.50 min at a flow rate of 3.0 mL/min. The desired product was

obtained as a foam (236 mg, 0.16 mmol, 47%).

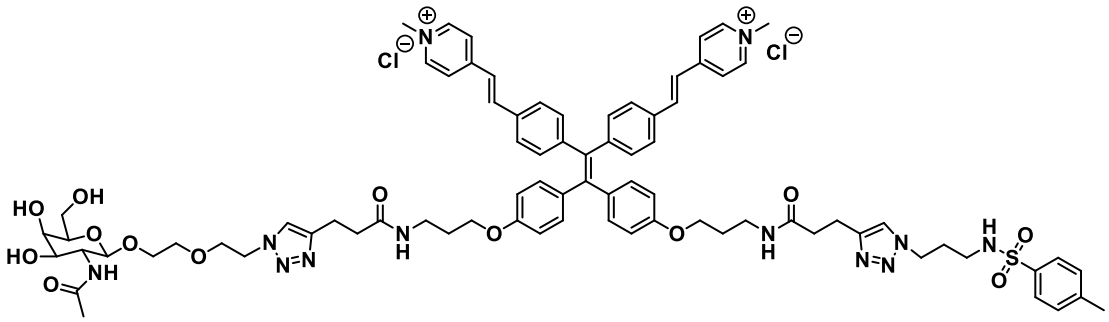


Physical state: Dark-red foam.

Retention time: 19.30 min.

^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ 8.64 (d, *J* = 6.8 Hz, 4H), 8.05 (d, *J* = 6.5 Hz, 4H), 7.85 (s, 1H), 7.76 (d, *J* = 16.2 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 4H), 7.25 (d, *J* = 16.2 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 4H), 6.90 (d, *J* = 8.1 Hz, 4H), 6.64 - 6.62 (m, 4H), 4.44 (t, *J* = 4.9 Hz, 2H), 4.34 (d, *J* = 8.4 Hz, 1H), 4.26 (s, 6H), 3.99 - 3.77 (m, 9H), 3.75 - 3.68 (m, 2H), 3.63 - 3.51 (m, 4H), 3.47 (t, *J* = 6.0 Hz, 1H), 3.29 - 3.24 (m, 4H), 2.95 (t, *J* = 7.3 Hz, 2H), 2.53 (t, *J* = 7.2 Hz, 2H), 2.41 - 2.37 (m, 2H), 2.34 - 2.30 (m, 2H), 2.16 (t, *J* = 2.6 Hz, 1H), 1.92 (s, 3H), 1.89 - 1.81 (m, 4H). **^{13}C NMR (100 MHz, MeOD-*d*$_4$)** δ 174.0, 160.8, 159.5, 155.0, 148.1, 146.0, 144.4, 142.4, 139.1, 137.0, 134.6, 133.8, 133.3, 129.1, 124.9, 123.6, 115.0, 103.4, 83.6, 76.7, 73.2, 71.3, 70.4, 70.2, 70.0, 69.6, 66.5, 62.6, 54.1, 51.7, 47.7, 37.5, 36.0, 30.1, 23.2, 22.3, 15.8. **HRMS (ESI-TOF)** Calcd for $C_{70}H_{80}N_8O_{11}$, $[M]^{2+}$: 604.2968. Found 604.2964.

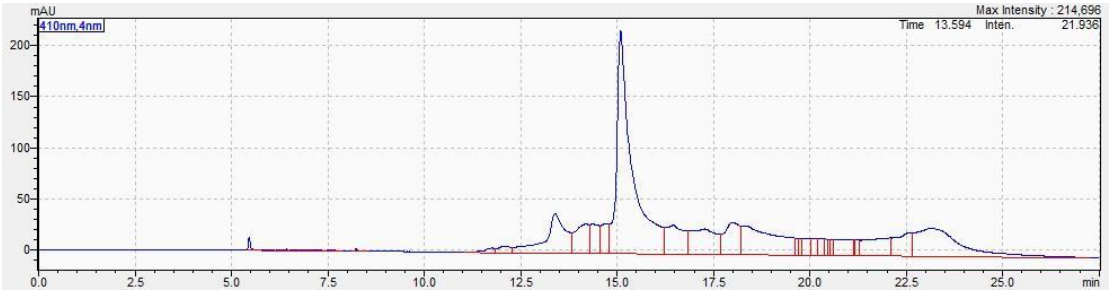
1.19 Synthesis of compound **18**



***gem*-TPEVP-TsG (18)**

A 10 mL one-neck round-bottom flask was charged with compound **17** (72.6 mg, 0.05 mmol, 1.00 equiv.) and compound **14** (38.1 mg, 0.15 mmol, 3.00 equiv.) in DMF/H_2O = 1:1 (1.0 mL). Subsequently, 0.3 M aqueous $CuSO_4$ (90 μL) and 1.0 M aqueous sodium L-ascorbate (270 μL) were added sequentially. The reaction mixture was stirred in an oil bath at 40 °C for 18 h. Upon completion, the mixture was gravity filtered and purified by preparative high-performance liquid chromatography (prep-HPLC) on a phenyl column (3 cm i.d.) using a linear gradient elution: 0.01 min, 100% H_2O (0.1% TFA); to 5.00 min, 70% H_2O (0.1% TFA)/30% CH_3CN; to 17.50 min, 45% H_2O (0.1% TFA)/55% CH_3CN; to 17.51 min, 100% CH_3CN; held to 27.50 min at a flow rate of 3.0 mL/min.

The collected fraction was concentrated and redissolved in 4 mL of MeOH in a 25 mL one-neck round-bottom flask, followed by adding 2 N HCl in Et_2O (1 mL). The resulting mixture was concentrated under reduced pressure using a rotary evaporator. This cycle was repeated several times to exchange residual trifluoroacetate counterions with chloride fully. The desired product was obtained as a foam (59.1 mg, 0.38 mmol, 75%).

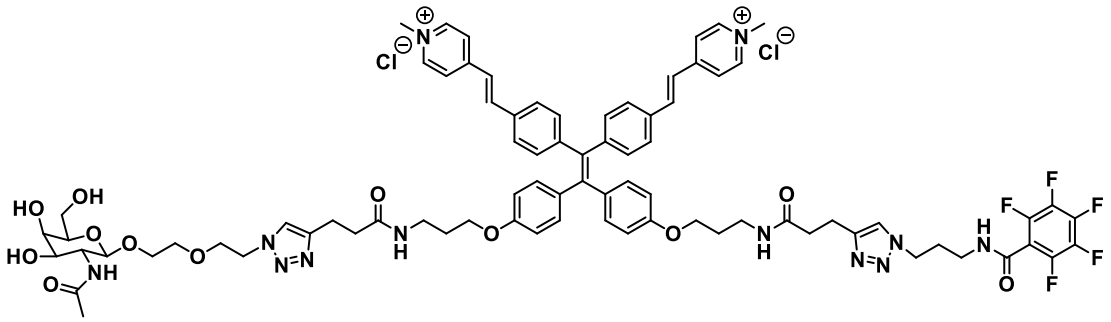


Physical state: Dark-red foam.

Retention time: 15.04 min.

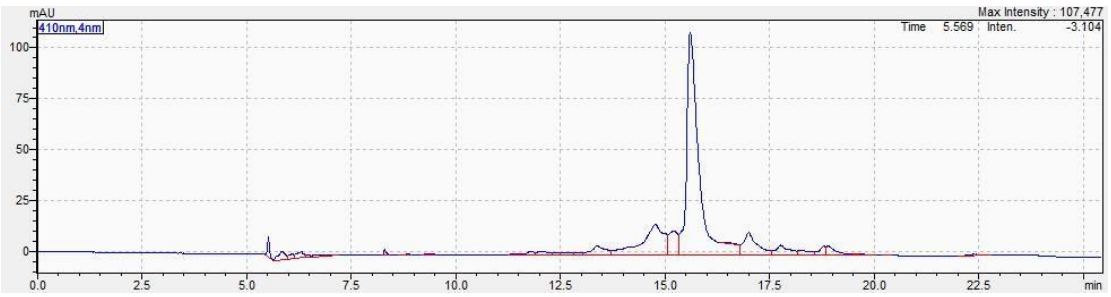
^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ 8.68 (d, *J* = 6.5 Hz, 2H), 8.66 (d, *J* = 6.0 Hz, 2H), 8.11 (d, *J* = 7.2 Hz, 2H), 8.09 (d, *J* = 7.1 Hz, 2H), 7.85 - 7.79 (m, 2H), 7.68 - 7.65 (m, 4H), 7.53 - 7.50 (m, 4H), 7.35 - 7.29 (m, 4H), 7.11 (d, *J* = 8.2 Hz, 4H), 6.95 (dd, *J* = 8.8, 2.3 Hz, 4H), 6.68 (d, *J* = 8.9 Hz, 4H), 4.47 (t, *J* = 5.1 Hz, 2H), 4.38 - 4.34 (m, 3H), 4.30 (s, 3H), 4.29 (s, 3H), 3.99 - 3.91 (m, 2H), 3.90 - 3.81 (m, 7H), 3.79 - 3.71 (m, 3H), 3.66 - 3.57 (m, 5H), 3.48 (t, *J* = 3.1 Hz, 2H), 3.00 - 2.93 (m, 4H), 2.78 (t, *J* = 6.5 Hz, 2H), 2.57 - 2.51 (m, 4H), 2.39 (s, 3H), 1.99 (t, *J* = 6.7 Hz, 2H), 1.95 (s, 3H), 1.92 - 1.85 (m, 4H). **^{13}C NMR (100 MHz, MeOD-*d*$_4$)** δ 173.0, 158.0, 153.6, 146.6, 144.5, 143.3, 142.9, 140.9, 137.7, 137.0, 135.6, 133.1, 132.3, 131.8, 129.4, 127.6, 126.5, 123.5, 122.6, 122.1, 113.5, 101.9, 75.2, 71.8, 69.9, 68.7, 68.6, 68.2, 65.1, 61.1, 52.7, 50.2, 46.3, 39.4, 36.0, 34.7, 29.7, 28.7, 21.7, 20.9, 20.0. **HRMS (ESI-TOF)** Calcd for $C_{80}H_{94}N_{12}O_{13}S$, $[M]^{2+}$: 731.3387. Found 731.3382.

1.20 Synthesis of compound **19**



***gem*-TPEVP-FBG (19)**

A 10 mL one-neck round-bottom flask was charged with compound **17** (99.5 mg, 0.07 mmol, 1.00 equiv.) and compound **15** (61.8 mg, 0.21 mmol, 3.00 equiv.) in DMF/H_2O = 1:1 (1.4 mL). Subsequently, 0.3 M aqueous $CuSO_4$ (130 μL) and 1.0 M aqueous sodium L-ascorbate (390 μL) were added sequentially. The reaction mixture was stirred in an oil bath at 40 °C for 18 h. Upon completion, the mixture was gravity filtered and purified by preparative high-performance liquid chromatography (prep-HPLC) on a phenyl column (3 cm i.d.) using a linear gradient elution: 0.01 min, 100% H_2O (0.1% TFA); to 5.00 min, 70% H_2O (0.1% TFA)/30% CH_3CN; to 17.50 min, 45% H_2O (0.1% TFA)/55% CH_3CN; to 17.51 min, 100% CH_3CN; held to 27.50 min at a flow rate of 3.0 mL/min. The collected fraction was concentrated and redissolved in 4 mL of MeOH in a 25 mL one-neck round-bottom flask, followed by adding 2 N HCl in Et_2O (1 mL). The resulting mixture was concentrated under reduced pressure using a rotary evaporator. This cycle was repeated several times to exchange residual trifluoroacetate counterions with chloride fully. The desired product was obtained as a foam (82.7 mg, 0.05 mmol, 75%).

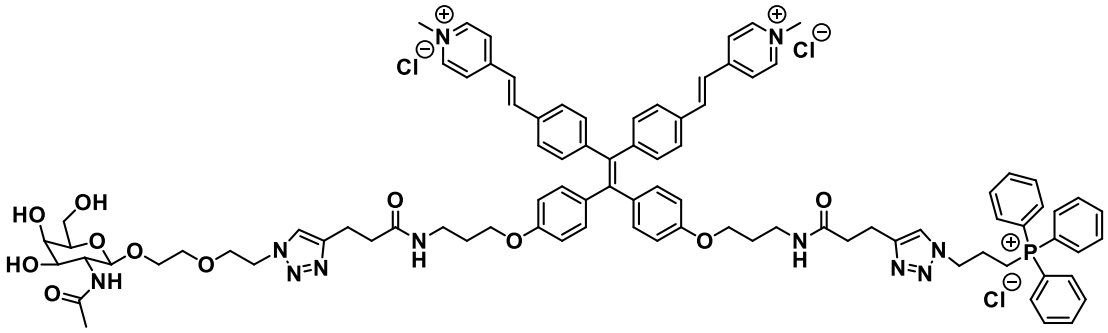


Physical state: Dark-red foam.

Retention time: 15.63 min.

^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ 8.68 (d, *J* = 6.8 Hz, 4H), 8.10 (d, *J* = 6.7 Hz, 4H), 7.88 - 7.78 (m, 4H), 7.52 (d, *J* = 8.4 Hz, 4H), 7.33 (d, *J* = 16.3 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 4H), 6.95 (d, *J* = 9.1 Hz, 4H), 6.68 (d, *J* = 8.7 Hz, 4H), 4.49 (t, *J* = 4.9 Hz, 2H), 4.43 (t, *J* = 6.9 Hz, 2H), 4.37 (d, *J* = 8.4 Hz, 1H), 4.30 (s, 6H), 4.00 - 3.94 (m, 2H), 3.94 - 3.82 (m, 8H), 3.80 - 3.72 (m, 3H), 3.66 - 3.57 (m, 5H), 3.49 (t, *J* = 6.0 Hz, 1H), 3.38 (t, *J* = 6.9 Hz, 2H), 3.01 - 2.96 (m, 4H), 2.59 - 2.53 (m, 4H), 2.21 - 2.14 (m, 2H), 1.95 (s, 3H), 1.92 - 1.82 (m, 4H). **^{13}C NMR (100 MHz, MeOD-*d*$_4$)** δ 173.0, 159.8, 159.3, 158.0, 153.6, 146.6, 144.5, 142.9, 141.0, 137.6, 135.6, 133.1, 133.0, 131.8, 127.6, 123.4, 122.5, 122.1, 113.4, 101.9, 75.2, 71.7, 69.9, 68.7, 68.6, 68.1, 65.0, 61.1, 52.6, 50.2, 46.2, 36.6 36.0, 34.7, 29.3, 28.7, 21.7, 20.9.; **^{19}F NMR (376 MHz, MeOD-*d*$_4$)** δ -143.9 (d, *J* = 20.8 Hz, 2F), -155.0 (t, 1F, J = 20.3 Hz), -163.5 ~ -163.6 (m, 2F). **HRMS (ESI-TOF)** Calcd for $C_{80}H_{87}F_5N_{12}O_{12}$, $[M]^{2+}$: 751.3238. Found 751.3192.

1.21 Synthesis of compound **20**

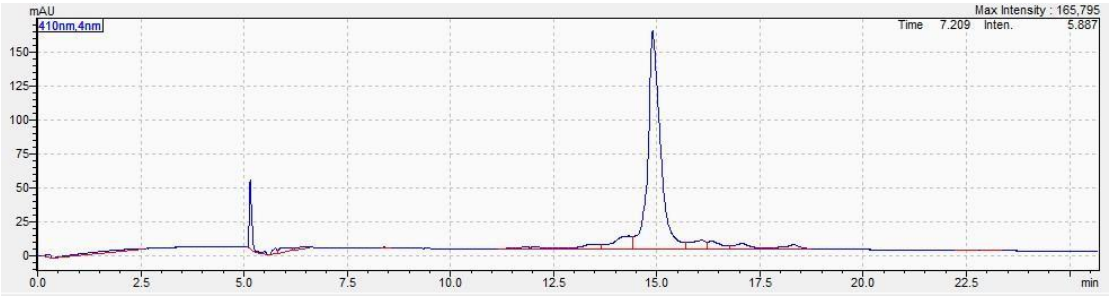


***gem*-TPEVP-TPPG (20)**

A 10 mL one-neck round-bottom flask was charged with compound **17** (100.5 mg, 0.07 mmol, 1.00 equiv.) and compound **16** (96.7 mg, 0.21 mmol, 3.00 equiv.) in DMF/H_2O = 1:1 (1.4 mL). Subsequently, 0.3 M aqueous $CuSO_4$ (130 μL) and 1.0 M aqueous sodium L-ascorbate (390 μL) were added sequentially. The reaction mixture

was stirred in an oil bath at 40 °C for 18 h. Upon completion, the mixture was gravity filtered and purified by preparative high-performance liquid chromatography (prep-HPLC) on a phenyl column (3 cm i.d.) using a linear gradient elution: 0.01 min, 100% H_2O (0.1% TFA); to 5.00 min, 70% H_2O (0.1% TFA)/30% CH_3CN; to 17.50 min, 45% H_2O (0.1% TFA)/55% CH_3CN; to 17.51 min, 100% CH_3CN; held to 27.50 min at a flow rate of 3.0 mL/min.

The collected fraction was concentrated and redissolved in 4 mL of MeOH in a 25 mL one-neck round-bottom flask, followed by adding 2 N HCl in Et_2O (1 mL). The resulting mixture was concentrated under reduced pressure using a rotary evaporator. This cycle was repeated several times to exchange residual trifluoroacetate counterions with chloride fully. The desired product was obtained as a foam (137.2 mg, 0.08 mmol, 85%).



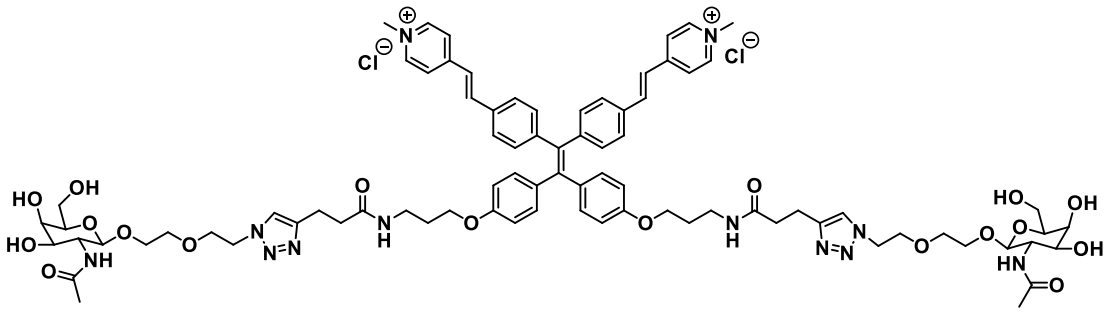
Physical state: Dark-red foam.

Retention time: 14.97 min.

^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ 8.68 (d, *J* = 6.8 Hz, 4H), 8.11 (d, *J* = 7.1 Hz, 2H), 8.10 (d, *J* = 7.0 Hz, 2H), 7.90 - 7.85 (m, 4H), 7.83 (d, *J* = 16.3 Hz, 2H), 7.77 - 7.71 (m, 13H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 16.2 Hz, 2H), 7.12 - 7.09 (m, 4H), 6.96 - 6.93 (m, 4H), 6.68 - 6.65 (m, 4H), 4.54 (t, *J* = 6.5 Hz, 2H), 4.46 (t, *J* = 5.0 Hz, 2H), 4.37 (d, *J* = 8.5 Hz, 1H), 4.31 (s, 3H), 4.30 (s, 3H), 4.00 - 3.93 (m, 2H), 3.91 - 3.81 (m, 7H), 3.77 - 3.72 (m, 2H), 3.65 - 3.58 (m, 4H), 3.50 - 3.38 (m, 4H),

3.26 (t, *J* = 6.9 Hz, 2H), 2.97 (t, *J* = 7.3 Hz, 4H), 2.55 (t, *J* = 7.3 Hz, 4H), 2.31 - 2.22 (m, 2H), 1.95 (s, 3H), 1.92 - 1.82 (m, 4H). **^{13}C NMR (100 MHz, MeOD-*d*$_4$)** δ 174.4, 174.0, 161.3, 160.9, 159.5, 155.1, 148.1, 146.0, 144.3, 142.4, 139.1, 137.0, 136.5, 134.8, 134.7, 133.8, 133.3, 131.7, 131.6, 129.0, 124.9, 124.3, 123.6, 119.6, 118.8, 115.8, 114.9, 103.4, 76.7, 73.2, 71.3, 70.2, 70.0, 69.6, 66.5, 62.6, 54.1, 51.7, 50.8, 50.6, 47.7, 37.5, 36.2, 36.0, 30.1, 24.5, 23.1, 22.4, 22.3, 20.7, 20.2.; **^{31}P NMR (162 MHz, CDCl$_3$)** δ 23.6 (1P). **HRMS (ESI-TOF)** Calcd for $C_{91}H_{101}N_{11}O_{11}P$, $[M]^{3+}$: 518.2468. Found 518.2467.

