Supporting Information

An activatable red emitting fluorescent probe for monitoring vicinal dithiol proteins fluctuations in stroke model

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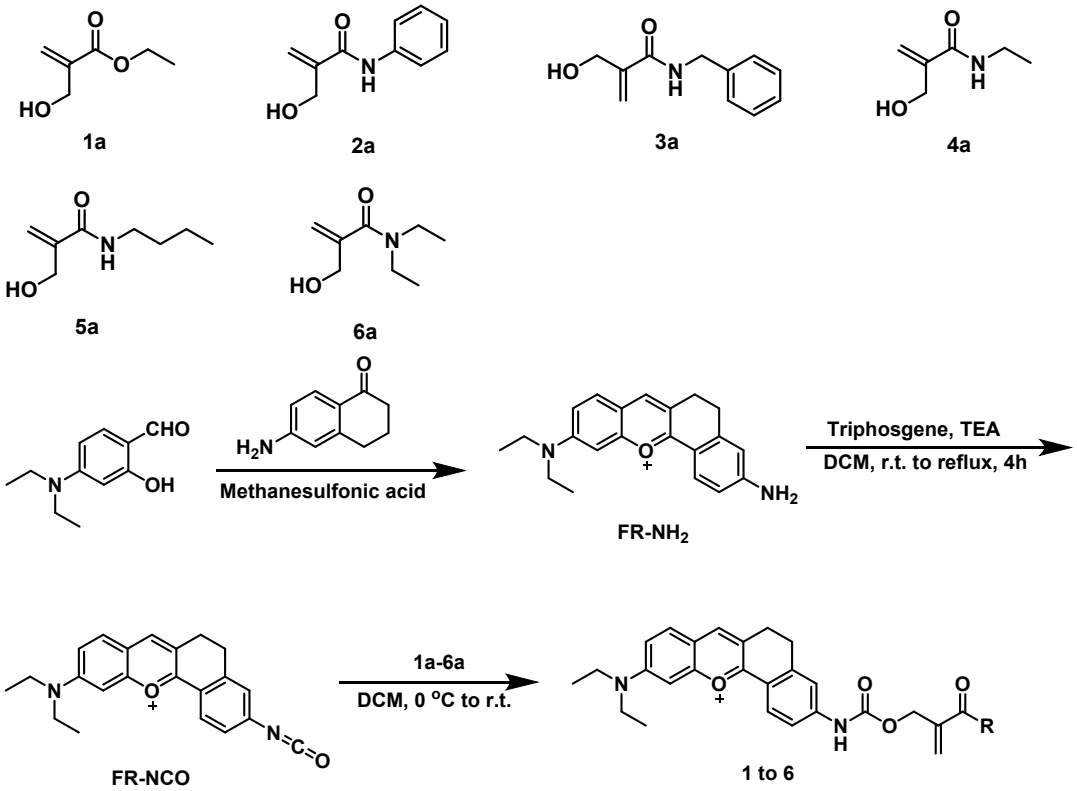
I. Materials and Instruments

All reagents and solvents used in this study were purchased from commercial sources. Tumor cells were obtained from the Shanghai Institute of Biochemistry and Cell Biology, *Escherichia coli* thioredoxin (*E*-Trx), Human thioredoxin (H-Trx) and the Cys35 Ser mutant of thioredoxin (*E*-Trx C35S) from *E. coli* were prepared as described.[1] UV-vis spectra were recorded from an UV-vis spectrometer (Evolution 200, Thermo Scientific). Fluorescence spectroscopic studies were performed with a Cary Eclipse Fluorescence Spectrophotometer (Agilent Technologies). The slit width was 5 nm for both excitation and emission. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Advance 400 or Varian 400, and using DMSO-d_6 as solvent. MS spectra were recorded on Bruker Daltonics esquire 6000 mass spectrometer. The fluorescence imaging of cells was performed with a Floid cell imaging station microscope. The fluorescence images of mice were taken with a fluorescence microscope (Olympus FV1000 microscope). HPLC was recorder on Shimadzu LCMS-2020 system with a Wondasil C18 Superb reversed-phase column (5 μm, 4.6 × 150 μm).

All procedures for *in vivo* experiments were carried out in accordance with the institutional guidelines (Guidance of the Care and Use of Laboratory Animals) and all *in vivo* experiments were approved by the Ethics Committee of Lanzhou University, China.