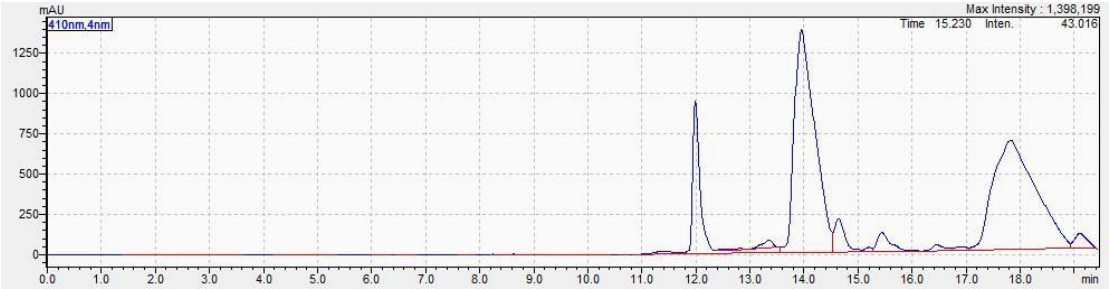
1.22 Synthesis of compound **21**



***gem*-TPEVP-G2 (21)**

A 10 mL one-neck round-bottom flask was charged with compound **17** (56.4 mg, 0.05 mmol, 1.00 equiv.) in DMF (500 μL), followed by the addition of a solution of compound **12** (50.1 mg, 0.15 mmol, 3.00 equiv.) in water (500 μL). Subsequently, 0.3 M aqueous $CuSO_4$ (45 μL) and 1.0 M aqueous sodium L-ascorbate (135 μL) were added sequentially. The reaction mixture was stirred in an oil bath at 40 °C for 18 h. Upon completion, the mixture was gravity filtered and purified by preparative high-performance liquid chromatography (prep-HPLC) on a phenyl column (3 cm i.d.) using a linear gradient elution: 0.01 min, 75% H_2O (0.1% TFA); to 5.00 min, 63% H_2O (0.1% TFA)/37% CH_3CN; to 17.50 min, 10% H_2O (0.1% TFA)/90% CH_3CN; to 17.51 min, 100% CH_3CN; held to 27.50 min at a flow rate of 3.0 mL/min.

The collected fraction was concentrated and redissolved in 4 mL of MeOH in a 25 mL one-neck round-bottom flask, followed by adding 2 N HCl in Et_2O (1 mL). The resulting mixture was concentrated under reduced pressure using a rotary evaporator. This cycle was repeated several times to exchange residual trifluoroacetate counterions with chloride fully. The desired product was obtained as a foam (48.4 mg, 0.03 mmol, 57%).



Physical state: Dark-red foam.

Retention time: 12.00 min.

^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ 8.68 (d, *J* = 7.0 Hz, 4H), 8.10 (d, *J* = 7.0 Hz, 4H), 7.86 (s, 2H), 7.83 (d, *J* = 16.2 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 4H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 4H), 6.95 (d, *J* = 8.7 Hz, 4H), 6.68 (d, *J* = 8.9 Hz, 4H), 4.48 (t, *J* = 5.0 Hz, 4H), 4.37 (t, *J* = 8.5 Hz, 2H), 4.30 (s, 6H), 4.00 - 3.72 (m, 22H), 3.66 - 3.57 (m, 8H), 3.45 (t, *J* = 6.4 Hz, 2H), 2.99 (t, *J* = 7.2 Hz, 4H), 2.57 (t, *J* = 7.2 Hz, 4H), 1.95 (s, 6H), 1.89 (t, *J* = 6.3 Hz, 4H). **^{13}C NMR (100 MHz, MeOD-*d*$_4$)** δ 157.8, 153.4, 146.4, 144.5, 142.7, 140.7, 137.8, 135.6, 133.1, 132.3, 131.7, 127.6, 123.6, 122.2, 113.6, 101.7, 75.1, 71.5, 69.7, 68.5, 68.1, 65.3, 61.0, 52.8, 46.6, 36.1, 34.0, 30.7. **HRMS (ESI-TOF)** Calcd for $C_{82}H_{102}N_{12}O_{18}$, $[M]^{2+}$: 771.3712. Found 771.3679.

2. Spectrum

2.1 Photostability measurements

UV-Vis absorption and fluorescence spectra were measured on Perkin-Elmer and Hitachi F-4500 fluorescence spectrophotometers. All measurements were made using a 1-cm quartz cuvette in different solvents at a concentration of 10 μM.

2.2 Photophysical data of ***gem*-TPEVP-TsG**, ***gem*-TPEVP-FBG**, ***gem*-TPEVP-TPPG** and ***gem*-TPEVP-G2**(Tables S1 to S3)

Table S1. Spectral properties of ***gem*-TPEVP-TsG**, ***gem*-TPEVP-FBG**, ***gem*-TPEVP-TPPG**, and ***gem*-TPEVP-** in H_2O.

Comp.	$\lambda_{abs1}{}^{\alpha}$	$\lambda_{abs2}{}^{\beta}$	$\varepsilon_1{}^{\gamma}$	$\varepsilon_2{}^{\delta}$	$\Delta\lambda^{\varepsilon}$	$\lambda_{em}{}^{\zeta}$	**FI**$^{\eta}$	$\sigma_s{}^{\theta}$
TsG	331	405	12.486	14.966	74	740	354	29,851
FBG	330	405	13.01	14.8	75	738	392	30,030
TPPG	333	415	13.12	14.61	82	752	318	29,674
G2	330	404	12.224	14.55	74	738	280	29,940

α. λ_{abs1} **(nm)**, the wavelength of the first major absorption band. β. λ_{abs2} **(nm)**, the wavelength of the second major absorption band. γ. ε_1 **(x10^4 M^{-1} cm^{-1})**, molar extinction of the first major absorption band. δ. ε_2 **(x10^4 M^{-1} cm^{-1})**, molar extinction of the second major absorption band. ε. **Δλ (nm)**, λ_{abs2}-λ_{abs1}. ζ. λ_{em}, maximum emission wavelength. η. **FI (a.u.)**, fluorescence intensity of the maximum emission wavelength. θ. σ_s **(cm^{-1})**, Stokes shift from λ_{abs2} to λ_{em}.

Table S2. Spectral properties of ***gem*-TPEVP-TsG**, ***gem*-TPEVP-FBG**, ***gem*-TPEVP-TPPG**, and ***gem*-TPEVP-G2** in DMSO.

Comp.	λ_{abs1}[α]	λ_{abs2}[β]	ε_1[γ]	ε_2[δ]	$\Delta\lambda$[ε]	λ_{em}[ζ]	**FI**[η]	σ_s[θ]
TsG	333	415	14.23	15.82	82	803	231	25,773
FBG	332	416	13	13.8	84	794	241	26,455
TPPG	331	414	13.11	14.6	83	796	195	26,178
G2	332	416	13.613	14.676	84	800	232	26,042

α. λ_{abs1} **(nm)**, the wavelength of the first major absorption band. β. λ_{abs2} **(nm)**, the wavelength of the second major absorption band. γ. ε_1 **(x10^4 M^{-1} cm^{-1})**, molar extinction of the first major absorption band. δ. ε_2 **(x10^4 M^{-1} cm^{-1})**, molar extinction of the second major absorption band. ε. **Δλ (nm)**, λ_{abs2}-λ_{abs1}. ζ. λ_{em}, maximum emission wavelength. η. **FI (a.u.)**, fluorescence intensity of the maximum emission wavelength. θ. σ_s **(cm^{-1})**, Stokes shift from λ_{abs2} to λ_{em}.

Table S3. Spectral properties of ***gem*-TPEVP-TsG**, ***gem*-TPEVP-FBG**, and ***gem*-TPEVP-TPPG** in 1,4-dioxane.

Comp.	$\lambda_{abs1}{}^{\alpha}$	$\lambda_{abs2}{}^{\beta}$	$\varepsilon_1{}^{\gamma}$	$\varepsilon_2{}^{\delta}$	$\Delta\lambda^{\varepsilon}$	$\lambda_{em}{}^{\zeta}$	**FI**$^{\eta}$	$\sigma_s{}^{\theta}$
TsG	340	436	13	14.37	96	667	650	43,290
FBG	348	459	12.06	13.2	111	672	677	46,948
TPPG	339	432	13.34	13.86	93	664	1192	43,103

α. λ_{abs1} **(nm)**, the wavelength of the first major absorption band. β. λ_{abs2} **(nm)**, the wavelength of the second major absorption band. γ. ε_1 **(x10^4 M^{-1} cm^{-1})**, molar extinction of the first major absorption band. δ. ε_2 **(x10^4 M^{-1} cm^{-1})**, molar extinction of the second major absorption band. ε. **Δλ (nm)**, λ_{abs2}-λ_{abs1}. ζ. λ_{em}, maximum emission wavelength. η. **FI (a.u.)**, fluorescence intensity of the maximum emission wavelength. θ. σ_s **(cm^{-1})**, Stokes shift from λ_{abs2} to λ_{em}

2.3 Absorption and Fluorescence spectra of ***gem*-TPEVP-G2** in H_2O and DMSO (Fig. S1)

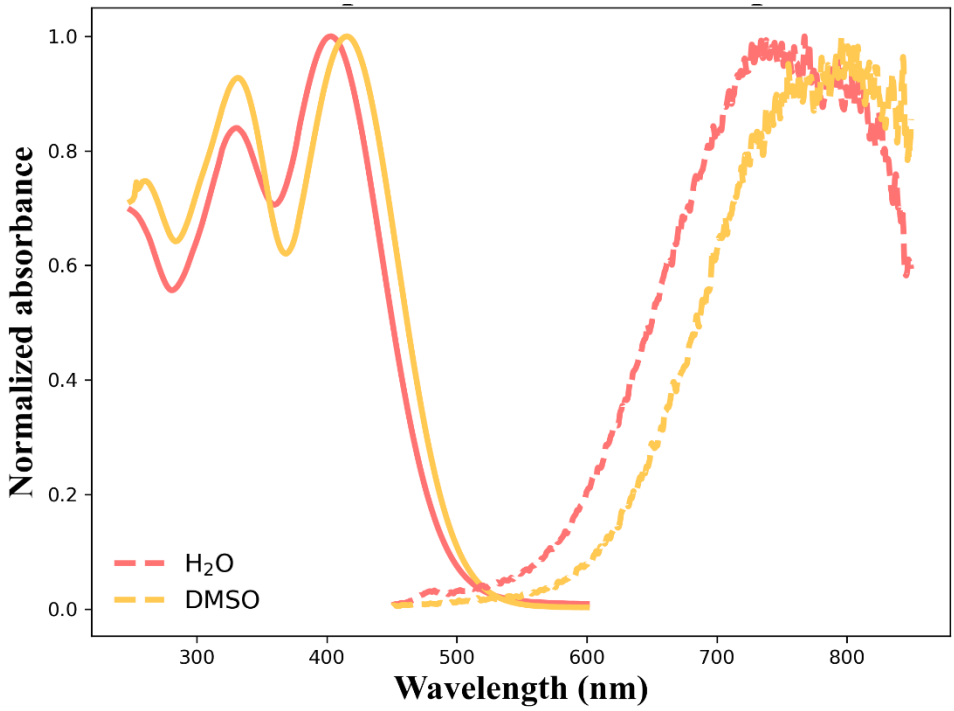


Fig. S1 Absorption and Fluorescence spectra of ***gem*-TPEVP-G2** in H_2O and DMSO.

3. ROS Detection

3.1 Total ROS Detection Using DCFH-DA Assay

The generation of reactive oxygen species (ROS) by ***gem*-TPEVP-TsG**, ***gem*-TPEVP-FBG**, ***gem*-TPEVP-TPPG**, and ***gem*-TPEVP-G2** was evaluated using the ROS-sensitive fluorescence probe 2',7'-dichlorofluorescin diacetate (DCFH-DA, Sigma-Aldrich, USA). A 1 mM stock solution of DCFH-DA was prepared in ethanol (1 mL), and a separate 1 mM NaOH stock solution was prepared in water (2 mL). To initiate hydrolysis, 0.5 mL of the 1 mM DCFH-DA solution was mixed with 2.0 mL of the 1 mM NaOH solution and stirred at room temperature for 30 min to allow complete hydrolysis of the diacetate groups. Subsequently, 7.5 mL of phosphate-buffered saline (PBS, 10 mM) was added to neutralize the solution, yielding a hydrolyzed DCFH solution with a final concentration of 50 μM, which was directly used in subsequent assays. For ROS detection, 5 μM of each compound (prepared from 5 mM stock solutions in H_2O/DMSO, 1:1 v/v) was mixed with hydrolyzed DCFH solution (5 μM, 200 μL from the 50 μM stock solution) and further diluted with PBS buffer to a final volume of 1 mL in 1.5 mL microcentrifuge tubes. After thorough mixing, 100 μL of each sample was transferred into wells of a 96-well microplate. The samples were irradiated with white light (50 mW/cm²) for various durations, and the fluorescence emission intensity of oxidized DCFH was recorded using a microplate reader, fluorescence intensity was immediately measured using a microplate reader (BioTek Synergy H1 Hybrid Multi-Mode Reader, BioTek Instruments, USA) with an excitation wavelength of 504 nm, an emission wavelength of 529 nm, and a fixed gain of 60.

3.2 Type I ROS Detection Using DHR123 Assay

The generation of Type I reactive oxygen species (ROS) by ***gem*-TPEVP-TsG**, ***gem*-TPEVP-FBG**, ***gem*-TPEVP-TPPG**, and ***gem*-TPEVP-G2** upon white-light

irradiation was evaluated using dihydrorhodamine 123(DHR123, Sigma-Aldrich, USA), a non-fluorescent probe that becomes fluorescent upon oxidation by species such as superoxide anion ($•O_2^-$) and hydroxyl radical (•OH). In a typical experiment, 5 μM of each compound (prepared from 5 mM stock solutions in H_2O/DMSO, 1:1 v/v) was mixed with DHR123 (5 μM, 5 μL from a 1 mM stock solution in methanol), and the resulting solution was diluted to a final volume of 1 mL with PBS buffer in 1.5 mL microcentrifuge tubes. After thorough mixing, 100 μL of each solution was transferred into wells of a 96-well microplate. The samples were irradiated with white light (50 mW/cm²) for various durations, and the fluorescence signal of oxidized rhodamine 123, indicative of Type I ROS formation, was recorded using a microplate reader, fluorescence intensity was immediately measured using a microplate reader (BioTek Synergy H1 Hybrid Multi-Mode Reader, BioTek Instruments, USA) with an excitation wavelength of 515 nm, an emission wavelength of 536 nm, and a fixed gain of 60.

3.3 Singlet Oxygen ($^1O_2$) Detection Using SOSG Assay

The generation of singlet oxygen ($^1O_2$) by ***gem*-TPEVP-TsG**, ***gem*-TPEVP-FBG**, ***gem*-TPEVP-TPPG**, and ***gem*-TPEVP-G2** upon white-light irradiation was evaluated using Singlet Oxygen Sensor Green (SOSG, Thermo Fisher Scientific, USA), a selective fluorescence probe for $^1O_2$. In a typical experiment, 5 μM of each compound (prepared from 5 mM stock solutions in H_2O/DMSO, 1:1 v/v) was mixed with SOSG (5 μM, 5 μL from a 1 mM stock solution in methanol), and the mixture was diluted to a final volume of 1 mL with PBS buffer in 1.5 mL microcentrifuge tubes. After thorough mixing, 100 μL of the reaction solution was transferred into wells of a 96-well microplate. The samples were irradiated with white light (50 mW/cm²) for various intervals, and the fluorescence signal of the oxidized SOSG, indicative of $^1O_2$ generation, was recorded using a microplate reader, fluorescence intensity was

immediately measured using a microplate reader (BioTek Synergy H1 Hybrid Multi-Mode Reader, BioTek Instruments, USA) with an excitation wavelength of 504 nm, an emission wavelength of 525 nm, and a fixed gain of 60.

3.4 Hydroxyl Radical Detection *via* DMPO Spin-Trapping and EPR Spectroscopy

The production of hydroxyl radicals (•OH) by ***gem*-TPEVP-TsG**, ***gem*-TPEVP-FBG**, ***gem*-TPEVP-TPPG**, and ***gem*-TPEVP-G2** was confirmed using the electron paramagnetic resonance (EPR) spin-trapping technique with 5,5-dimethyl-1-pyrroline N-oxide (DMPO, Sigma-Aldrich, USA) as the spin trap. In a typical experiment, 50 μM of each compound (prepared from 5 mM stock solutions in DMSO/H_2O, 1:1 v/v) was mixed with 25 μM DMPO in 2 mL of PBS buffer. The solution was irradiated with white light (50 mW/cm²) for 30 min, and the EPR spectra were immediately recorded on a Bruker ELEXSYS-II E500 spectrometer operating in the X-band. The formation of DMPO-OH adducts was observed as a characteristic four-line signal pattern, confirming the generation of hydroxyl radicals through a Type I ROS pathway.

3.5 Singlet Oxygen Detection *via* TMP Spin-Trapping and EPR Spectroscopy

The production of singlet oxygen ($^1O_2$) by ***gem*-TPEVP-TsG**, ***gem*-TPEVP-FBG**, ***gem*-TPEVP-TPPG**, and ***gem*-TPEVP-G2** was confirmed using the electron paramagnetic resonance (EPR) spin-trapping technique with 2,2,6,6-tetramethylpiperidine (TMP, Sigma-Aldrich, USA) as the spin trap. In a typical experiment, 10 μM of each compound (prepared from 5 mM stock solutions in DMSO/H_2O, 1:1 v/v) was mixed with 25 μM TMP in 2 mL of PBS buffer. The solution was irradiated with white light (50 mW/cm²) for 30 min, and the EPR spectra were immediately recorded on a Bruker ELEXSYS-II E500 spectrometer operating in the X-band. The formation of TEMPO was detected as a characteristic three-line signal

pattern, confirming the generation of $^1O_2$ through a Type II ROS pathway.

3.6 Spin-trapping EPR analysis of Type I and Type II ROS (Figs. S2-S3)

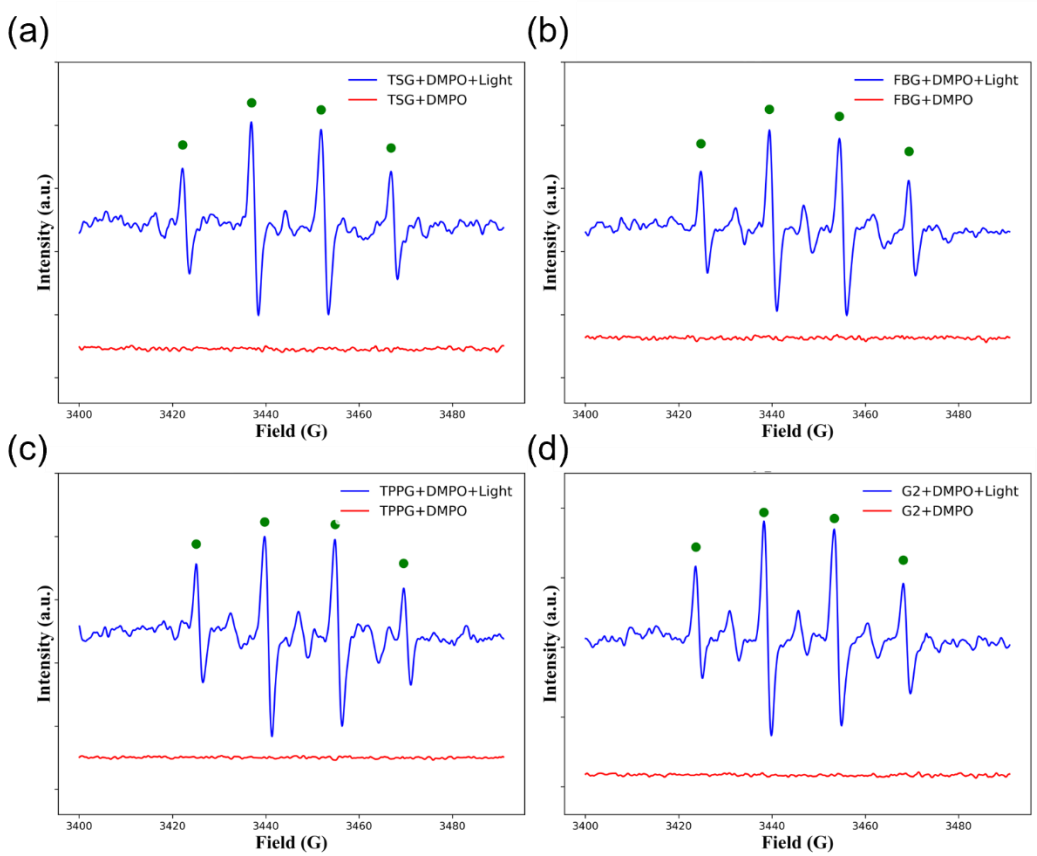


Fig. S2 EPR signals of DMPO (25 μM) and (a) ***gem*-TPEVP-TsG**, (b) ***gem*-TPEVP-FBG**, (c) ***gem*-TPEVP-TPPG**, (d) ***gem*-TPEVP-G2**, in PBS buffer with and without white-light (30 min).