II. Chemical Synthesis



The compounds **1a**-**6a** was obtained by this mean reported in previous literature.[2]

Synthesis of compound **FR-NH_2**. The compound **FR-NH_2** was synthesized according to the previously reported literature.[3] The mixture of 4-(Diethylamino) salicylaldehyde (1.03 mmol, 1.0 eq.) and 6-Amino-3,4-dihydro-1(2 H)-naphthalenone (1.13 mmol, 1.1 eq) in methanesulfonic acid was stirred at 90 °C for 5 h. Subsequently, the reaction mixture cooled down to room temperature. And the reaction mixture poured into ice water mixture (200 mL). Perchloric acid (70%; 7 mL) was then slowly added to the reaction mixture. Filter and obtain black solid product **FR-NH_2** (76%).

Synthesis of compound **FR-NCO**. **FR-NH_2** (0.28 mmol, 1.0 eq.) was dissolved in 10 mL of dry DCM. Triphosgene (0.14 mmol, 0.5 eq.) and TEA (0.34 mmol, 1.2 eq.) were then added. The reaction mixture was stirred at 45 °C for 4 h. After cooling to room temperature. The organic layer was concentrated to obtain crude product **FR-NCO**.

General steps for synthesis of compound **1**-**6**. To a solution of crude **FR-NCO** (0.28 mmol, 1.0 eq.) solution in dry DCM (2 mL), α-hydroxyalkenones (**1a**-**6a**) (0.28 mmol, 1.0 eq.) and TEA (0.34 mmol, 1.2 eq.) were added at 0 °C. The reaction mixture was

stirred for 10-120 min. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH=100/1) to get compounds **1-6**.

Synthesis of compound **1**. Following the general procedure, compound **1a** (0.28 mmol, 1.0 eq.) was reacted with **FR-NCO** (0.28 mmol, 1.0 eq.) for 5 min to get the title compound. (32%, black solid). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.66 (s, 1H), 8.20 (d, J = 8.7 Hz, 1H), 7.93 (d, J = 9.4 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.57 (s, 1H), 7.45 (d, J = 9.4 Hz, 1H), 7.28 (s, 1H), 6.33 (s, 1H), 6.03 (s, 1H), 4.87 (s, 2H), 4.19 (q, J = 7.1 Hz, 2H), 3.69 (q, J = 7.0 Hz, 4H), 3.12 (d, J = 7.3 Hz, 4H), 1.24 (t, J = 7.0 Hz, 9H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.19, 163.13, 158.53, 155.64, 153.15, 148.70, 145.57, 144.29, 135.96, 132.26, 128.75, 127.87, 121.16, 120.80, 118.52, 118.28, 117.74, 117.43, 96.11, 63.38, 61.21, 55.38, 45.86, 27.10, 25.00, 14.50. HRMS: $[M]^+$ calculated for $C_{28}H_{31}N_2O_5^+$: 476.2306; found: 476.2272.

Synthesis of compound **2**. Following the general procedure, compound **2a** (0.28 mmol, 1.0 eq.) was reacted with **FR-NCO** (0.28 mmol, 1.0 eq.) for 20 min to get the title compound. (45%, black solid). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.47 (s, 1H), 10.07 (s, 1H), 8.66 (s, 1H), 8.19 (d, J = 8.7 Hz, 1H), 7.93 (d, J = 9.4 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 8.7 Hz, 1H), 7.58 (s, 1H), 7.45 (dd, J = 9.4, 2.5 Hz, 1H), 7.33 (dd, J = 8.5, 7.3 Hz, 2H), 7.30-7.26 (m, 1H), 7.09 (t, J = 7.4 Hz, 1H), 6.14 (s, 1H), 5.90 (s, 1H), 4.96 (s, 2H), 3.69 (q, J = 7.1 Hz, 4H), 3.03 (s, 4H), 1.24 (t, J = 7.1 Hz, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.18, 163.16, 158.52, 155.63, 153.27, 148.70, 145.65, 144.30, 140.05, 139.25, 132.26, 129.10, 127.86, 124.21, 123.16, 121.16, 120.76, 120.60, 118.51, 118.27, 117.74, 117.42, 96.11, 64.44, 45.86, 27.10, 25.00. HRMS: $[M]^+$ calculated for $C_{32}H_{32}N_3O_4^+$: 523.2466; found: 523.2426.

Synthesis of compound **3** (**VDP-red**). Following the general procedure, compound **3a** (0.28 mmol, 1.0 eq.) was reacted with **FR-NCO** (0.28 mmol, 1.0 eq.) for 20 min to get the title compound. (43%, black solid). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.47 (s, 1H), 8.78 (t, J = 6.1 Hz, 1H), 8.66 (s, 1H), 8.20 (d, J = 8.7 Hz, 1H), 7.93 (d, J = 9.3 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.58 (s, 1H), 7.45 (dd, J = 9.4, 2.4 Hz, 1H), 7.34-7.21 (m, 6H), 6.03 (s, 1H), 5.75 (s, 1H), 4.89 (s, 2H), 4.37 (d, J = 6.0 Hz, 2H), 3.69 (q, J = 7.1 Hz, 4H), 3.04 (s, 4H), 1.25 (t, J = 7.2 Hz, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.04, 163.19, 158.53, 155.63, 153.27, 148.70, 145.71, 144.31, 139.89, 139.70, 132.27, 128.76, 127.88, 127.63, 127.24, 122.01, 121.17, 120.73, 118.50, 118.26, 117.73,

117.42, 96.12, 64.38, 45.86, 42.68, 27.11, 25.01. HRMS: $[M]^+$ calculated for $C_{33}H_{34}N_3O_4^+$: 536.2549; found: 536.2547.

Synthesis of compound **4**. Following the general procedure, compound **4a** (0.28 mmol, 1.0 eq.) was reacted with **FR-NCO** (0.28 mmol, 1.0 eq.) for 1 h to get the title compound. (44%, black solid). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.47 (s, 1H), 8.67 (s, 1H), 8.29-8.14 (m, 2H), 7.93 (d, J = 9.4 Hz, 1H), 7.67 (dd, J = 8.7, 2.1 Hz, 1H), 7.58 (s, 1H), 7.45 (dd, J = 9.4, 2.5 Hz, 1H), 7.29 (s, 1H), 5.94 (s, 1H), 5.69 (s, 1H), 4.85 (s, 2H), 3.69 (q, J = 7.0 Hz, 4H), 3.20-3.12 (m, 2H), 3.03 (s, 4H), 1.24 (t, J = 7.0 Hz, 6H), 1.06 (t, J = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.71, 163.16, 158.51, 155.62, 153.26, 148.67, 145.70, 144.28, 139.86, 132.25, 127.85, 121.42, 121.13, 120.70, 118.49, 118.25, 117.70, 117.40, 96.11, 64.34, 45.86, 34.14, 27.10, 25.00, 15.13. HRMS: $[M]^+$ calculated for $C_{28}H_{32}N_3O_4^+$: 474.2387; found: 474.2895.

Synthesis of compound **5**. Following the general procedure, compound **5a** (0.28 mmol, 1.0 eq.) was reacted with **FR-NCO** (0.28 mmol, 1.0 eq.) for 1 h to get the title compound. (52%, black solid).^{1}H NMR (600 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.66 (s, 1H), 8.28-8.14 (m, 2H), 7.93 (d, J = 9.4 Hz, 1H), 7.65 (d, J = 8.7 Hz, 1H), 7.58 (s, 1H), 7.44 (d, J = 9.3 Hz, 1H), 7.28 (s, 1H), 5.95 (s, 1H), 5.68 (s, 1H), 4.84 (s, 2H), 3.68 (q, J = 7.1 Hz, 4H), 3.12 (t, J = 6.4 Hz, 2H), 3.03 (s, 4H), 1.44 (p, J = 7.4 Hz, 2H), 1.30 (q, J = 7.5 Hz, 2H), 1.24 (t, J = 7.1 Hz, 6H), 0.87 (t, J = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.88, 163.13, 158.49, 155.61, 153.27, 148.67, 145.72, 144.25, 139.87, 132.25, 127.83, 121.31, 121.10, 120.66, 118.48, 118.23, 117.68, 117.40, 96.12, 64.34, 45.86, 31.61, 29.49, 27.11, 25.00, 22.57, 20.10, 14.19. HRMS: $[M]^+$ calculated for $C_{30}H_{36}N_3O_4^+$: 502.2700; found: 502.3238.