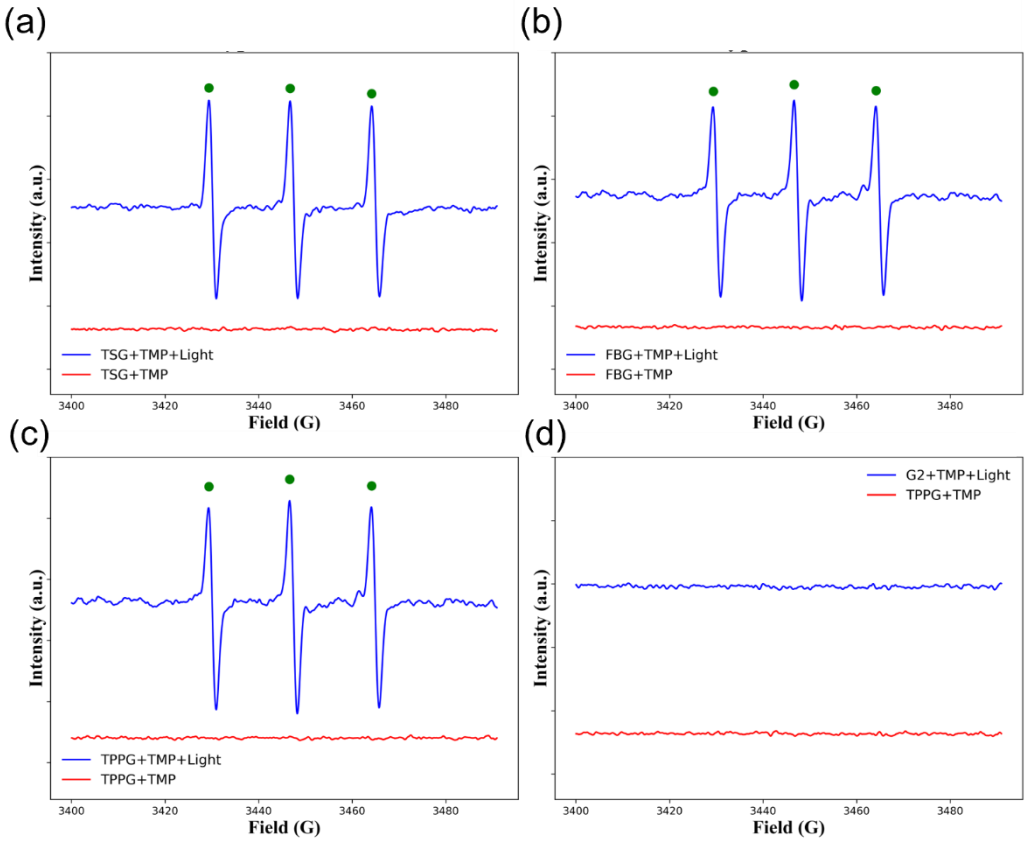


Fig. S3 EPR signals of TMP (25 μM) and (a) ***gem*-TPEVP-TsG**, (b) ***gem*-TPEVP-FBG**, (c) ***gem*-TPEVP-TPPG**, (d) ***gem*-TPEVP-G2**, in PBS buffer with and without white-light (30 min).

4. Computational Section (CS)

4.1 Theoretical Calculation Method

All calculations were performed with the Gaussian 16 package at the CAM-B3LYP/6-31+G(d,p) level. Density functional theory (DFT) calculations were carried out for structural optimization. The energy minima were confirmed with no imaginary frequencies by vibrational frequency calculations. Optical excitation energies and frontier molecular orbitals were obtained using the time-dependent density functional theory (TD-DFT) method. Natural transition orbitals (NTOs) were evaluated to characterize the nature of the first excited singlet and triplet states for those with complex transition compositions. The solvent effects were considered using the polarizable continuum model (PCM) with water (dielectric constant ε = 78.39) as solvent. Spin-orbit coupling (SOC) constants were computed with ORCA version 5.0.3.

4.2 Computational Results (Tables S4, S5)

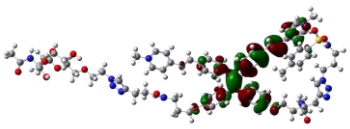
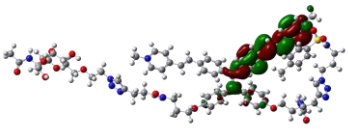
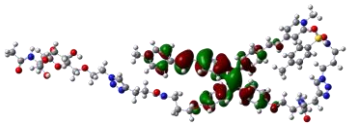
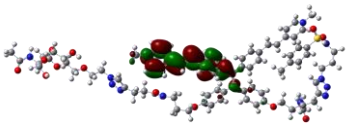
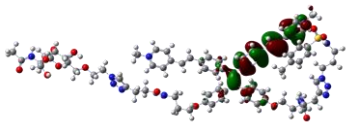
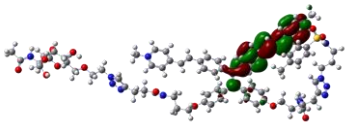
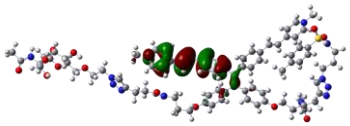
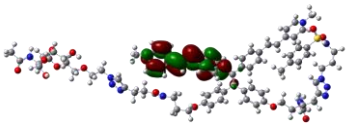
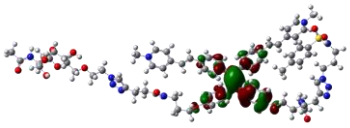
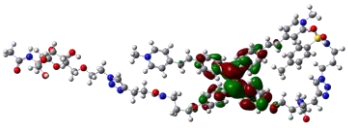
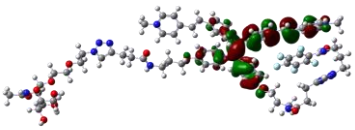
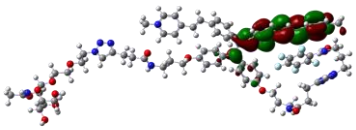
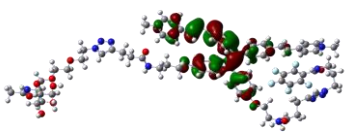
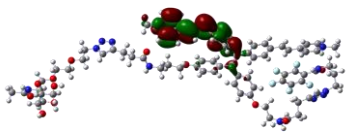
Table S4. Optical excitation and molecular orbital contributions for the S_0-optimized of ***gem*-TPEVP-TsG**, ***gem*-TPEVP-FBG**, ***gem*-TPEVP-TPPG**, and ***gem*-TPEVP-G2**.

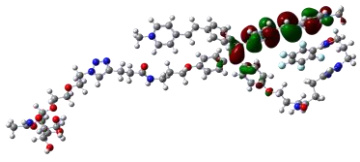
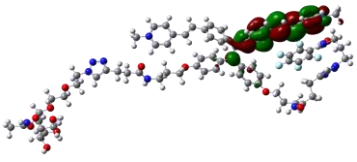
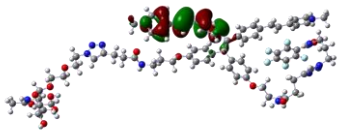
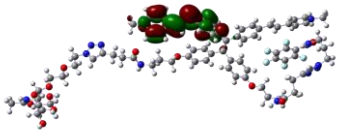
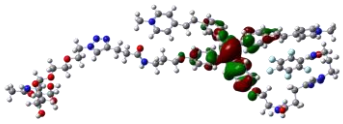
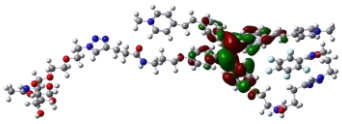
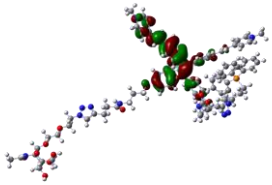
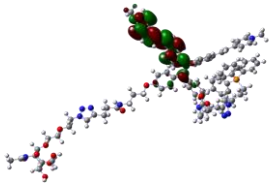
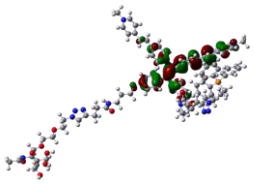
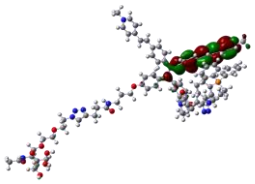
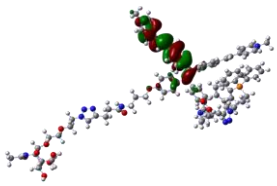
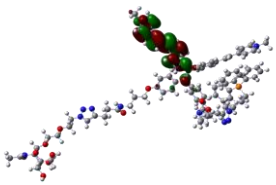
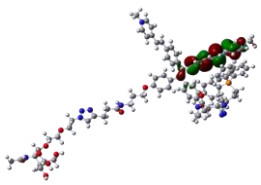
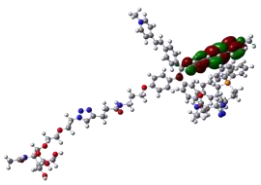
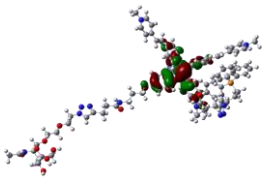
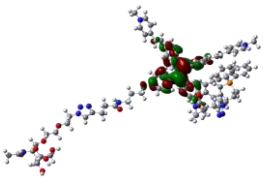
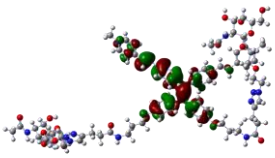
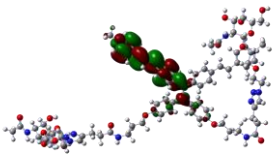
Comp.	no.	E (eV)	nm	f	Contribution	Amplitude
TsG	S_1	3.14	374.0	0.9214	HOMO → LUMO	0.60
	S_2	3.20	386.6	1.2574	HOMO → LUMO+1	0.58
	T_1	1.95	637.1	0	HOMO → LUMO+1 HOMO-2 → LUMO+1 HOMO → LUMO+2	0.40 0.34 0.22
	T_2	2.06	601.3	0	HOMO-3 → LUMO+1 HOMO → LUMO HOMO-2 → LUMO+1	0.40 0.34 0.20

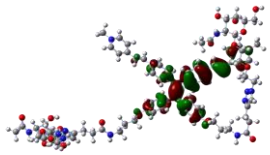
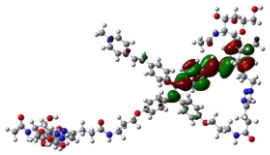
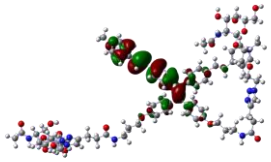
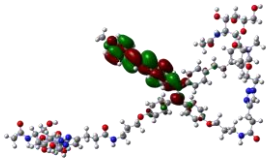
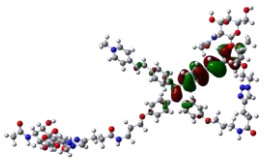
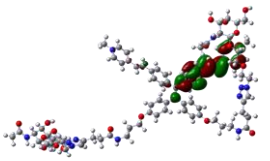
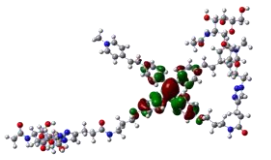
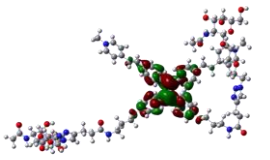
	T_3	2.56	484.2	0	HOMO → LUMO+2	0.44
FBG	S_1	3.13	396.2	1.0238	HOMO → LUMO	0.60
	S_2	3.33	372.0	0.8294	HOMO → LUMO+1	0.57
	T_1	1.95	635.2	0	HOMO → LUMO HOMO-3 → LUMO	0.40 0.39
	T_2	2.15	578.0	0	HOMO-2 → LUMO+1 HOMO-1 → LUMO+1 HOMO → LUMO+1	0.46 0.27 0.27
	T_3	2.62	474.0	0	HOMO → LUMO+3 HOMO → LUMO+4	0.30 0.27
TPPG	S_1	3.17	391.1	1.2471	HOMO → LUMO	0.54
	S_2	3.30	375.7	1.0214	HOMO → LUMO+1	0.51
	T_1	1.96	631.8	0	HOMO-2 → LUMO HOMO → LUMO HOMO → LUMO+1	0.40 0.32 0.25
	T_2	2.12	584.1	0	HOMO-3 → LUMO+1 HOMO-2 → LUMO+1 HOMO → LUMO+1	0.35 0.27 0.25
	T_3	2.61	485.4	0	HOMO → LUMO+5	0.40
G2	S_1	3.15	393.8	0.9685	HOMO → LUMO	0.59
	S_2	3.24	382.6	1.3609	HOMO → LUMO+1	0.58
	T_1	1.96	631.7	0	HOMO → LUMO HOMO-3 → LUMO	0.33 0.29
	T_2	2.09	593.3	0	HOMO → LUMO+1 HOMO-2 → LUMO+1	0.33 0.30

	T_3	2.59	478.8	0	HOMO → LUMO+2	0.40

Table S5. Natural transition orbital (NTO) analysis of the first and second excited singlet states (S_1, S_2) and the first three triplet states (T_1-T_3) for ***gem*-TPEVP-TsG**, ***gem*-TPEVP-FBG**, ***gem*-TPEVP-TPPG**, and ***gem*-TPEVP-G2**.

	state	**weight**	**Hole**	**Electron**
TsG	S1	95.3%		
	S2	94.7%		
	T1	79.5%		
	T2	81.6%		
	T3	66.9%		
FBG	S1	96.0%		
	S2	96.2%		

	T1	88.5%		
	T2	91.9%		
	T3	67.9%		
TPPG	S1	95.9%		
	S2	95.5%		
	T1	86.7%		
	T2	88.6%		
	T3	67.5		
G2	S1	95.0%		

	S2	92.0%		
	T1	71.0%		
	T2	66.5%		
	T3	58.7%		

5. Cell Culture

5.1 Materials

HepG2 (HB-8065™, human hepatocellular carcinoma), Huh-7 (RRID: CVCL 0336, human hepatocellular carcinoma), A549 (CRM-CCL-185™, human lung adenocarcinoma), and HEK-293 (CRL-1573™, human embryonic kidney) cell lines were obtained from the Bioresource Collection and Research Center (BCRC, Hsinchu, Taiwan). Cells were cultured in Gibco™ Dulbecco's Modified Eagle Medium (DMEM, low glucose, with L-glutamine, sodium pyruvate, and phenol red; Thermo Fisher Scientific, USA), supplemented with 10% fetal bovine serum (FBS; Gibco™, Value Plus, USA), and 1% penicillin-streptomycin (5,000 U/mL; Gibco™, Thermo Fisher Scientific, USA). Cells were maintained in a humidified incubator (Hipoint IB-20) at 37 °C with 5% CO_2. The medium was replaced every 48 h, and cells were passaged at ~80% confluence using 0.05% trypsin-EDTA (Gibco™, Thermo Fisher Scientific, USA). Phosphate-buffered saline (PBS, 1X, pH 7.4, without Ca^{2+}, Mg^{2+}, and phenol red; Gibco™, Thermo Fisher Scientific, USA) was prepared from a 10X stock by dilution with ddH_2O and sterilized before use. Dimethyl sulfoxide (DMSO; J.T. Baker, Phillipsburg, NJ, USA) and Alamar Blue (Sigma-Aldrich, USA; prepared as a 1 mg/mL stock in dd-H_2O and diluted 10-fold in PBS, then further diluted 100-fold with fresh DMEM for experiments) were used for cytotoxicity and viability assays.

5.2 Procedure of Alamar Blue Assay

The cytotoxicity of ***gem*-TPEVP-TsG**, ***gem*-TPEVP-FBG**, ***gem*-TPEVP-TPPG**, and ***gem*-TPEVP-G2** was evaluated using the Alamar Blue method. HepG2, Huh7, A549, and HEK293 cells were seeded into 96-well plates at a density of 5×10^4 cells per well in 100 μL of DMEM and incubated for 20 h at 37 °C with 5% CO_2. After

incubation, the culture medium was removed, and each well was washed twice with 100 μL of sterile 1X PBS buffer prior to drug treatment. The compounds were prepared from a 2.5 mM DMSO stock solution. Stock solutions were first diluted 100-fold to 25 μM in DMEM, followed by two-fold serial dilutions to generate final concentrations of 25, 12.5, 6.25, 3.13, 1.56, 0.78, and 0.39 μM. For the 0 μM control group, cells were treated with fresh DMEM containing 1% DMSO without the compound. The final concentration of DMSO was maintained at 1% in all treatments. Cells were then incubated with the compounds for 80 min at 37 °C with 5% CO_2.

For DARK-treated samples, the culture medium of each well was removed, washed with PBS solution (100 μL × 3), and replaced with 100 μL of fresh medium containing Alamar Blue. Alamar Blue stock solution (1 mg/mL) was first diluted 10-fold in PBS, then further diluted 100-fold with fresh DMEM before use. The plates were incubated for 4 h at 37 °C with 5% CO_2. For LIGHT-treated samples, cells were irradiated with white light (50 mW/cm²) for two 10-minute sessions, separated by a 5-minute dark interval, resulting in a total irradiation time of 20 minutes. After irradiation, the medium was removed, cells were washed with PBS solution (100 μL × 3), and incubated with 100 μL of fresh DMEM containing Alamar Blue solution under the same dilution conditions as above for 4 h at 37 °C with 5% CO_2.

Fluorescence intensity was immediately measured using a microplate reader (BioTek Synergy H1 Hybrid Multi-Mode Reader, BioTek Instruments, USA) with an excitation wavelength of 544 nm, an emission wavelength of 590 nm, and a fixed gain of 60. Cell viability was calculated according to the following formula:

$$Cell\ viability\ (\%) = \frac{F_{sample} - F_{blank}}{F_{control} - F_{blank}} \times 100$$

Where F_{sample}, $F_{control}$, and F_{blank} represent the fluorescence intensity of compound-treated cells, untreated control cells (with 1% DMSO), and blank wells (without cells), respectively. IC_{50} values were determined by nonlinear dose-response fitting.

5.3 GalNAc Competition Assay

The GalNAc competition assay was performed using the Alamar Blue method. HepG2 cells were seeded into 96-well plates at a density of 5×10^4 cells per well in 100 μL of DMEM and incubated for 20 h at 37 °C with 5% CO_2. After incubation, the culture medium was removed, and each well was washed twice with 100 μL of sterile 1X PBS buffer. Cells were treated with fresh DMEM (10% FBS, 1% DMSO) containing 50 μM GalNAc for 2 h. Following GalNAc pretreatment, the medium was removed, cells were washed twice with 100 μL of sterile 1X PBS, and then treated with different concentrations of ***gem*-TPEVP-TsG**, ***gem*-TPEVP-FBG**, ***gem*-TPEVP-TPPG**, or ***gem*-TPEVP-G2**. The compounds were prepared from a 2.5 mM DMSO stock solution, diluted to 25 μM in DMEM, and serially diluted two-fold to yield final concentrations of 25, 12.5, 6.25, 3.13, 1.56, 0.78, and 0.39 μM. The 0 μM control group was treated with fresh DMEM containing 1% DMSO without the compound. The final DMSO concentration was maintained at 1% in all treatments. Cells were incubated with the compounds for 80 min at 37 °C with 5% CO_2.

For DARK-treated samples, the culture medium was removed, wells were washed three times with 100 μL of PBS, and replenished with 100 μL of fresh DMEM containing Alamar Blue. The Alamar Blue stock solution (1 mg/mL) was first diluted 10-fold in PBS and then diluted 100-fold with fresh DMEM before use. Plates were incubated for an additional 4 h at 37 °C with 5% CO_2. For LIGHT-treated samples, cells were irradiated with white light (50 mW/cm²) for two 10 min sessions separated by a

5 min dark interval (total light dose: 20 min). The medium was then removed, wells were washed three times with 100 μL of PBS, and replenished with 100 μL of fresh DMEM containing Alamar Blue solution under the same dilution conditions as above, followed by incubation for 4 h at 37 °C with 5% CO_2.

Fluorescence intensity was immediately measured using a microplate reader ([Instrument model, to be added]) with an excitation wavelength of 544 nm, an emission wavelength of 590 nm, and a fixed gain of 60. Cell viability was calculated according to the following formula:

$$Cell\ viability\ (\%) = \frac{F_{sample} - F_{blank}}{F_{control} - F_{blank}} \times 100$$

Where F_{sample}, $F_{control}$, and F_{blank} represent the fluorescence intensity of compound-treated cells, untreated control cells (with 1% DMSO), and blank wells (without cells), respectively.

5.4 Cell Viability Profiles (Figs. S4 to S8)

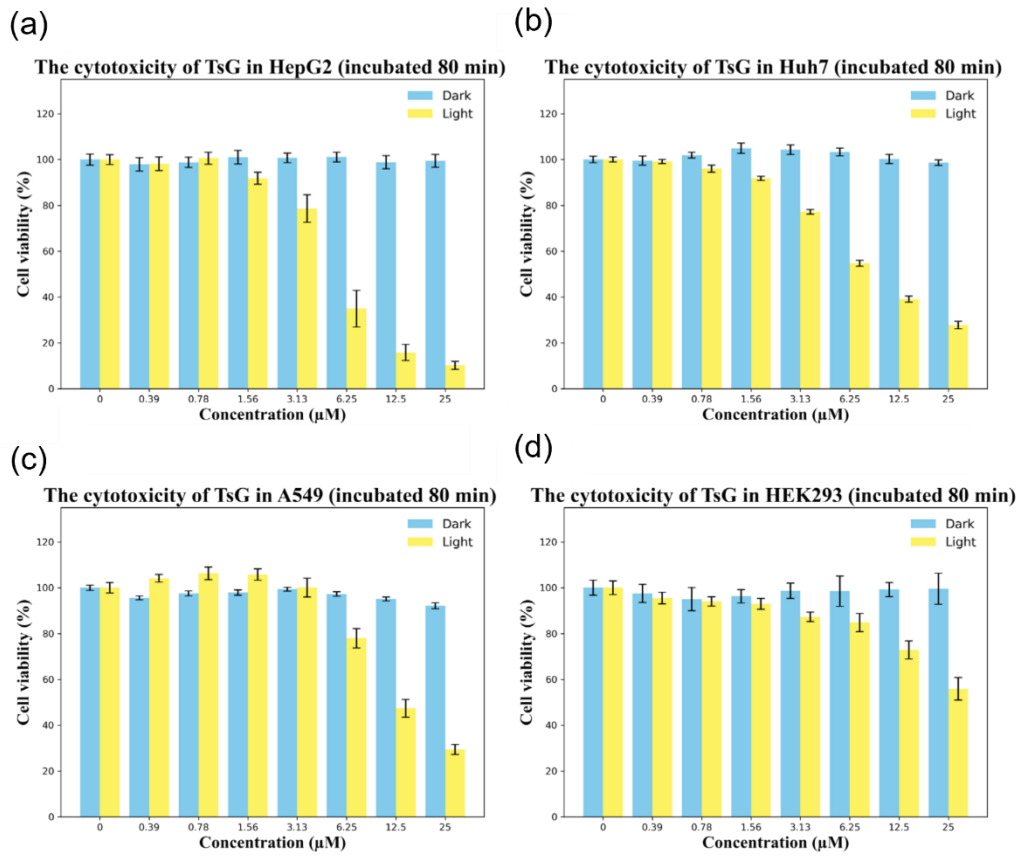


Figure S4. Cell viability profiles of ***gem*-TPEVP-TsG** after 80-minute incubation with varying concentrations (0-25 μM) under light irradiation in (a) HepG2 cells, (b) Huh7 cells, (c) A549 cells, and (d) HEK293 cells.

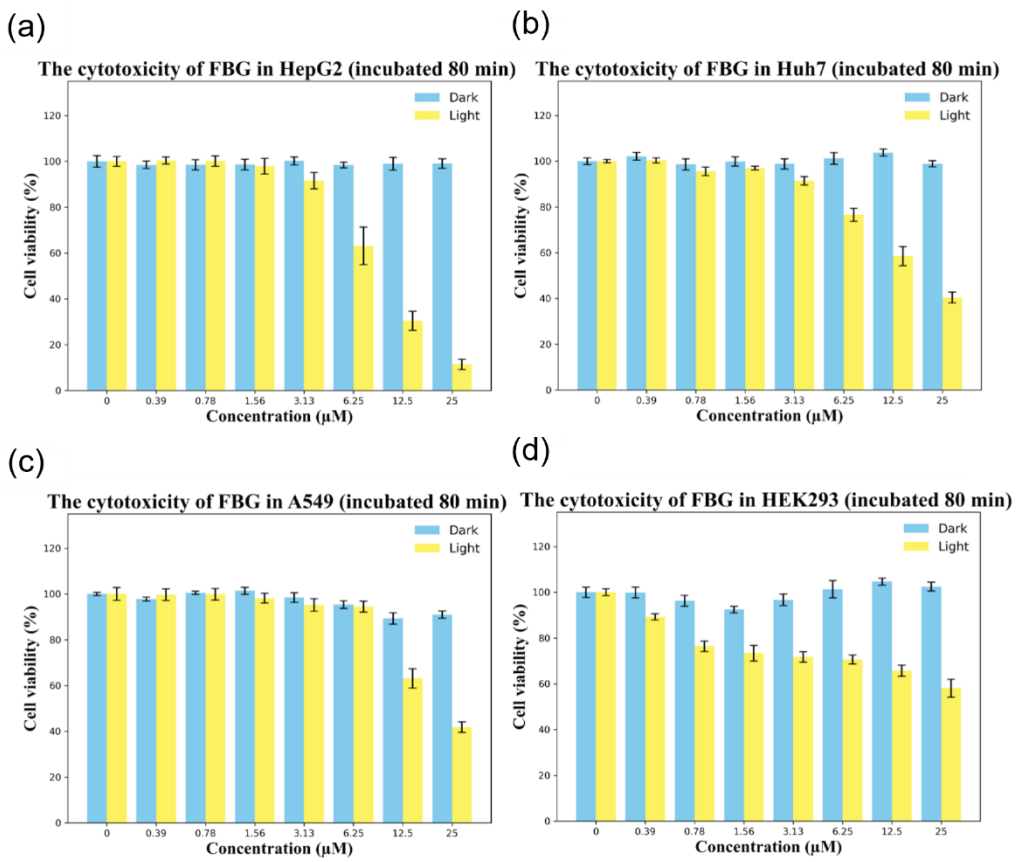


Figure S5. Cell viability profiles of ***gem*-TPEVP-FBG** after 80-minute incubation with varying concentrations (0-25 μM) under light irradiation in (a) HepG2 cells, (b) Huh7 cells, (c) A549 cells, and (d) HEK293 cells.

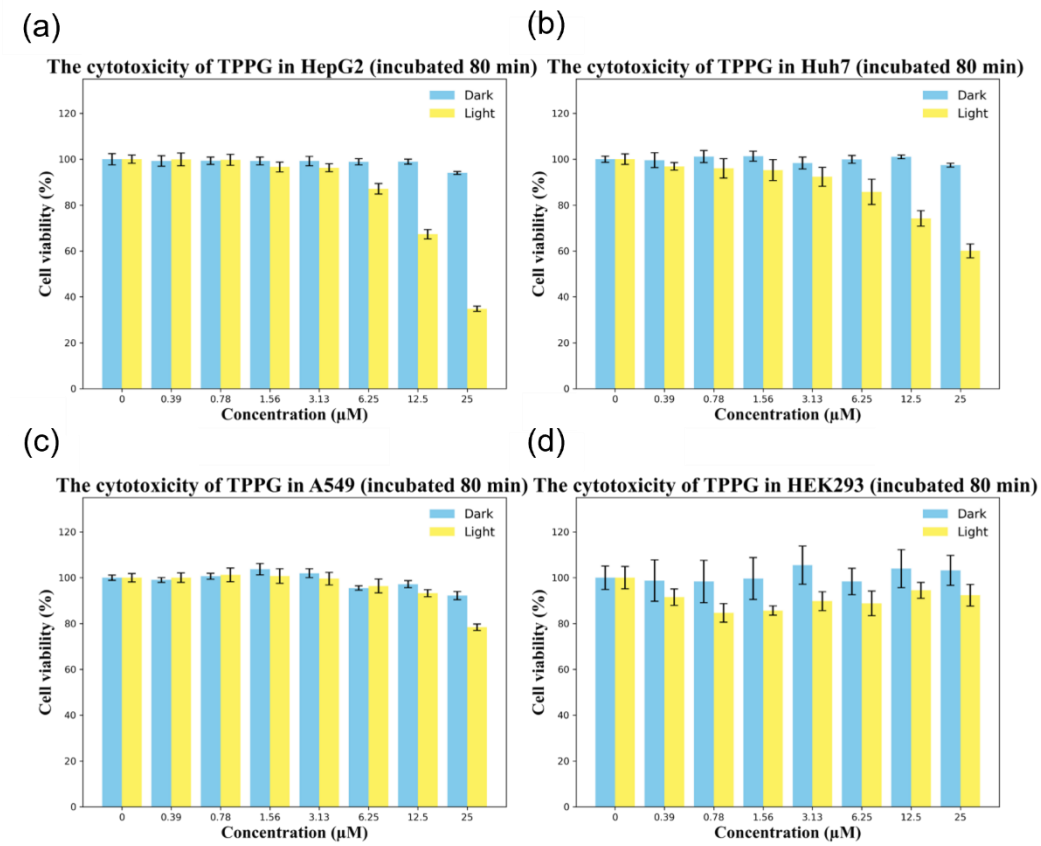


Figure S6. Cell viability profiles of ***gem*-TPEVP-TPPG** after 80-minute incubation with varying concentrations (0-25 μM) under light irradiation in (a) HepG2 cells, (b) Huh7 cells, (c) A549 cells, and (d) HEK293 cells.

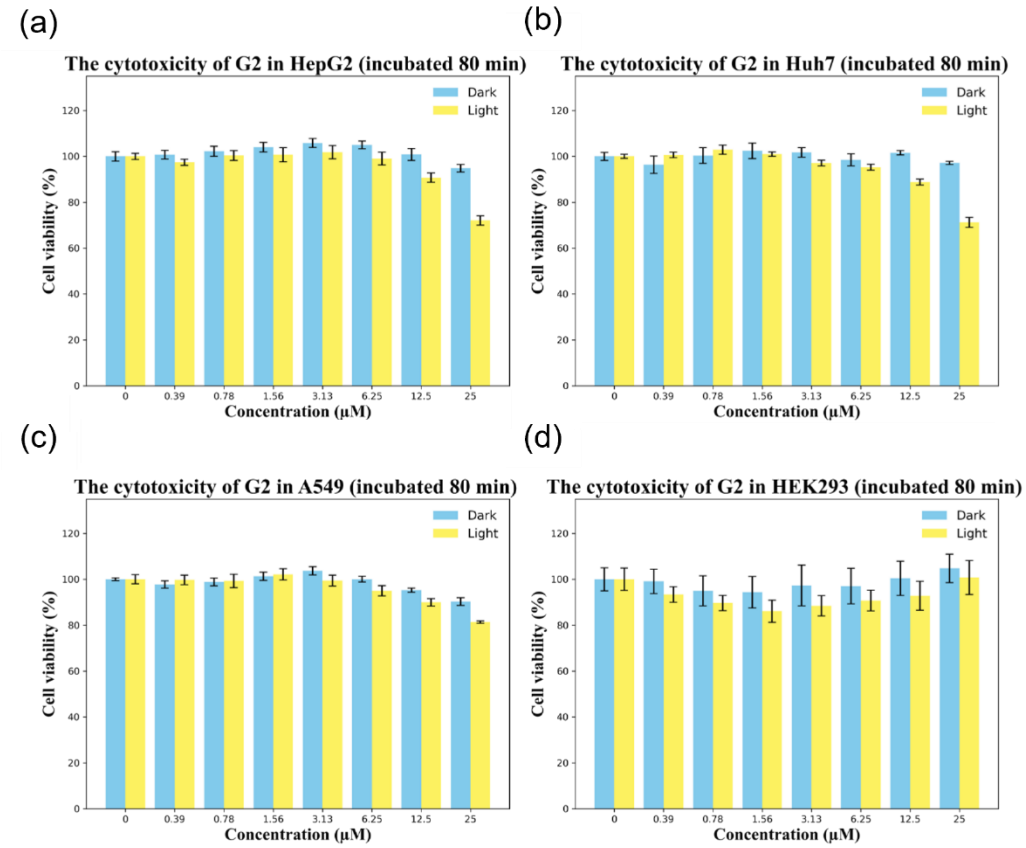


Figure S7. Cell viability profiles of ***gem*-TPEVP-G2** after 80-minute incubation with varying concentrations (0-25 μM) under light irradiation in (a) HepG2 cells, (b) Huh7 cells, (c) A549 cells, and (d) HEK293 cells.

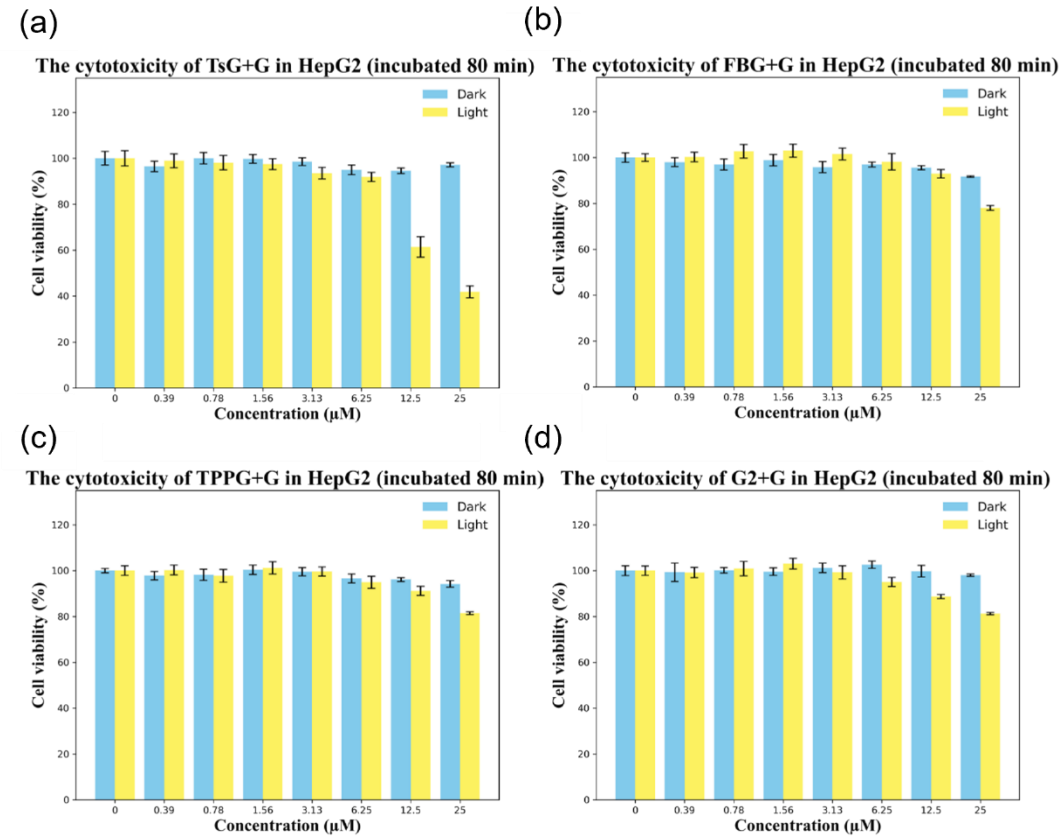


Figure S8. Cell viability profiles of HepG2 cells were evaluated following a 2 h preincubation with GalNAc, followed by co-incubation with (a) ***gem*-TPEVP-TsG**, (b) ***gem*-TPEVP-FBG**, (c) ***gem*-TPEVP-TPPG**, or (d) ***gem*-TPEVP-G2** for 80 minutes. After treatment, cells were exposed to varying concentrations of each compound (0-25 μM) under light irradiation, and cell viability was subsequently assessed.

5.5 Intracellular Total ROS Detection Assay

The intracellular generation of reactive oxygen species (ROS) was evaluated using the DCFH-DA probe. HepG2 cells were seeded into confocal dishes at a density of 1 × 10^5 cells per dish in DMEM (10% FBS) and incubated for 20 h at 37 °C with 5% CO_2. ***gem*-TPEVP-TsG**, ***gem*-TPEVP-FBG**, or ***gem*-TPEVP-TPPG** (10 μM) was first incubated with the cells for 80 min, followed by treatment with DCFH-DA (5 μM, Sigma-Aldrich, USA) for 30 min in serum-free DMEM at 37 °C and 5% CO_2. Cells were then divided into DARK and LIGHT groups. For DARK-treated samples, the culture medium was removed, and cells were washed with PBS (500 μL × 3 per dish), then replenished with 1000 μL of fresh phenol red-free DMEM for confocal imaging. For LIGHT-treated samples, cells were irradiated with white light (50 mW/cm^2) for 5 min, washed with PBS (500 μL × 3 per dish), and replenished with 1000 μL of fresh phenol red-free DMEM for imaging.

Confocal laser scanning microscopy (CLSM) was performed on a Leica TCS SP8 microscope equipped with a 60× oil immersion objective. Green fluorescence was collected using an excitation wavelength of 504 nm and an emission range of 520-570 nm. Cells without probe and drug were used as background control.

5.6 Intracellular Type I ROS Detection Assay

The intracellular generation of Type I ROS was evaluated using the DHR-123 probe. HepG2 cells were seeded into confocal dishes at a density of 1 × 10^5 cells per dish in DMEM (10% FBS) and incubated for 20 h at 37 °C with 5% CO_2. ***gem*-TPEVP-TsG**, ***gem*-TPEVP-FBG**, or ***gem*-TPEVP-TPPG** (10 μM) was first incubated with the cells for 80 min, followed by treatment with DHR-123 (5 μM, Sigma-Aldrich, USA) for 30 min in serum-free DMEM at 37 °C and 5% CO_2. Cells were then divided into DARK and LIGHT groups. For DARK-treated samples, the

culture medium was removed, and cells were washed with PBS (500 μL × 3 per dish), then replenished with 1000 μL of fresh phenol red-free DMEM for confocal imaging. For LIGHT-treated samples, cells were irradiated with white light (50 mW/cm²) for 5 min, washed with PBS (500 μL × 3 per dish), and replenished with 1000 μL of fresh phenol red-free DMEM for imaging.

Confocal laser scanning microscopy (CLSM) was performed on a Leica TCS SP8 microscope equipped with a 60× oil immersion objective. Green fluorescence was collected using an excitation wavelength of 515 nm and an emission range of 530-570 nm. Cells without probe and drug were used as background control.

5.7 Intracellular Type II ROS Detection Assay

The intracellular generation of Type II ROS was evaluated using the SOSG probe. HepG2 cells were seeded into confocal dishes at a density of 1 × 10^5 cells per dish in DMEM (10% FBS) and incubated for 20 h at 37 °C with 5% CO_2. ***gem*-TPEVP-TsG**, ***gem*-TPEVP-FBG**, or ***gem*-TPEVP-TPPG** (10 μM) was first incubated with the cells for 80 min, followed by treatment with SOSG (5 μM, Thermo Fisher Scientific, USA) for 30 min in serum-free DMEM at 37 °C and 5% CO_2. ells were then divided into DARK and LIGHT groups. For DARK-treated samples, the culture medium was removed, and cells were washed with PBS (500 μL × 3 per dish), then replenished with 1000 μL of fresh phenol red-free DMEM for confocal imaging. For LIGHT-treated samples, cells were irradiated with white light (50 mW/cm²) for 5 min, washed with PBS (500 μL × 3 per dish), and replenished with 1000 μL of fresh phenol red-free DMEM for imaging.

Confocal laser scanning microscopy (CLSM) was performed on a Leica TCS SP8 microscope equipped with a 60× oil immersion objective. Green fluorescence was

collected using an excitation wavelength of 504 nm and an emission range of 520-570 nm. Cells without probe and drug were used as background control.

5.8 CLSM Images of Intracellular ROS Detection (Figs. S9 to S11)

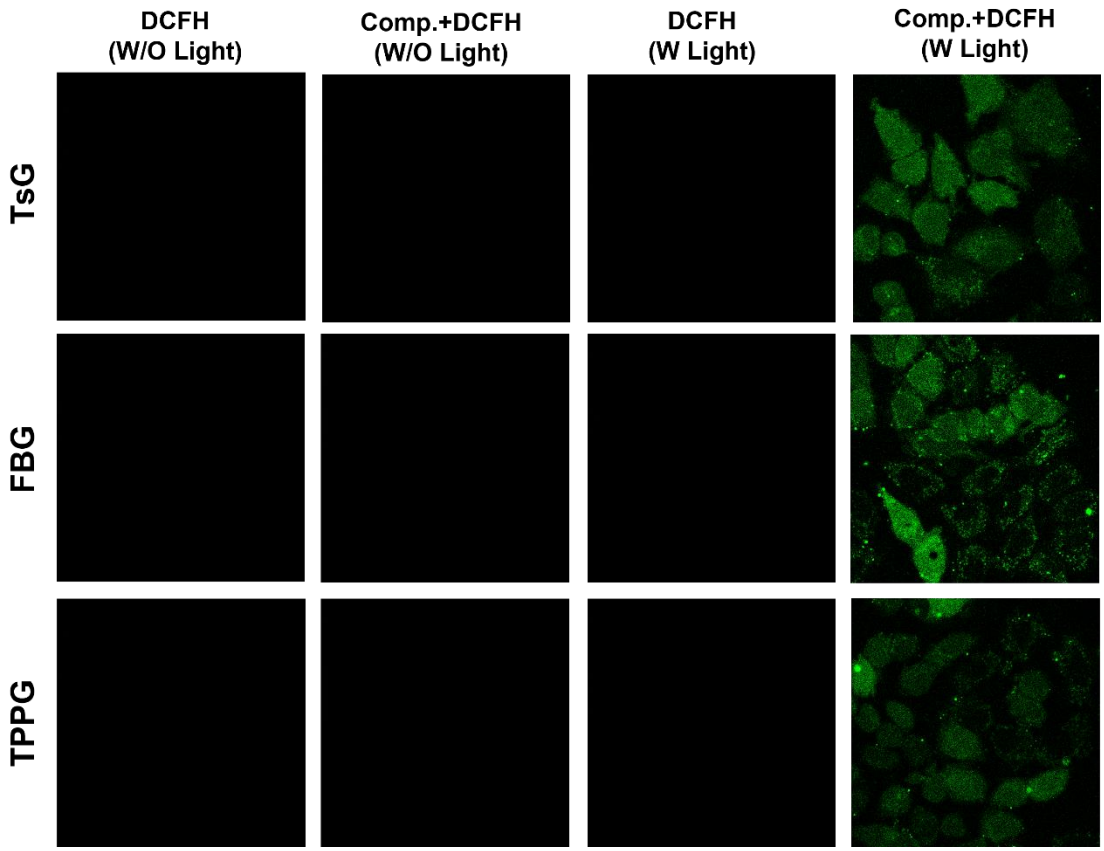


Figure S9. CLSM images of HepG2 cells incubated with 5 μM DCFH and (a) ***gem*-TPEVP-TsG**, (b) ***gem*-TPEVP-FBG**, (c) ***gem*-TPEVP-TPPG** with and without white-light irradiation (50 mW cm^{-2})