Synthesis of compound **6**. Following the general procedure, compound **6a** (0.28 mmol, 1.0 eq.) was reacted with **FR-NCO** (0.28 mmol, 1.0 eq.) for 2 h to get the title compound. (35%, black solid). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.45 (s, 1H), 8.65 (s, 1H), 8.18 (d, J = 8.7 Hz, 1H), 7.92 (d, J = 9.4 Hz, 1H), 7.64 (d, J = 9.3 Hz, 1H), 7.57 (s, 1H), 7.44 (d, J = 9.4 Hz, 1H), 7.27 (s, 1H), 5.48 (s, 1H), 5.29 (s, 1H), 4.82 (s, 2H), 3.68 (q, J = 7.1 Hz, 4H), 3.35-3.27 (m, 4H), 3.02 (s, 4H), 1.24 (t, J = 7.1 Hz, 7H), 1.11-1.03 (m, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.45, 163.07, 158.49, 155.63, 153.17, 148.67, 145.55, 144.23, 140.83, 132.25, 127.81, 121.11, 120.76, 118.51,

118.26, 117.76, 117.46, 116.28, 96.10, 65.46, 45.87, 27.08, 24.98. HRMS: $[M]^+$ calculated for $C_{30}H_{36}N_3O_4^+$: 502.2700; found: 502.3215

III. Experimental Methods

Experimental preparation procedure.

VDP-red was dissolved in DMSO to obtain the stock solution and diluted to the required concentration with PBS buffer (10 mM, pH = 7.4, with 0.5% DMSO). The proteins were reduced with tris (2-carboxyethyl) phosphine (TCEP) prior to use, and then the excess TCEP was removed by Sephadex G-25 desalting column to obtain the reduced protein. Then the probe was added to the protein solution to detect VDPs. The probe was incubated with different concentrations of analytes in PBS buffer at 37 ^oC, and the absorption and fluorescence spectra of the samples were recorded. The fluorescence enhancement ratio (F/F_0) was normalized to the basic fluorescence intensity of the probe.

Spectral response of **VDP-red** to rBSA.

The fluorescence spectrum was measured by fluorescence spectrometer. Under the excitation of 580 nm, the fluorescence of **VDP-red** was collected between 593 nm and 750 nm. **VDP-red** (2 μM) and rBSA (2 μM) were incubated in PBS buffer at 37 °C and the mixture was scanned with the interval of 2 min, for a total of 30 min to obtain the response rate of **VDP-red** towards rBSA. To record the response of **VDP-red** towards different concentrations of rBSA, **VDP-red** was further incubated at 37 ^oC with increasing rBSA concentration for 10 min in PBS buffer. In addition, rBSA (2 μM) was reacted with different concentrations of PAO (4-Aminophenol) (0-5 μM) for 30 min, then the probe (2 μM) was added to PBS buffer and incubated at 37 °C for another 10 min, and the fluorescence change at 625 nm was measured.

The pH-dependent fluorescence response of **VDP-red** to rBSA

VDP-red (2 μM) and the mixture of **VDP-red** (2 μM) and rBSA (2 μM) were incubated in buffer solution (Sodium citrate buffer solution: pH range 3.0-5.0; PBS: pH range 6.0-8.0; Sodium carbonate buffer solution: pH range 9.0-11.0) at 37 °C for 10 min to obtain their fluorescence response under varying pH level. The fluorescence at 625 nm was

collected under excitation at 580 nm and each experiment was repeated at least three times.

Selectivity of **VDP-red** to VDPs

In this experiment, **VDP-red** (2 μM) was incubated with various test substances including 1, blank, 2, GSH; 3, Hcy; 4 Cys; 5, *E*-Trx; 6, reduced *E*-Trx; 7, H-Trx; 8, reduced H-Trx; 9, lysozyme; 10, reduced lysozyme; 11, BSA; and 12, rBSA, at 37°C in PBS buffer for 10 min. The concentration of small molecules and proteins were 100 eq. and 0.1 mg/mL, respectively. After co-incubation, under excitation at 580 nm, the fluorescence intensity of **VDP-red** was measured at 625 nm. Each experiment was repeated at least three times.

Cytotoxicity test.