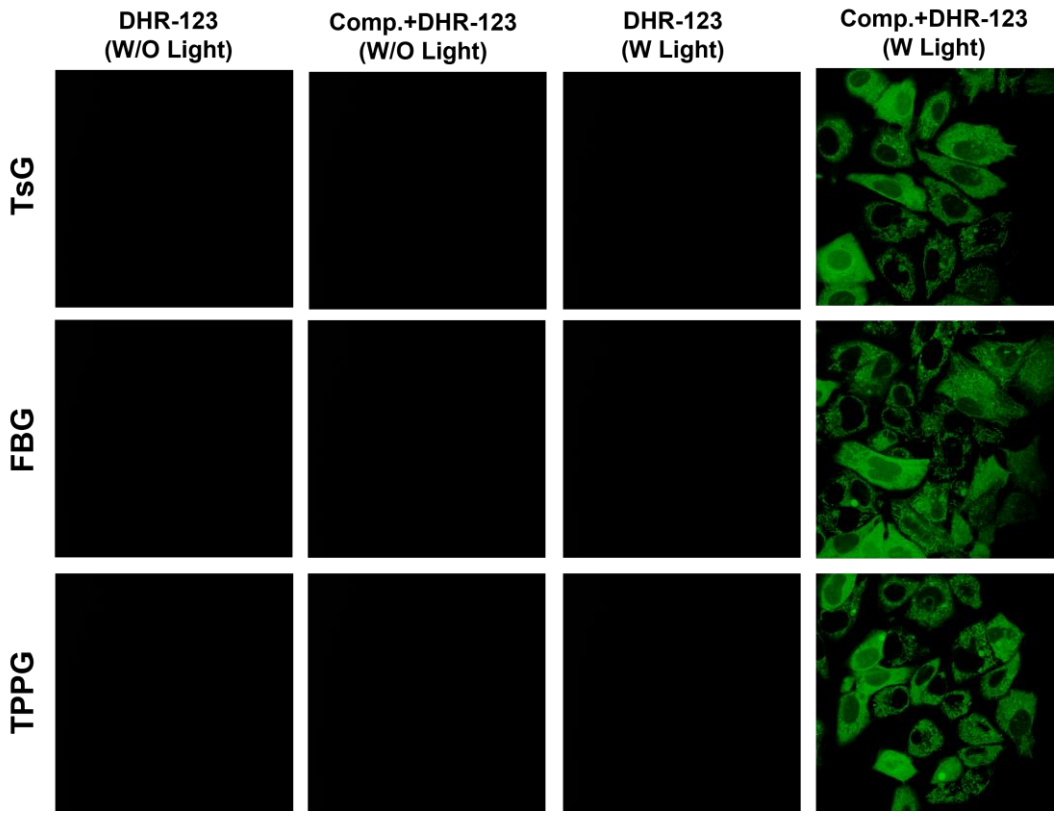


Figure S10. CLSM images of HepG2 cells incubated with 5 μM DHR-123 and (a) ***gem*-TPEVP-TsG**, (b) ***gem*-TPEVP-FBG**, (c) ***gem*-TPEVP-TPPG** with and without white-light irradiation (50 mW cm^{-2})

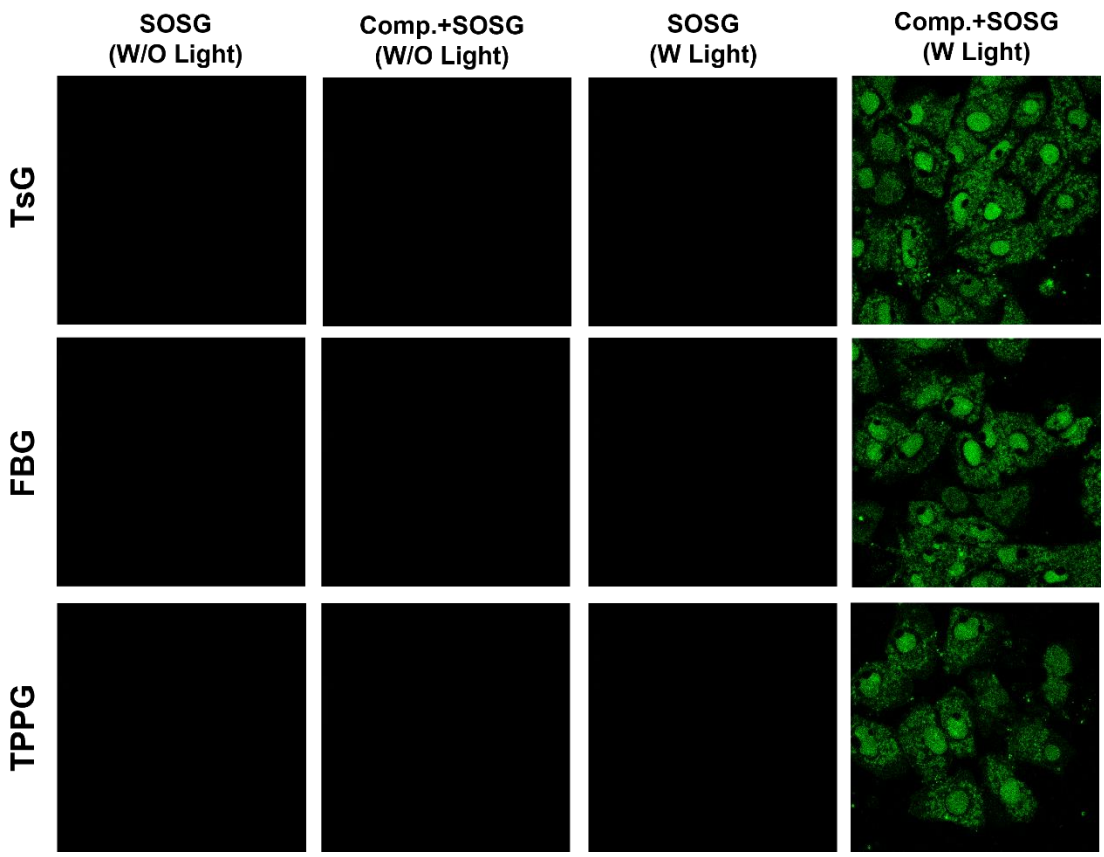


Figure S11. CLSM images of HepG2 cells incubated with 5 μM SOSG and (a) ***gem*-TPEVP-TsG**, (b) ***gem*-TPEVP-FBG**, (c) ***gem*-TPEVP-TPPG** with and without white-light irradiation (50 mW cm^{-2})

5.9 Cell Imaging Assay

HepG2 cells were cultured in Dulbecco's Modified Eagle Medium (DMEM, 10% FBS) at 37 °C in a humidified environment containing 5% CO_2. Cells were subcultured into 35 × 12 mm confocal dishes and incubated for 24 h under the same conditions. Cells were then treated with ***gem*-TPEVP-TsG**, ***gem*-TPEVP-FBG**, ***gem*-TPEVP-TPPG**, or ***gem*-TPEVP-G2** (5 μM, in 1% DMSO solution of 10% FBS DMEM) for 80 min at 37 °C with 5% CO_2. After incubation, cells were washed with PBS (500 μL × 3 per dish) and simultaneously stained with commercial organelle-specific probes (all from Thermo Fisher Scientific, USA): ER-Tracker Green (50 nM, 30 min), MitoTracker Green (50 nM, 30 min), and LysoTracker Deep Red (50 nM, 30 min), each at 37 °C with 5% CO_2. The staining medium was then removed, and cells were rewashed with PBS (500 μL × 3 per dish), followed by replenishment with 1000 μL of phenol red-free DMEM for confocal imaging.

Confocal laser scanning microscopy (CLSM) was performed using a Leica TCS SP8 microscope equipped with a 60× oil-immersion objective. The imaging parameters were as follows: ***gem*-TPEVP-TsG**, ***gem*-TPEVP-FBG**, ***gem*-TPEVP-TPPG**, and ***gem*-TPEVP-G2** (λ_{ex} = 400 nm, λ_{em} = 600-750 nm); ER-Tracker Green (λ_{ex} = 504 nm, λ_{em} = 515-565 nm); MitoTracker Green (λ_{ex} = 490 nm, λ_{em} = 520-570 nm); LysoTracker Deep Red (λ_{ex} = 647 nm, λ_{em} = 680-750 nm). Scale bar = 20 μm.

5.10 CLSM Imaging Results of Subcellular Localization (Figs. S12 to S14, Table S6)

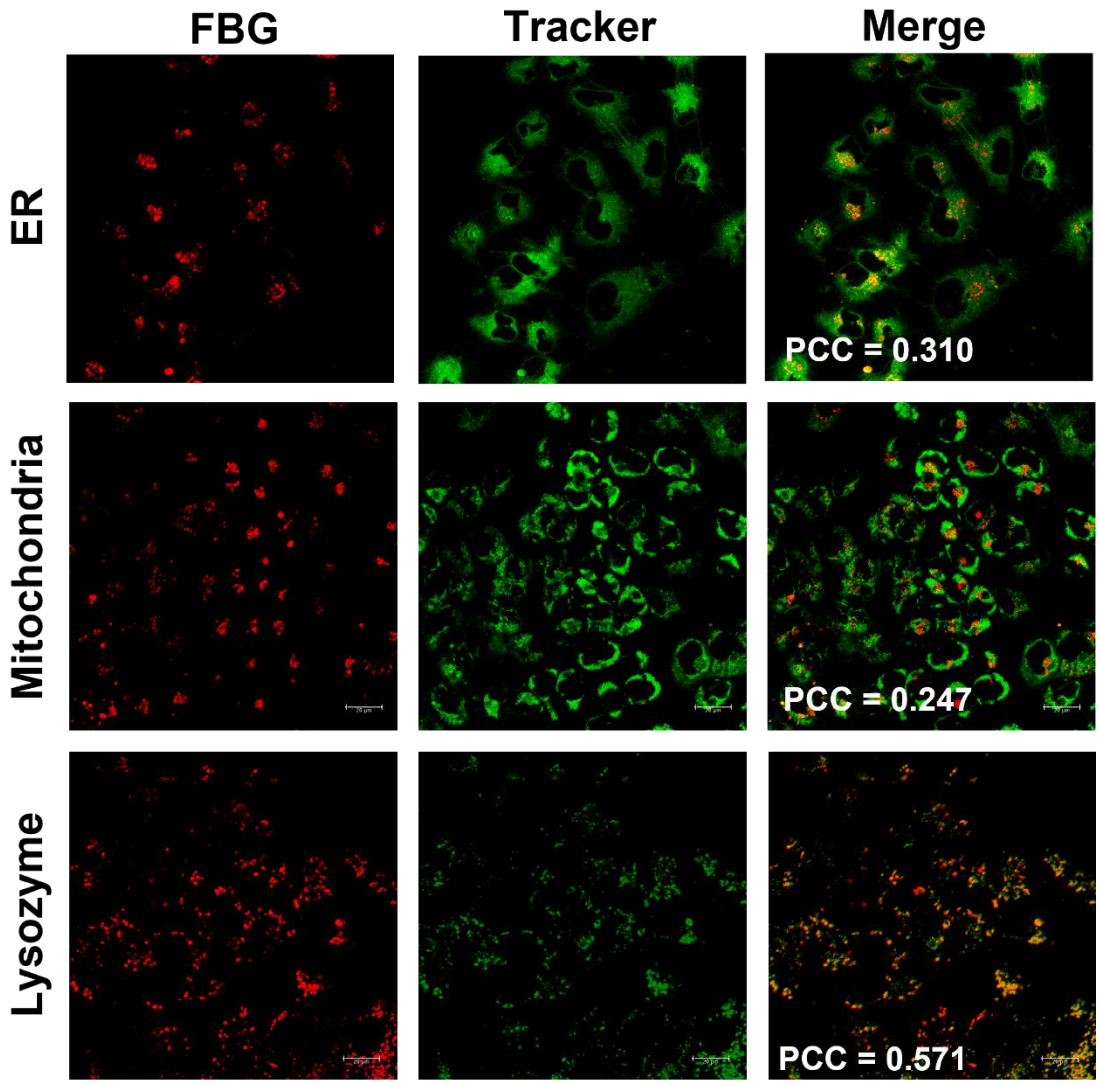


Figure S12. CLSM images of HepG2 cells after 80 min incubation with ***gem*-TPEVP-FBG**, followed by co-staining with ER-Tracker Green for 30 min, Mitotracker Green for 30 min, and Lyso-Tracker Deep Red for 30 min. (Parameters of CLSM: ***gem*-TPEVP-FBG** (λ_{ex} = 400 nm, λ_{em} = 600-750 nm); ER-Tracker Deep Red (λ_{ex} = 504 nm, λ_{em} = 515-565 nm); Mitotracker Green (λ_{ex} = 490 nm, λ_{em} = 520-570 nm); Lyso-Tracker Deep Red (λ_{ex} = 647 nm, λ_{em} = 680-750 nm); scale bar = 20 μm.

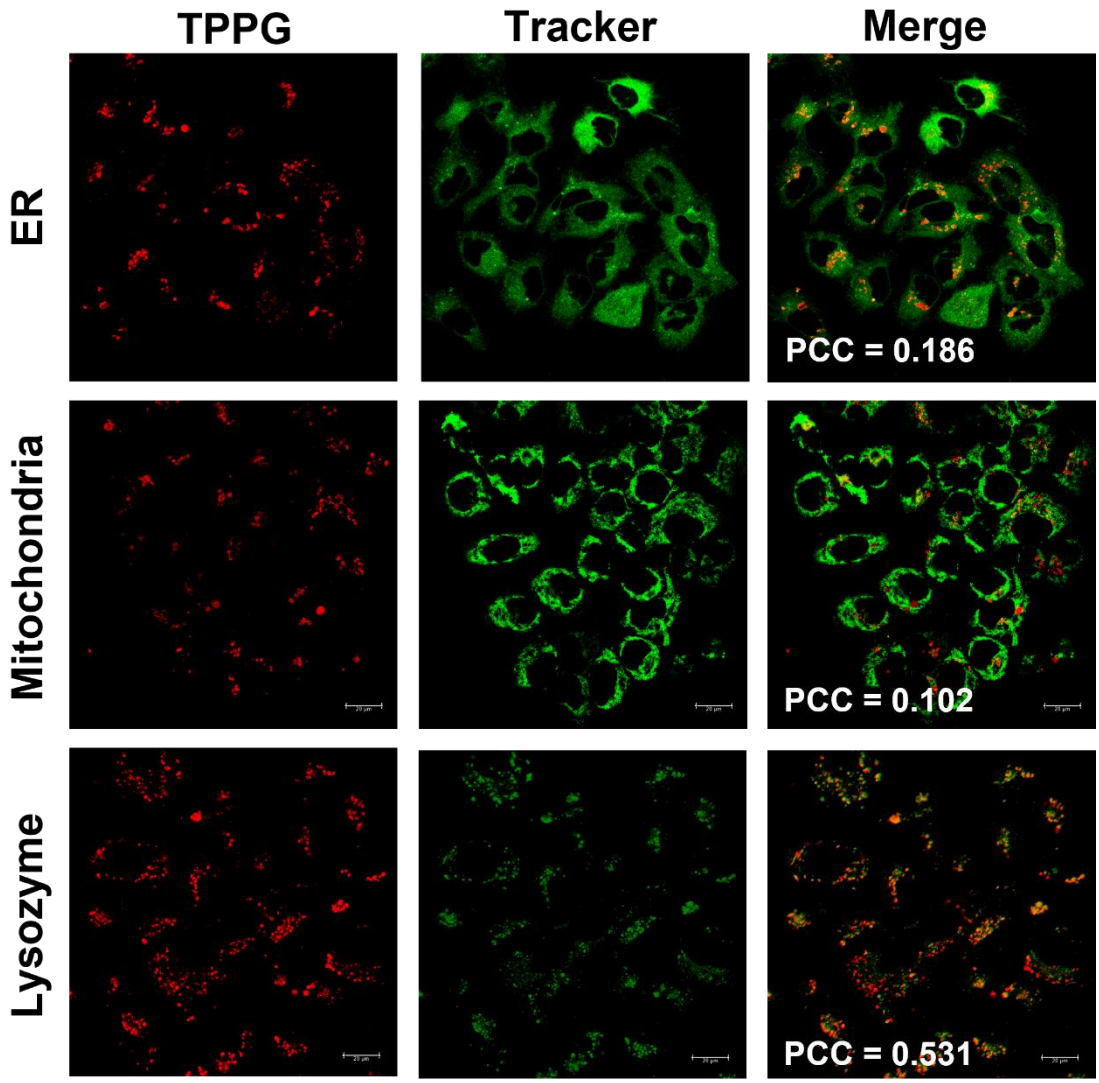


Figure S13. CLSM images of HepG2 cells after 80 min incubation with ***gem*-TPEVP-TPPG**, followed by co-staining with ER-Tracker Green for 30 min, Mitotracker Green for 30 min, and Lyso-Tracker Deep Red for 30 min. (Parameters of CLSM: ***gem*-TPEVP-TPPG** (λ_{ex} = 400 nm, λ_{em} = 600-750 nm); ER-Tracker Deep Red (λ_{ex} = 504 nm, λ_{em} = 515-565 nm); Mitotracker Green (λ_{ex} = 490 nm, λ_{em} = 520-570 nm); Lyso-Tracker Deep Red (λ_{ex} = 647 nm, λ_{em} = 680-750 nm); scale bar = 20 μm.

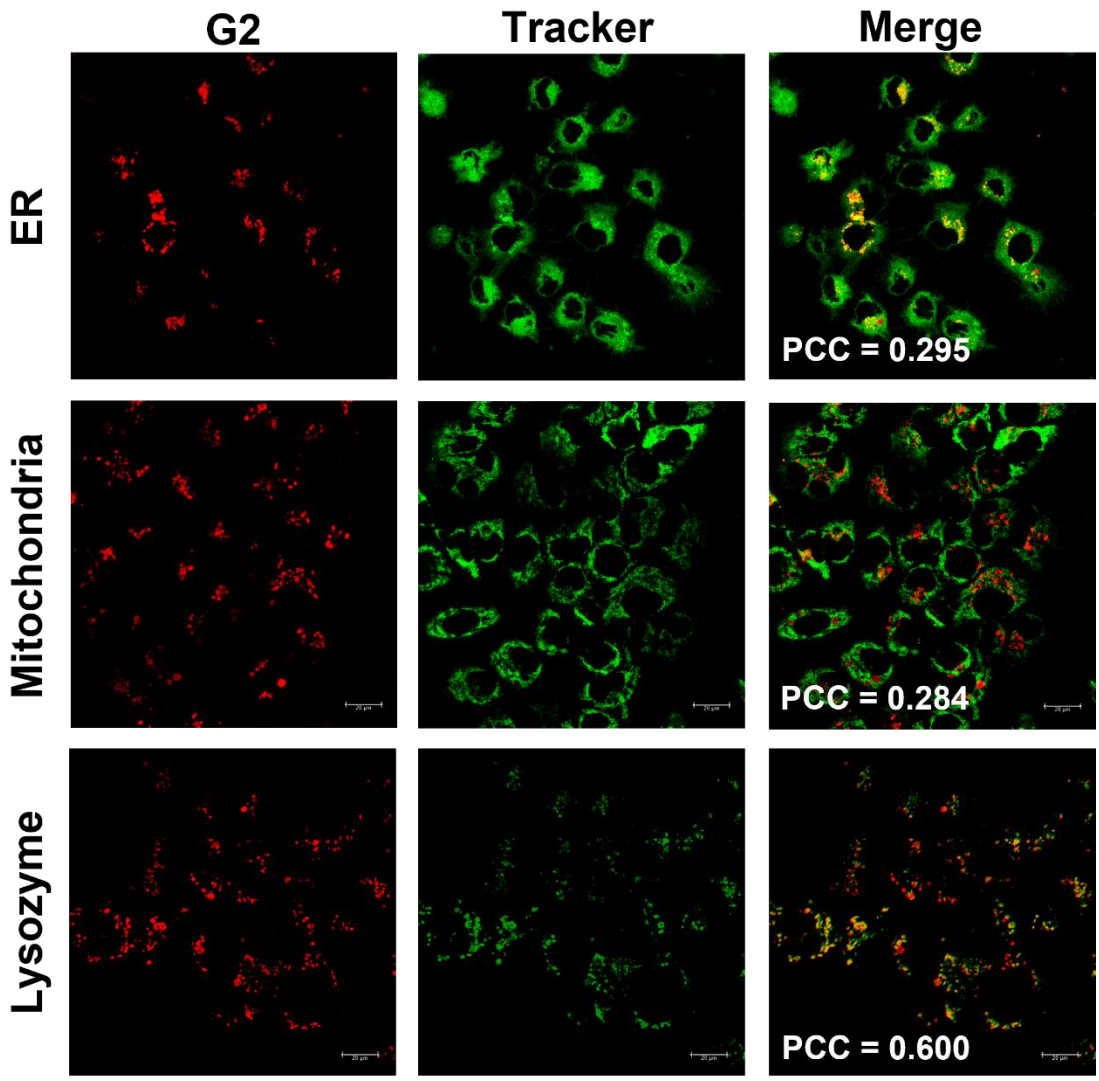


Figure S14. CLSM images of HepG2 cells after 80 min incubation with ***gem*-TPEVP-G2**, followed by co-staining with ER-Tracker Green for 30 min, Mitotracker Green for 30 min, and Lyso-Tracker Deep Red for 30 min. (Parameters of CLSM: ***gem*-TPEVP-G2** (λ_{ex} = 400 nm, λ_{em} = 600-750 nm); ER-Tracker Deep Red (λ_{ex} = 504 nm, λ_{em} = 515-565 nm); Mitotracker Green (λ_{ex} = 490 nm, λ_{em} = 520-570 nm); Lyso-Tracker Deep Red (λ_{ex} = 647 nm, λ_{em} = 680-750 nm); scale bar = 20 μm.

Table S6. Pearson's correlation coefficient (PCC) values for co-localization between each photosensitizer (***gem*-TPEVP-TsG**, ***gem*-TPEVP-FBG**, ***gem*-TPEVP-TPPG**, and ***gem*-TPEVP-G2)** and organelle markers in HepG2 cells, derived from CLSM images.

PCC	**TsG**	**FBG**	**TPPG**	**G2**
ER	0.247	0.310	0.186	0.295
Mito	0.208	0.247	0.102	0.284
Lyso	0.597	0.571	0.531	0.600

6. NMR (^{1}H, ^{13}C, ^{19}F, and ^{31}P) (Figs. S15 to S38)

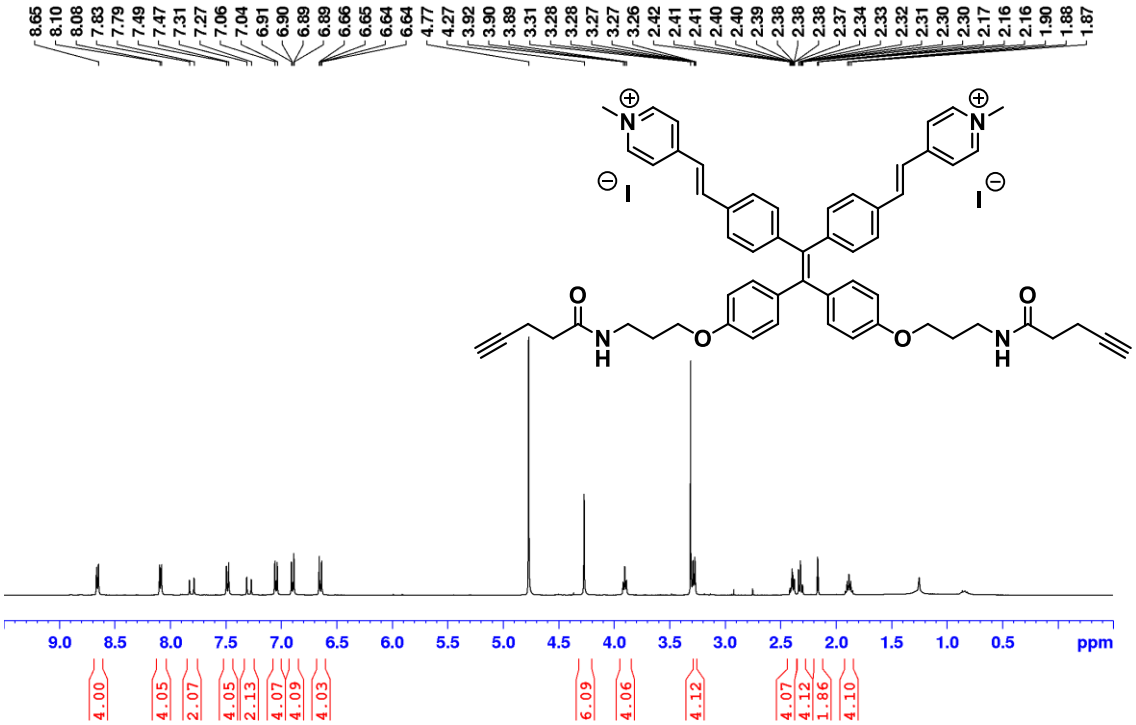


Figure S15. ^{1}H NMR spectrum (400MHz) of **8** in d_4-MeOD

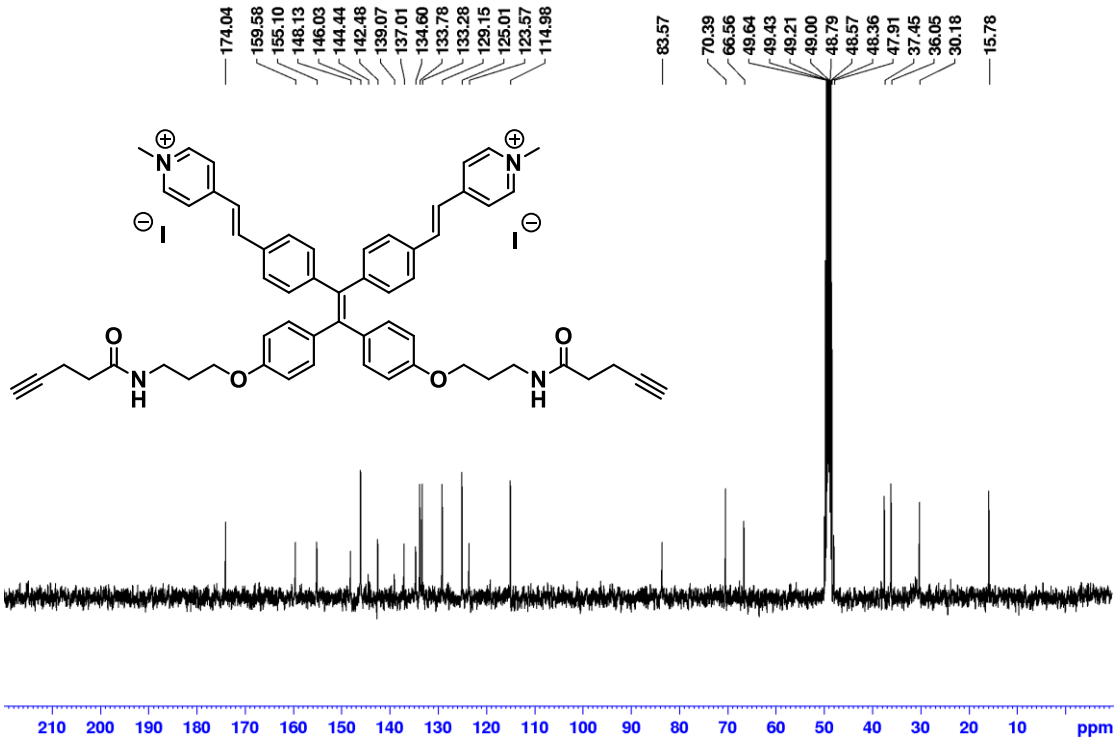


Figure S16. ^{13}C NMR spectrum (100MHz) of **8** in d_4-MeOD

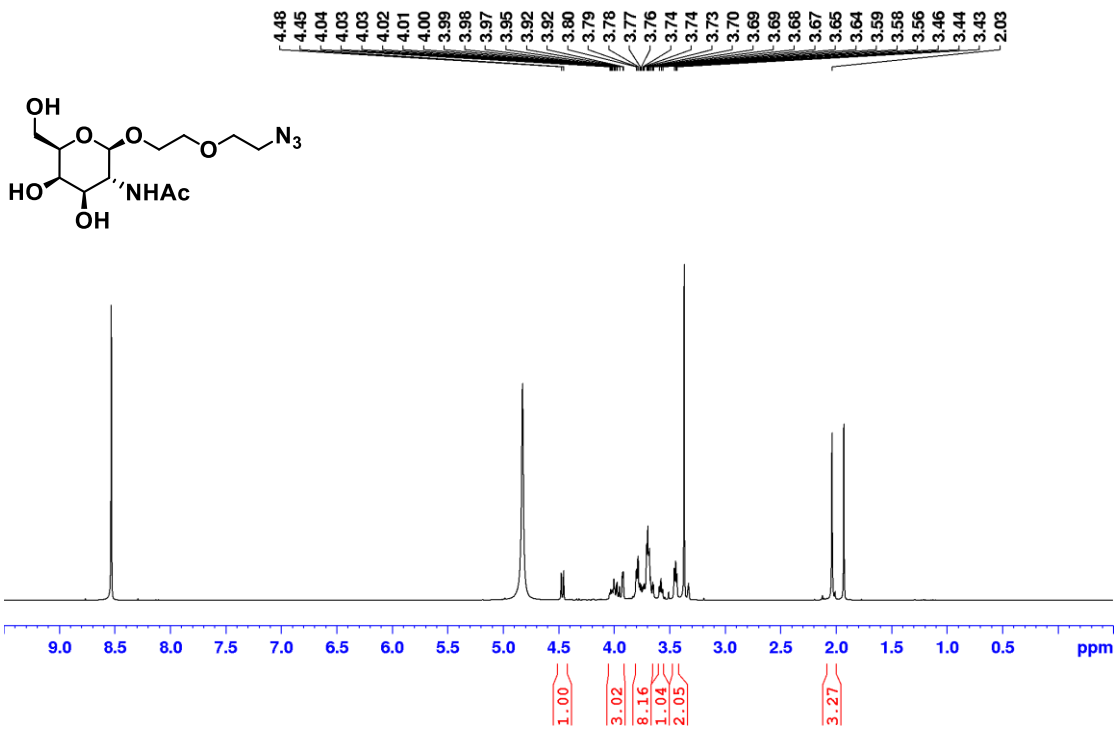


Figure S17. ^{1}H NMR spectrum (400MHz) of **12** in *d*$_4$-MeOD + D_2O

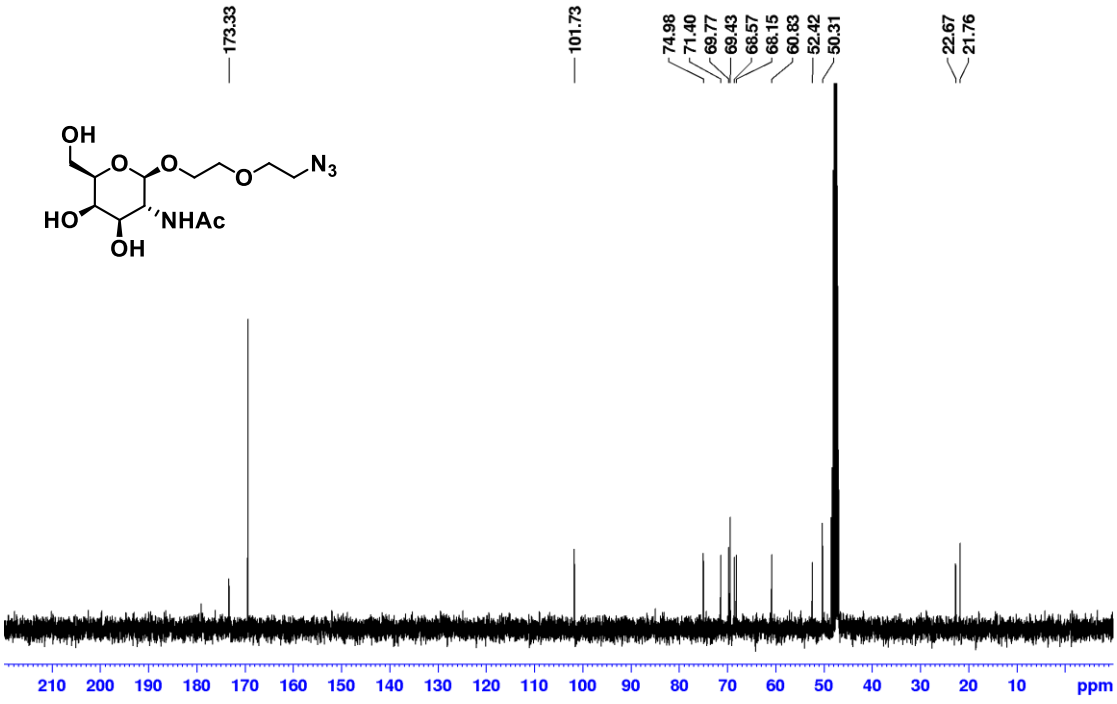


Figure S18. ^{13}C NMR spectrum (100MHz) of **12** in *d*$_4$-MeOD + D_2O

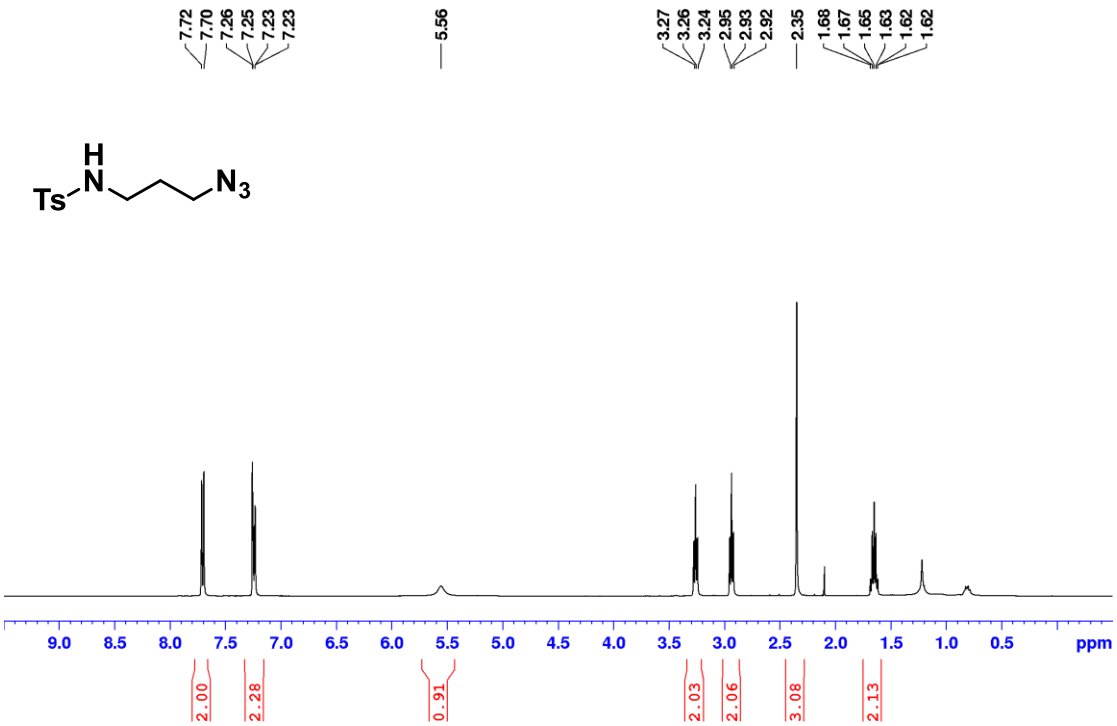


Figure S19. ^{1}H NMR spectrum (400MHz) of **14** in $CDCl_3$