The MTT was used to detect the toxicity of **VDP-red** on HepG2, HT1080, A549, HeLa and 293T cells. 1×10^4 cells and **VDP-red** (10 μM) were cultured in a 96-well plate at 37 °C in triplicate, and the last volume was 100 μL. Cells treated with dimethyl sulfoxide alone served as controls. At the end of the treatment (24 h), 10 μL of MTT (5 mg/mL) was added to each well, and incubated for another 4 h at 37 °C. An extraction buffer (100 μL, add 10% sodium lauryl sulfate, 5% isobutanol, 0.1% hydrochloric acid) was added, and the cells were incubated 4 h at 37 °C. The absorbance was measure at 580 nm (Thermo Scientific).

Cells imaging.

HepG2 cells were seeded on a 12-well plate with 2×10^4 cells per well in 1 mL of medium, and then **VDP-red** (5 μM) was used for 10 min at 37 °C. The control group was pretreated with PAO (10 μM) for 30 min, and then **VDP-red** (10 μM) at 37 °C for 10 min. After washing the cells three times with PBS buffer, fluorescence images were obtained under the microscope of the Floid cell imaging station (Life-Technology).

HepG2 cells were seeded on a 12-well plate with 2×10^4 cells per well in 1 mL of medium, and then **VDP-red** (5 μM) was add at 37 °C. After incubation with cells for 5, 10, and 20 min, respectively. Washing the cells three times with PBS buffer, fluorescence images were obtained under the microscope of the Floid cell imaging station (Life-Technology).

Mouse imaging.

Kunming mice were used in this study, which were obtained from Jackson Laboratory and fed in animal facilities at School of Basic Medical Sciences of Lanzhou University. All animal experiments have been approved by the university's Ethics Committee. Firstly, **VDP-red** was dissolved in PBS buffer to prepare 500 μM solution (with 5% ethanol). After anesthetizing the mice with isoflurane, 100 μL of **VDP-red** was injected into the abdomen of mice, and the mice were subjected to image at different time points. IVIS Lumina LT Series 3 was used as the imaging instrument from Platinum Elmer. The mice images were obtained under 620-650 nm excitation light and near-infrared emission wavelengths at 690-740 nm.

Pathological model

In this research, bilateral common carotid artery ligation (BCAL) ischemic model was used to induce the global ischemia upon mice cerebrum.[4] Procedures were following several preliminary studies. Briefly, mice were anesthetized with a mixed solution of ketamine hydrochloride (150 mg/kg body weight) and xylazine (25 mg/kg), then positioned gently on a heating pad to maintain the body temperature at 37 ^{o}C ± 0.5 ^{o}C. After making an incision along the scalp over skull, a custom-made metal frame was adhered onto the skull with Superglue and then fixed tightly to a steel plate. Subsequently, an area with the diameter of 2 mm was thinned to 20 μm on the skull using high speed dental drill, aiming to observe the blood flow of vessels within dura. Then, another incision was made along the neck, bilateral common carotid arteries were carefully separated from carotid sheaths and encircled with surgical sutures. To induce ischemia, those surgical sutures were tightened carefully, and mouse was softly moved under a stereomicroscope. The impaired and stasis of blood flow confirmed the successful establishment of ischemic model. Mice were subjected to 60 min ischemia, afterwards, sutures were loosened to induce cerebral ischemia-reperfusion injury (CIRI).

CIRI mice model imaging

After the successful establishment of the CIRI mouse model. A cranial window above mouse skull was made to incubate the cerebral tissue with **VDP-red** (500 μM, 20 μL)

for 1 h. During which period the body temperature of the animal was kept by a heating pad.[5, 6] After the incubation has been well achieved, the mouse was moved gently under a 25 times water immersion objective (Olympus FV1000) to be subjected to intravital imaging. Fluorescence microscopy images were obtained by exciting the probes at 800 nm with a femtosecond pulsed laser source The cortical region was imaged through cranial window repeatedly and 1024*1024 image stacks were collected with a step size of 1 μm. Note that the cortex should be exposed to the laser as less as possible to avoid possible tissue damages. Analyses were performed using ImageJ software.