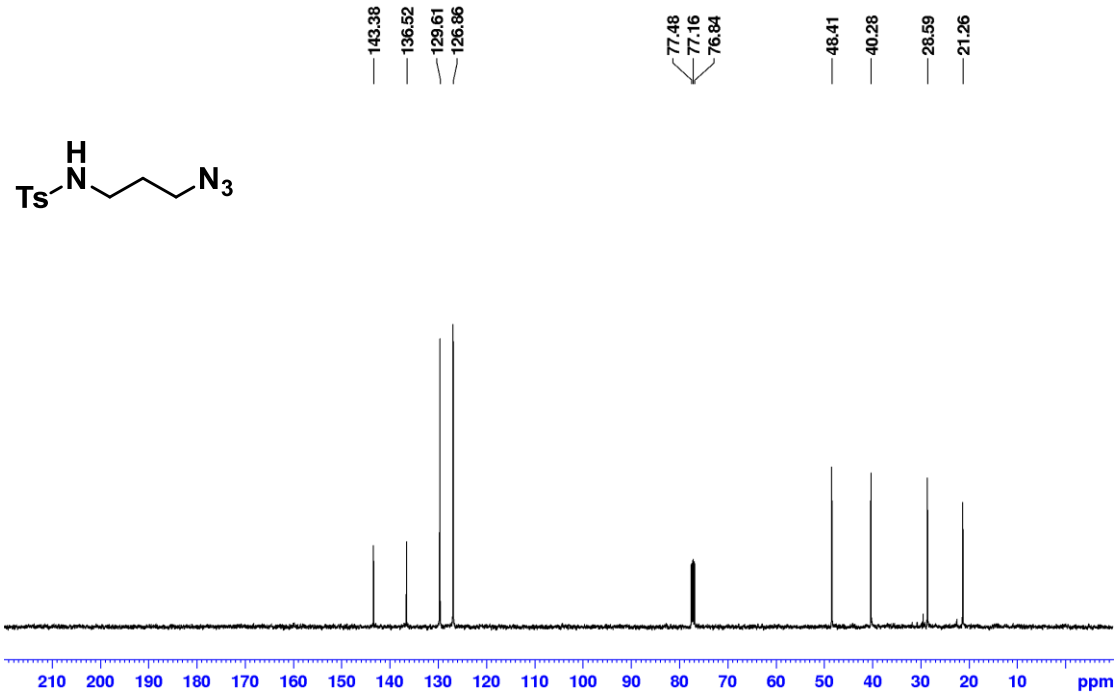


Figure S20. ^{13}C NMR spectrum (100MHz) of **14** in $CDCl_3$

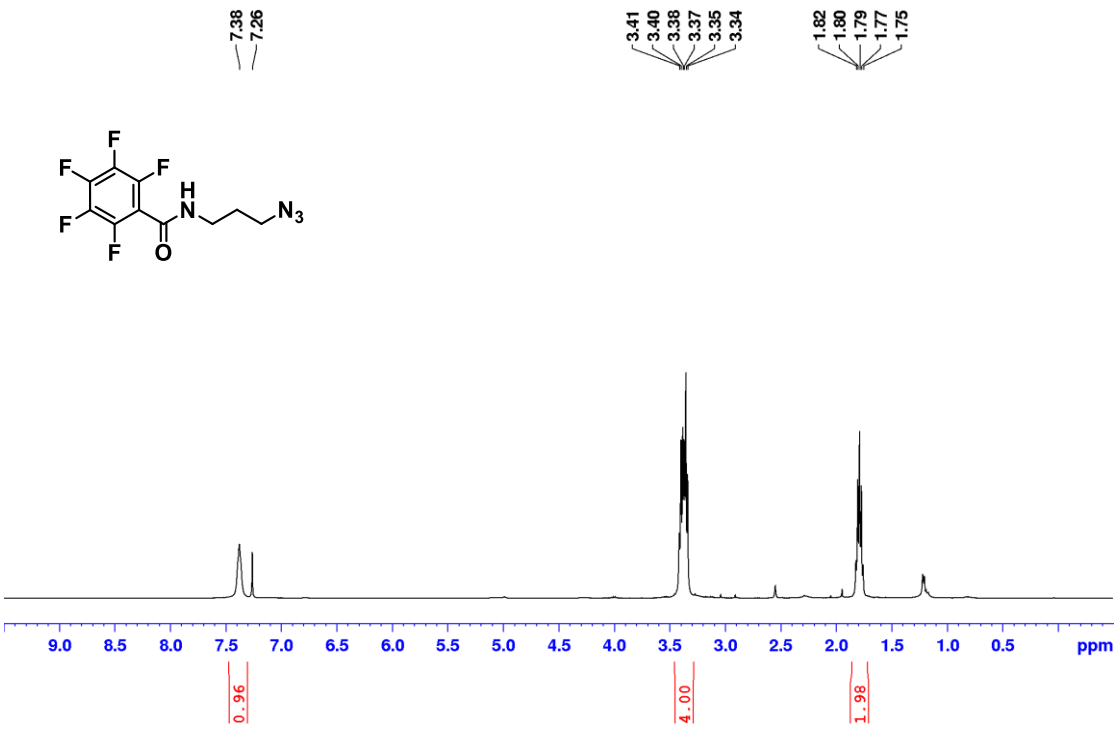


Figure S21. ^{1}H NMR spectrum (400MHz) of **15** in $CDCl_3$

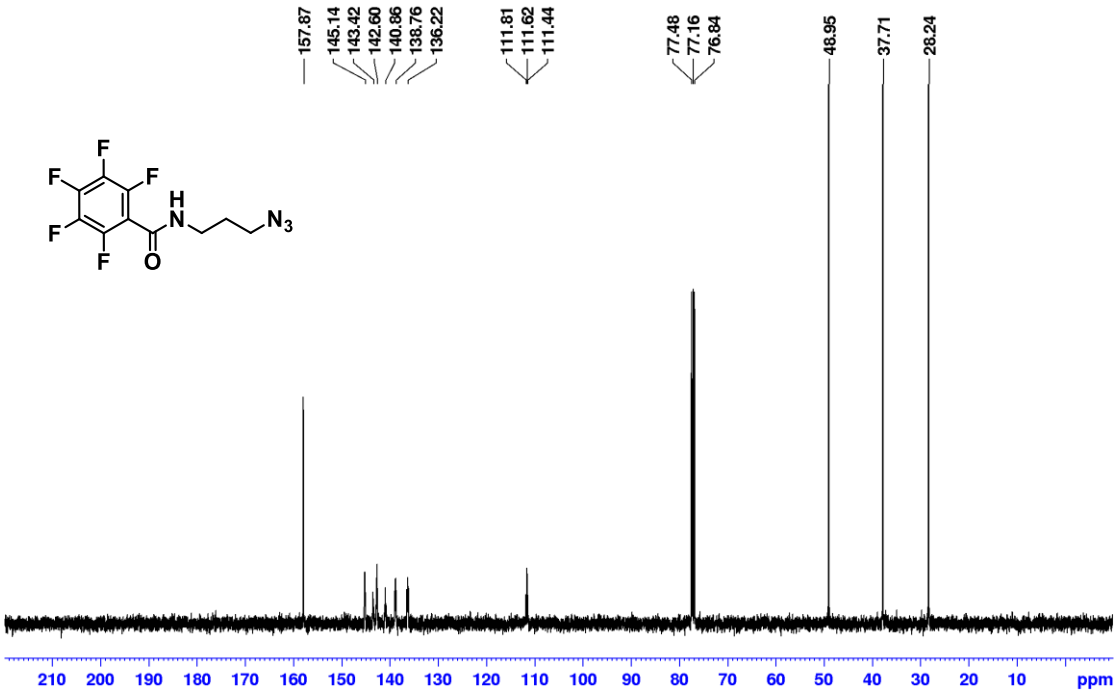


Figure S22. ^{13}C NMR spectrum (100MHz) of **15** in $CDCl_3$

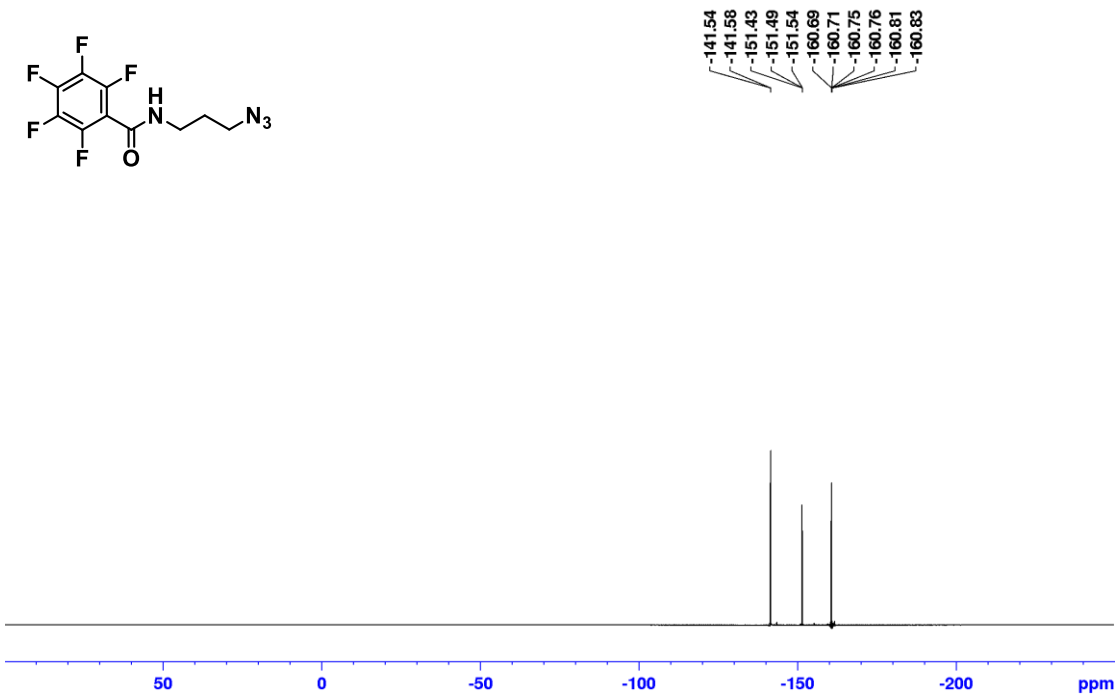


Figure S23. ^{19}F NMR spectrum (376MHz) of **15** in $CDCl_3$

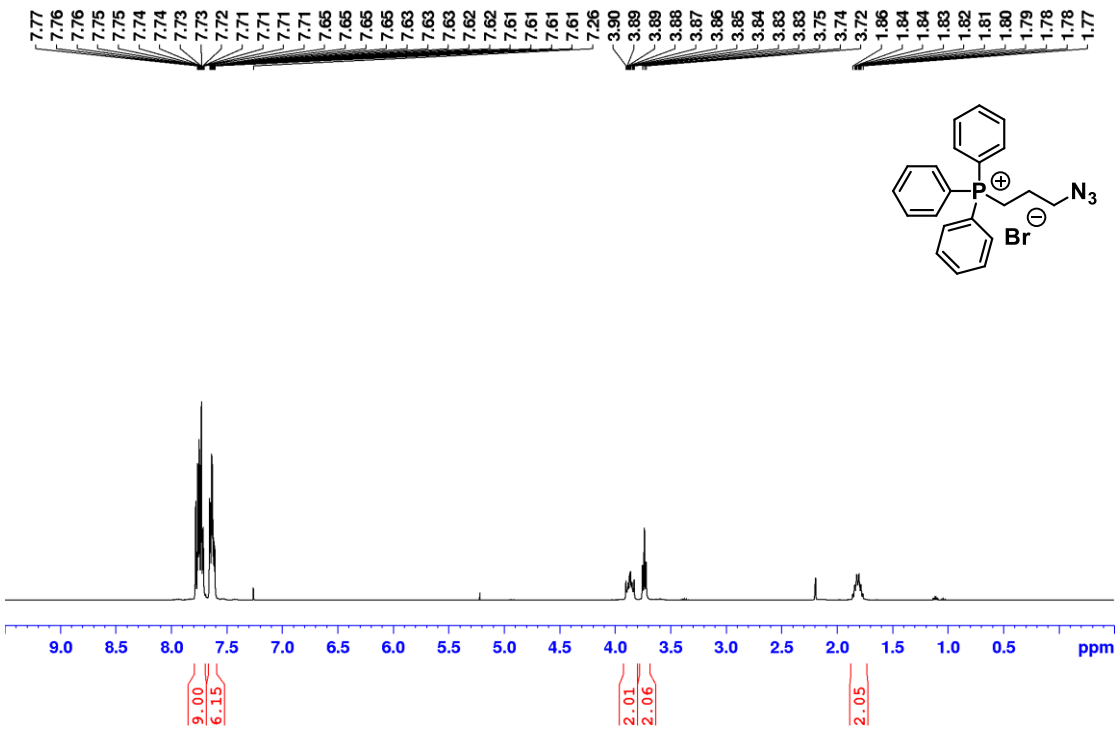


Figure S24. ^{1}H NMR spectrum (400MHz) of **16** in $CDCl_3$

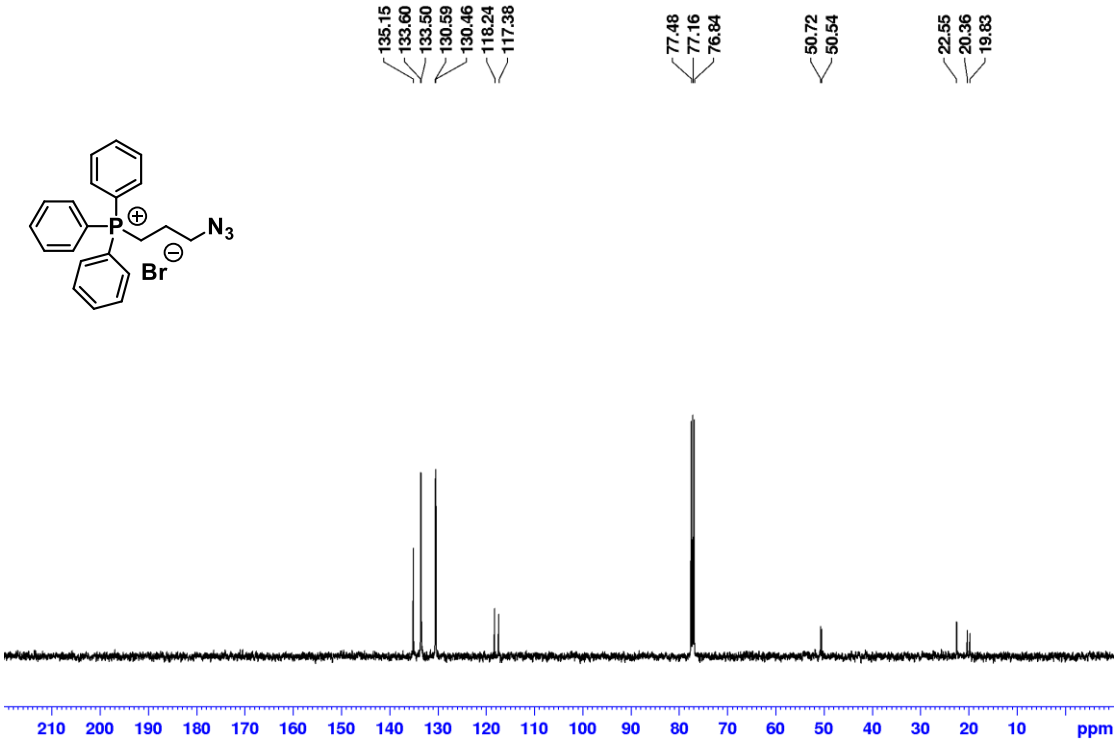


Figure S25. ^{13}C NMR spectrum (100MHz) of **16** in $CDCl_3$

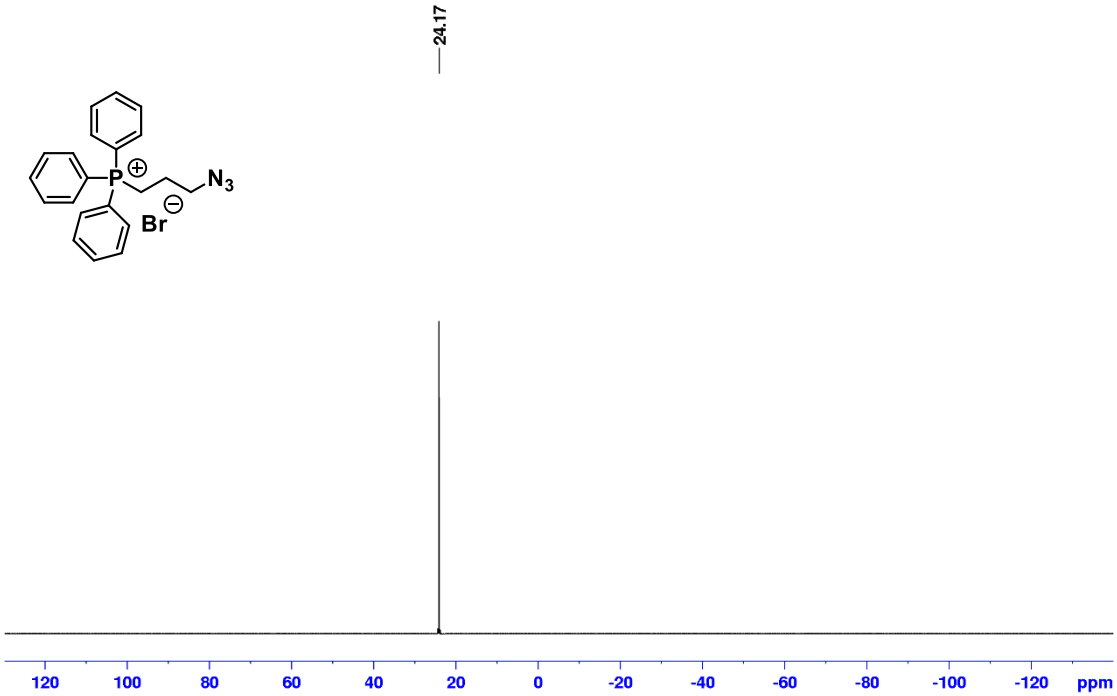


Figure S26. ^{31}P NMR spectrum (162MHz) of **16** in $CDCl_3$

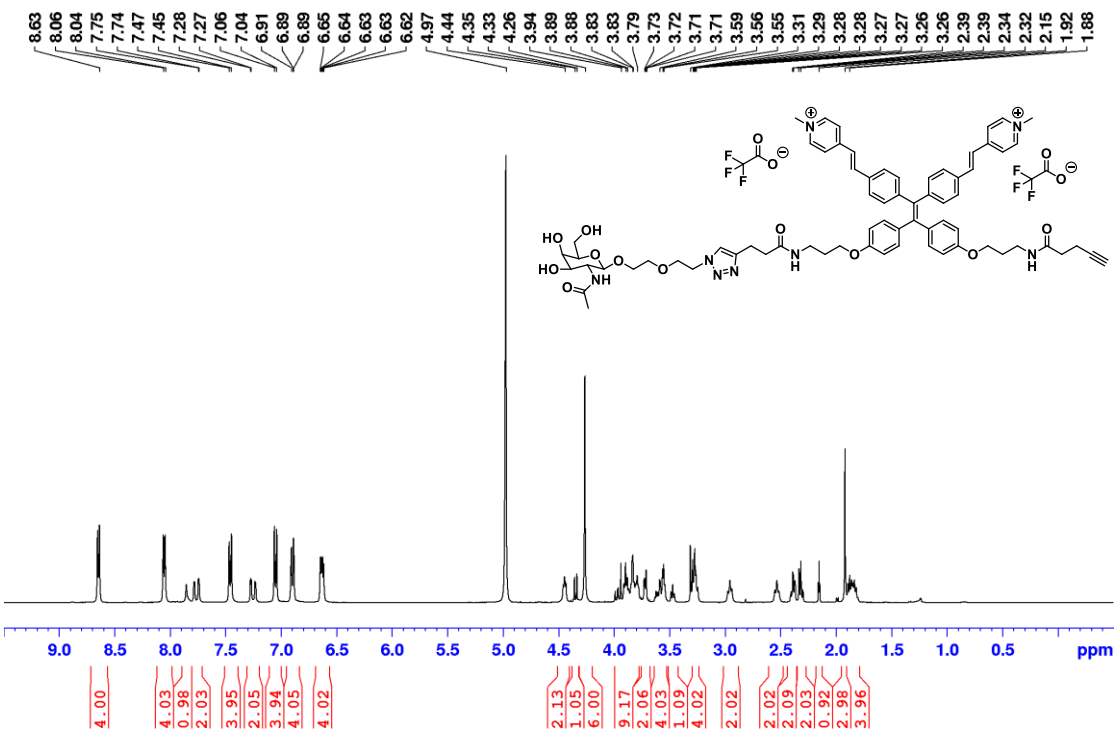


Figure S27. ^{1}H NMR spectrum (400MHz) of **17** in d_4-MeOD

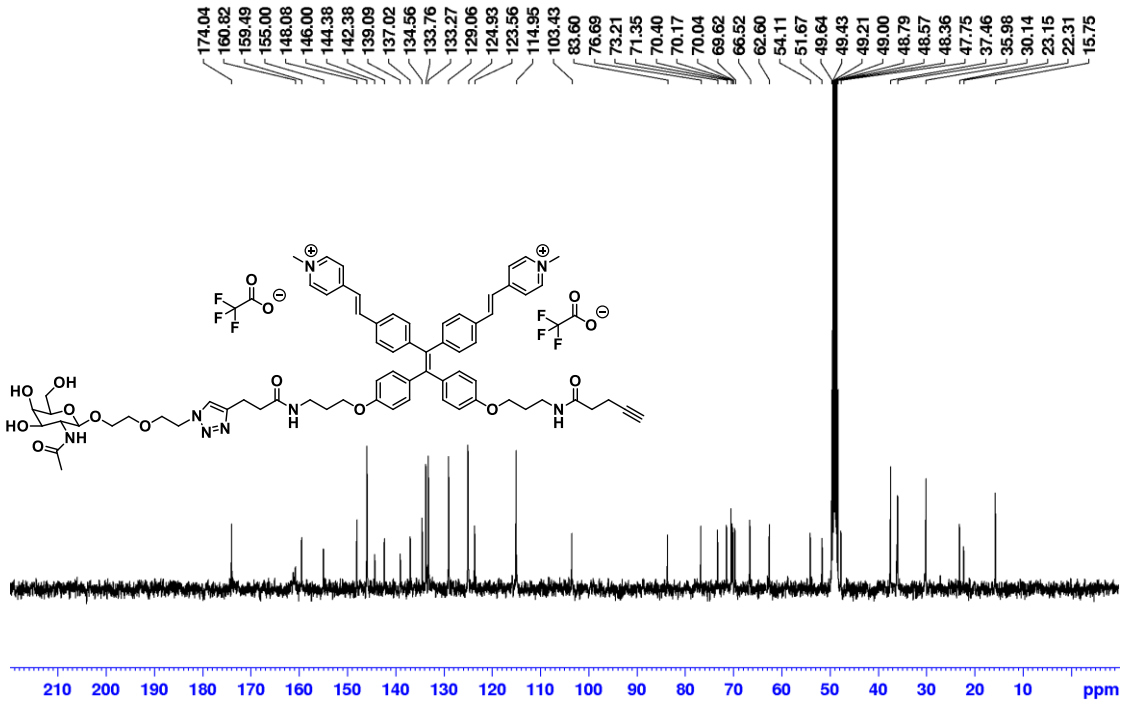


Figure S28. ^{13}C NMR spectrum (100MHz) of **17** in d_4-MeOD

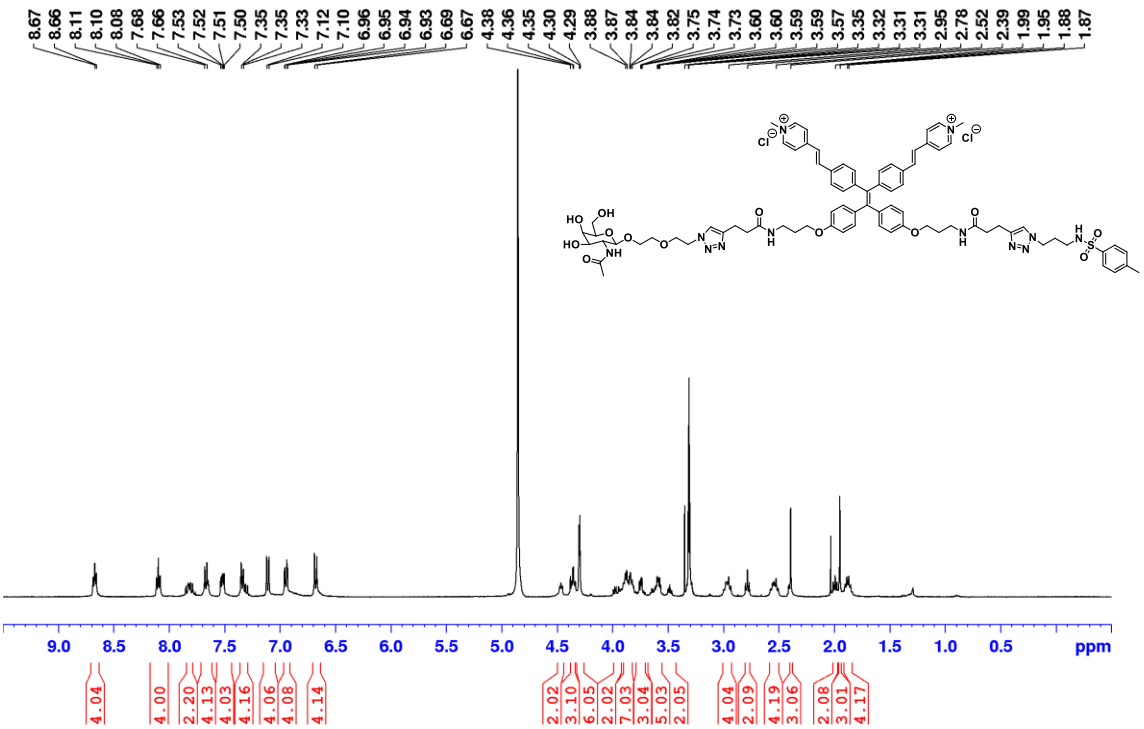


Figure S29. ^{1}H NMR spectrum (400MHz) of **18** in d_4-MeOD

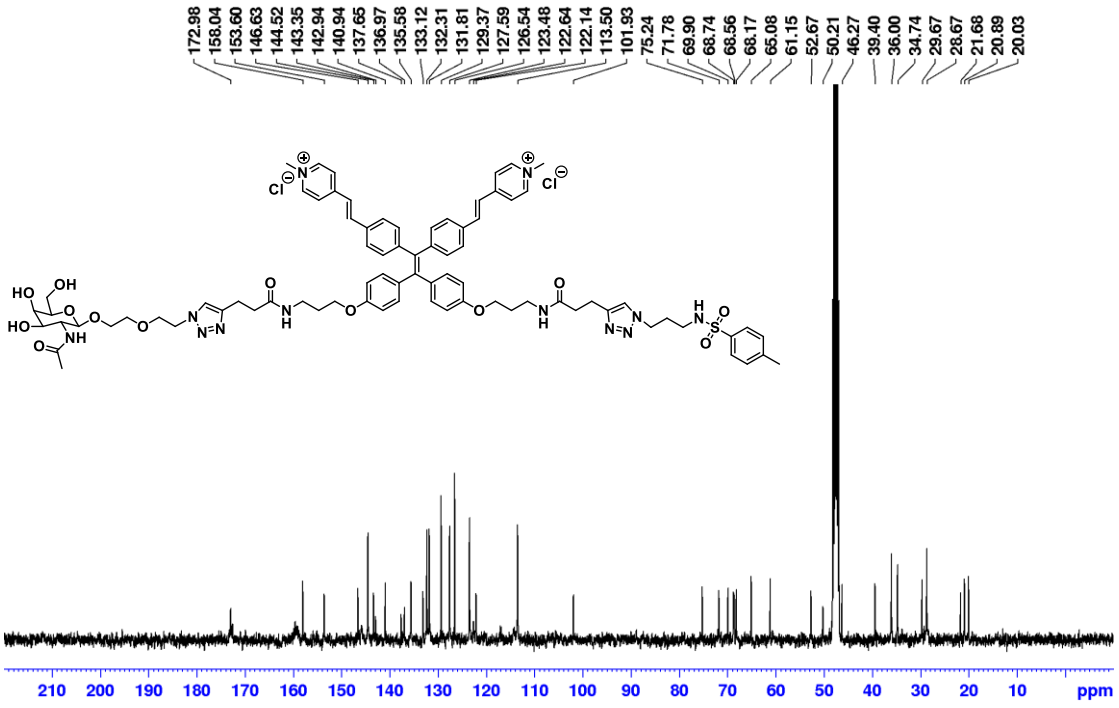


Figure S30. ^{13}C NMR spectrum (100MHz) of **18** in d_4-MeOD

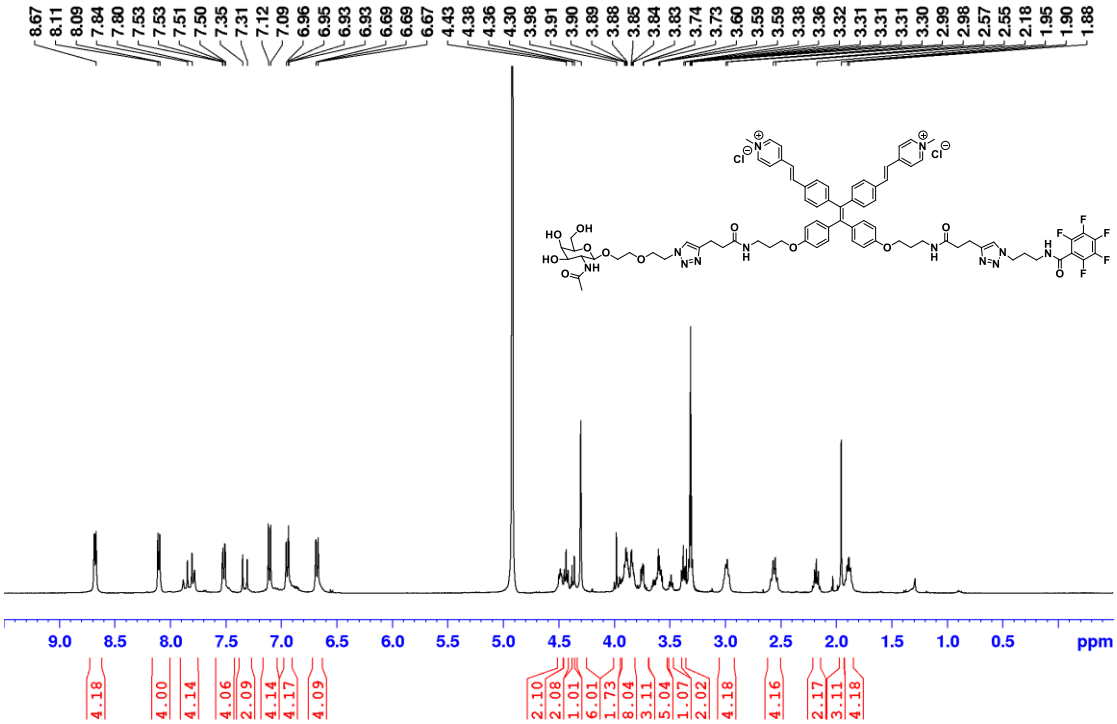


Figure S31. ^{1}H NMR spectrum (400MHz) of **19** in d_4-MeOD

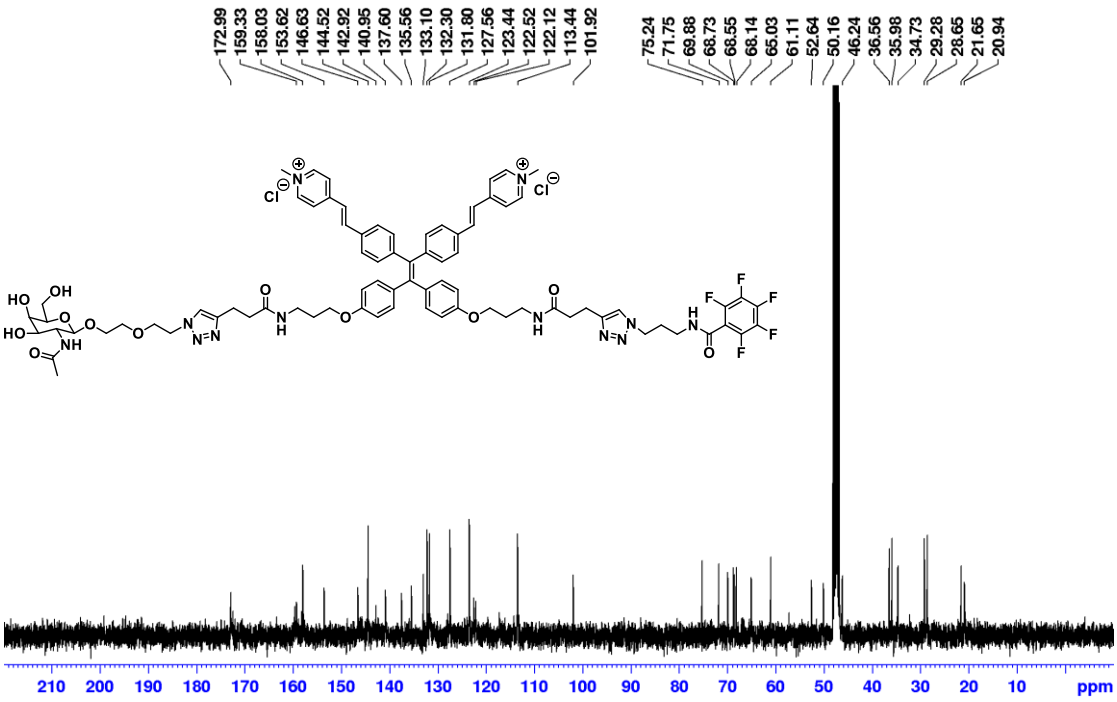


Figure S32. ^{13}C NMR spectrum (100MHz) of **19** in d_4-MeOD

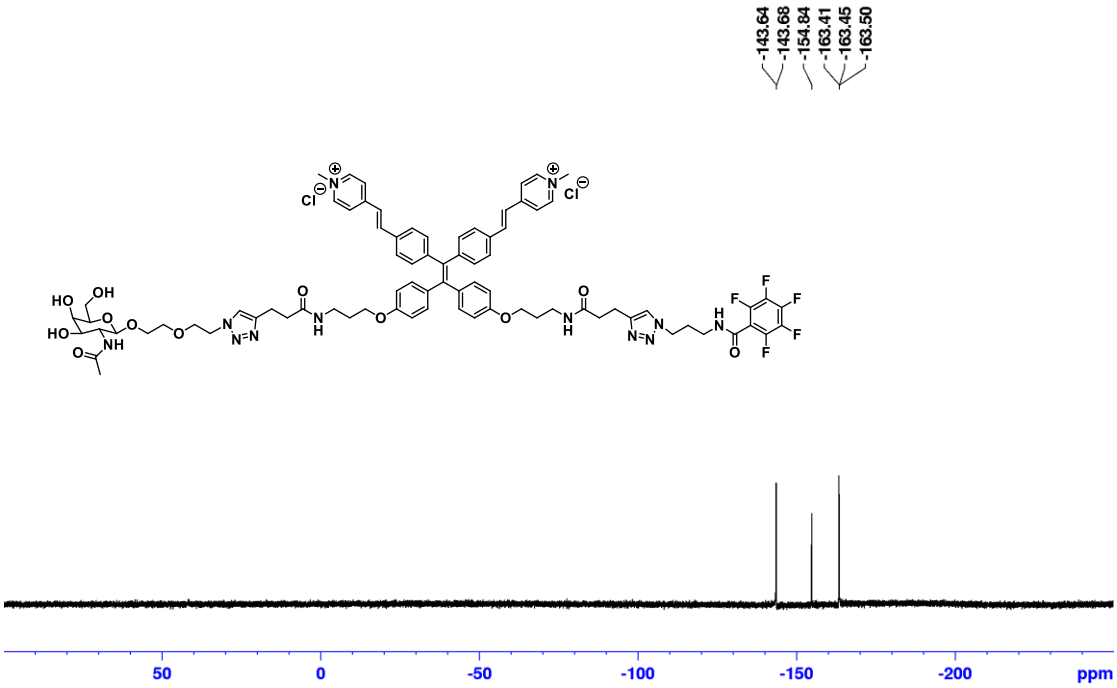


Figure S33. ^{19}F NMR spectrum (376MHz) of **19** in d_4-MeOD

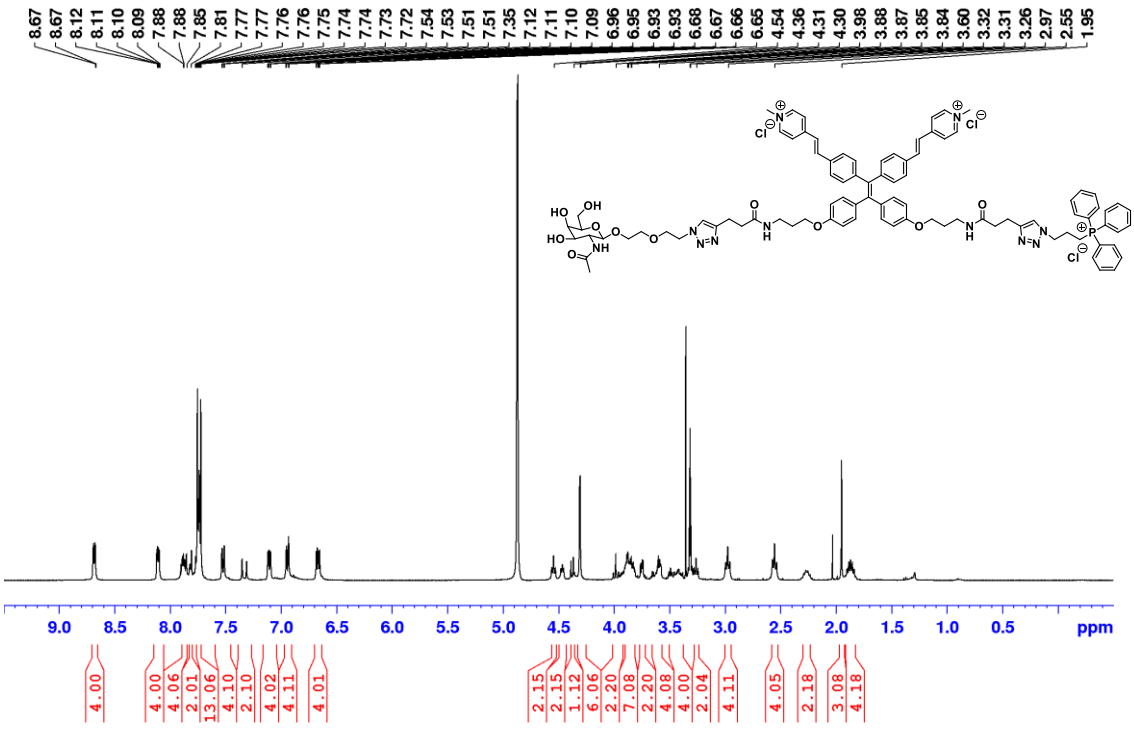


Figure S34. ^{1}H NMR spectrum (400MHz) of **20** in d_4-MeOD

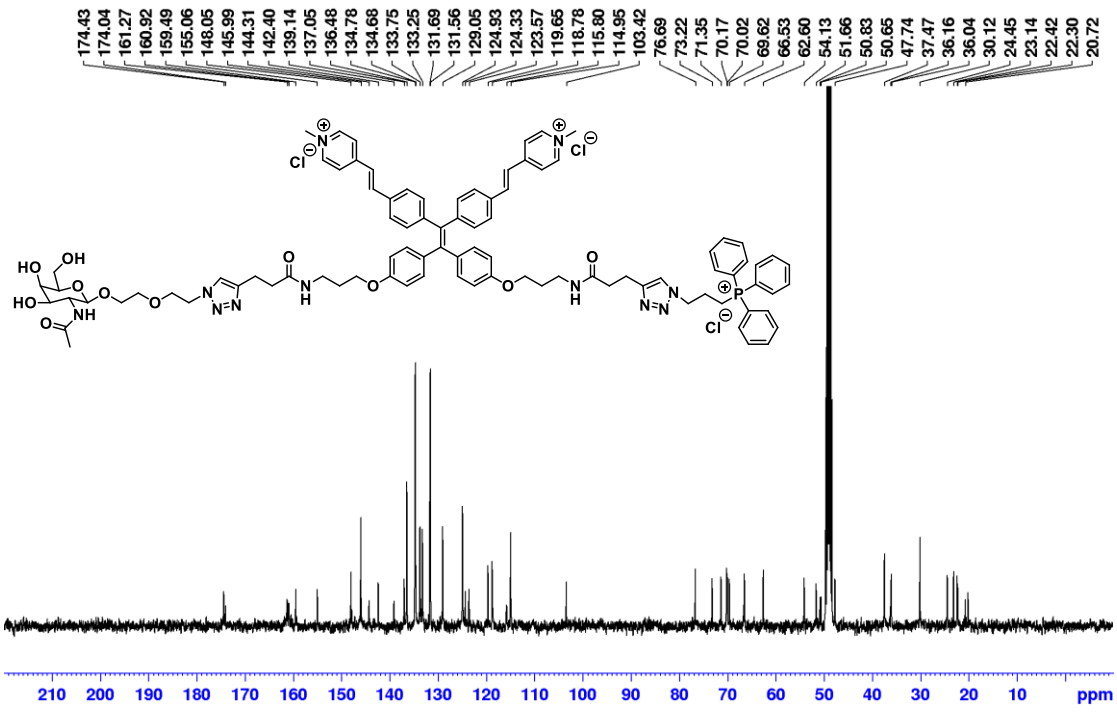


Figure S35. ^{13}C NMR spectrum (100MHz) of **20** in d_4-MeOD

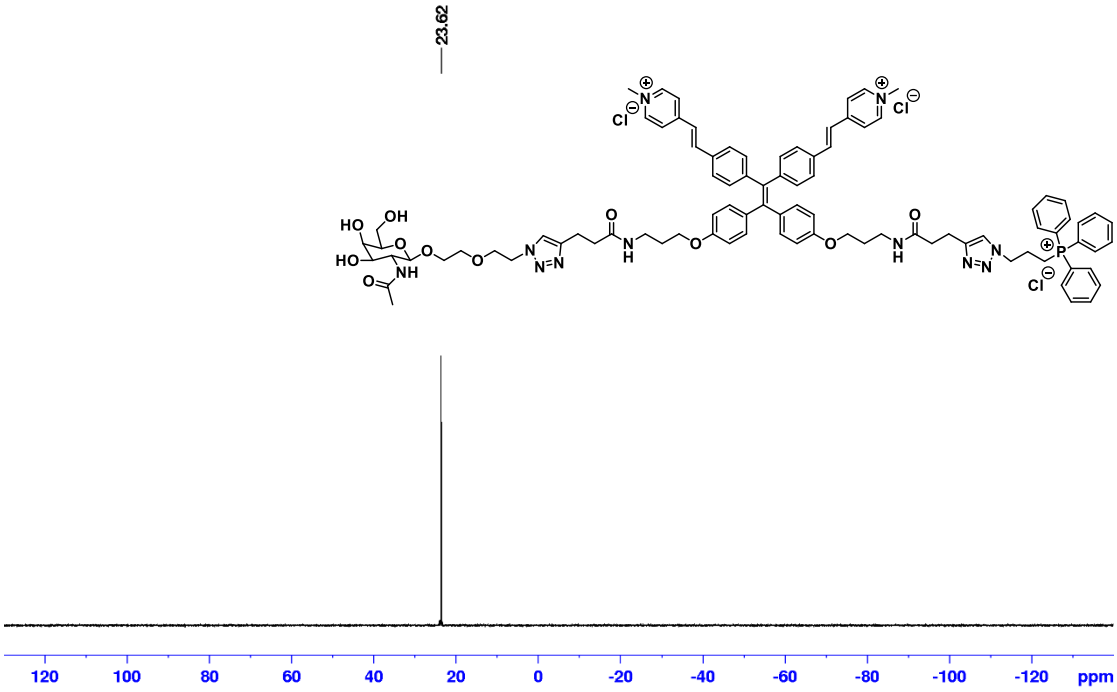


Figure S36. ^{31}P NMR spectrum (162MHz) of **20** in d_4-MeOD

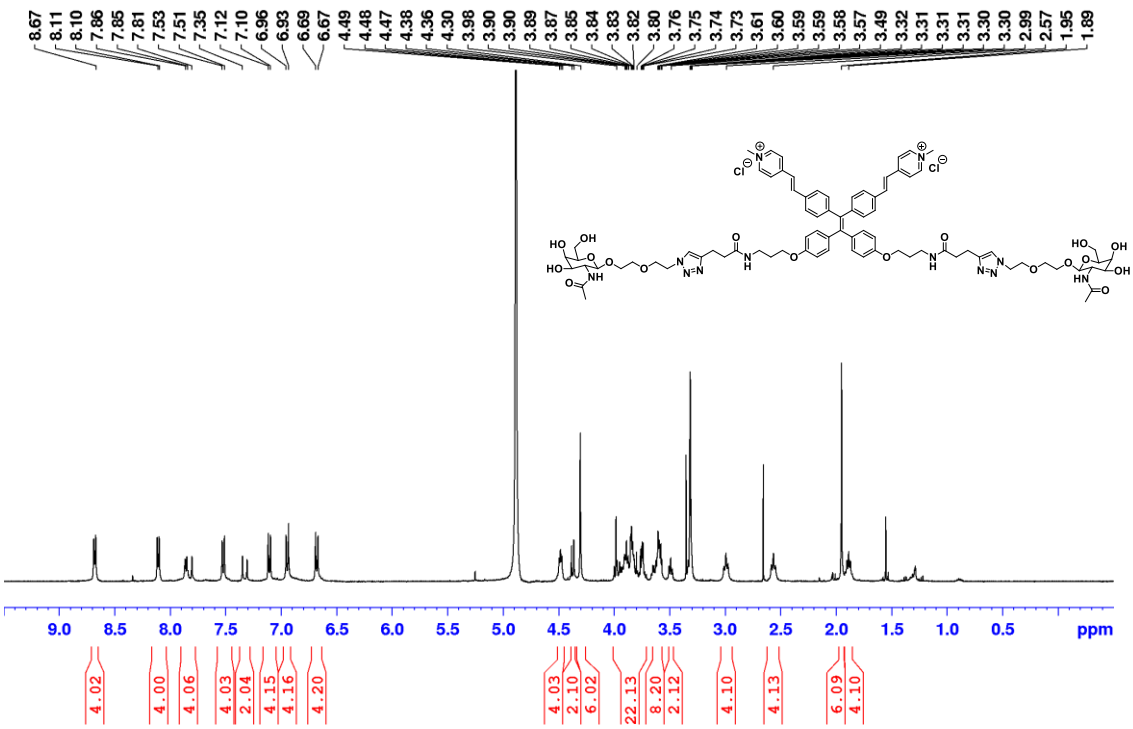


Figure S37. [1]H NMR spectrum (400MHz) of **21** in d_4-MeOD

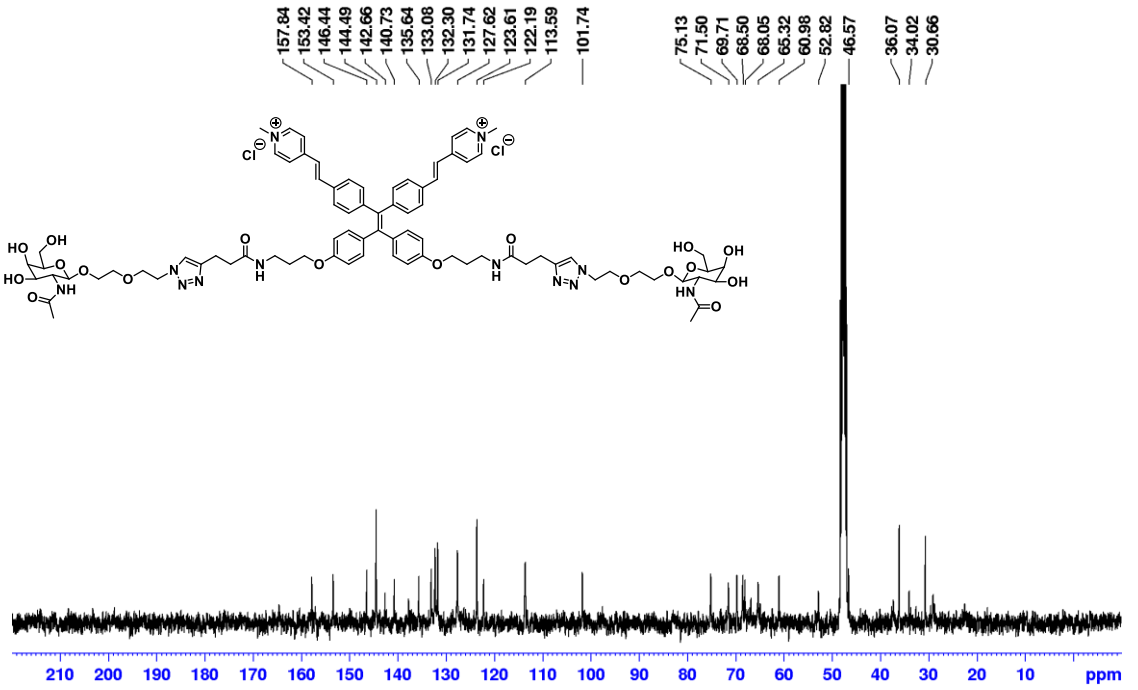


Figure S38. [13]C NMR spectrum (100MHz) of **21** in d_4-MeOD