IV. Supplementary Figures

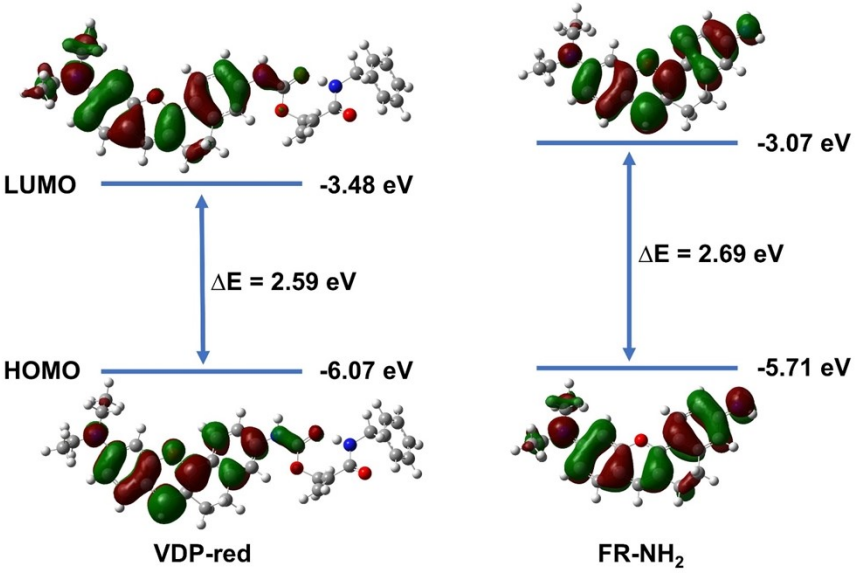


Fig. S1. The optimized molecular structure, HOMO and LUMO of **VDP-red** and **FR-NH_2**.

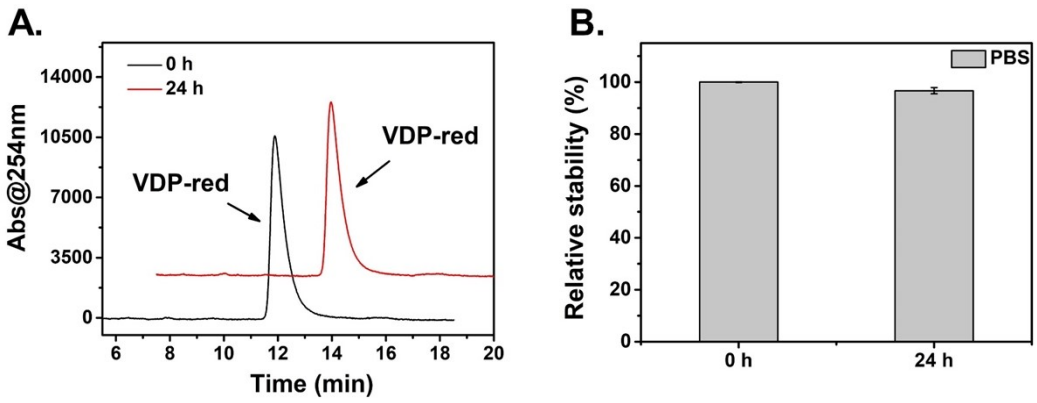


Fig. S2. Stability testing of VDP-red. VDP-red was performed in PBS (with 0.1% DMSO) under open air at 37°C, and samples of the reaction mixture were taken out after 24 h and examined by HPLC. HPLC mobile phase was as follows: H_2O/MeOH = 35/65 (v/v); flow rate: 0.4 mL/min.

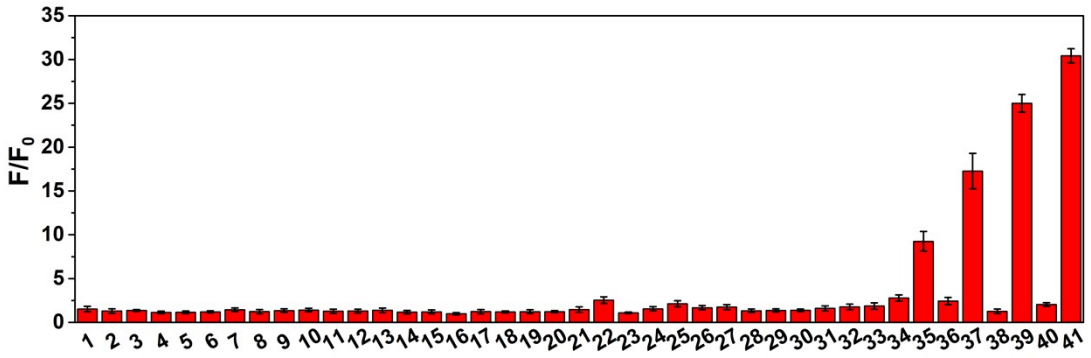


Fig. S3. Fluorescence intensity of VDP-red (2 μM) upon mixing with different species at 37 °C for 10 min in PBS buffer. 1, blank; 2, Ala (Alanine); 3, Asp (Asparagic acid); 4, Gln (Glutamine); 5, Asn (Asparagin); 6, Gly (Glycine); 7, Ile (Isoleucine); 8, Met (Methionine); 9, Val (Valine); 10, Trp (Tryptophan); 11, Lys (Lysine); 12, Thr (Threonine); 13, His (Histidine); 14, Pro (Proline); 15, Arg (Arginine); 16, Ser (Serine); 17, Phe (Phenylanine); 18, Leu (Leucine); 19, Tyr (tyrosine); 20, Glu (Glutamate); 21, Hcy (Homocysteine); 22, Cys; 23,GSH; 24, $MgCl_2$; 25, $FeCl_3$; 26, $FeSO_4$; 27, $CuSO_4$; 28, $NiCl_2$; 29, NaHS; 30, H_2O_2; 31, O_2^-; 32, ClO^-; 33, $ONOO^-$ (100 eq. of each). 34, *E*-Trx (Escherichia coli thioredoxin); 35, reduced *E*-Trx; 36, H-Trx (Human thioredoxin); 37, reduced H-Trx; 38, lysozyme; 39, reduced lysozyme; 40, BSA (Bovine serum albumin); 41, rBSA (Reduced bovine serum albumin); (0.1 mg/mL of each). $\lambda_{ex}/\lambda_{em}$ = 580/625 nm.

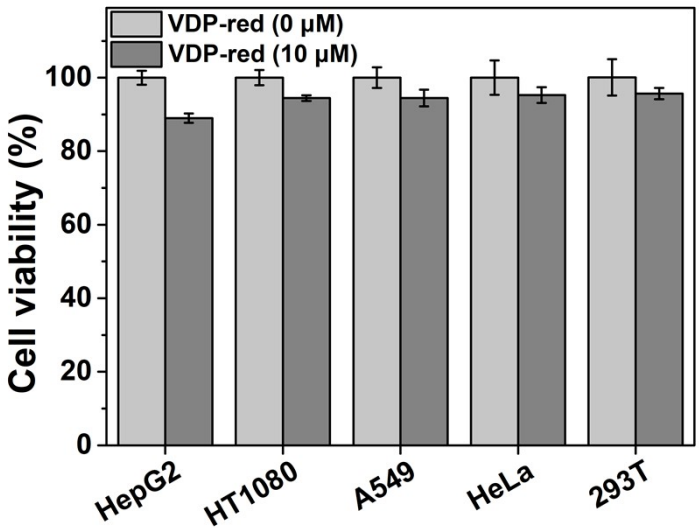


Fig. S4. The viability testing of VDP-red in cells. HepG2, HT1080, A549, HeLa and 239T cells were incubated with or without **VDP-red** (10 μM) for 24 h. The cell viability was assessed using the MTT assay.

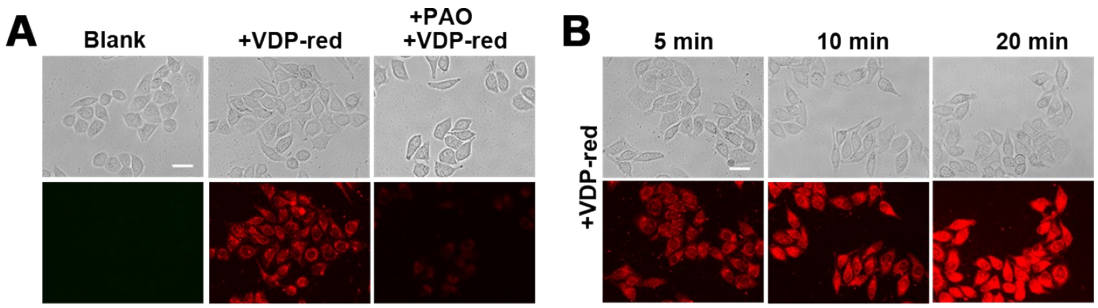
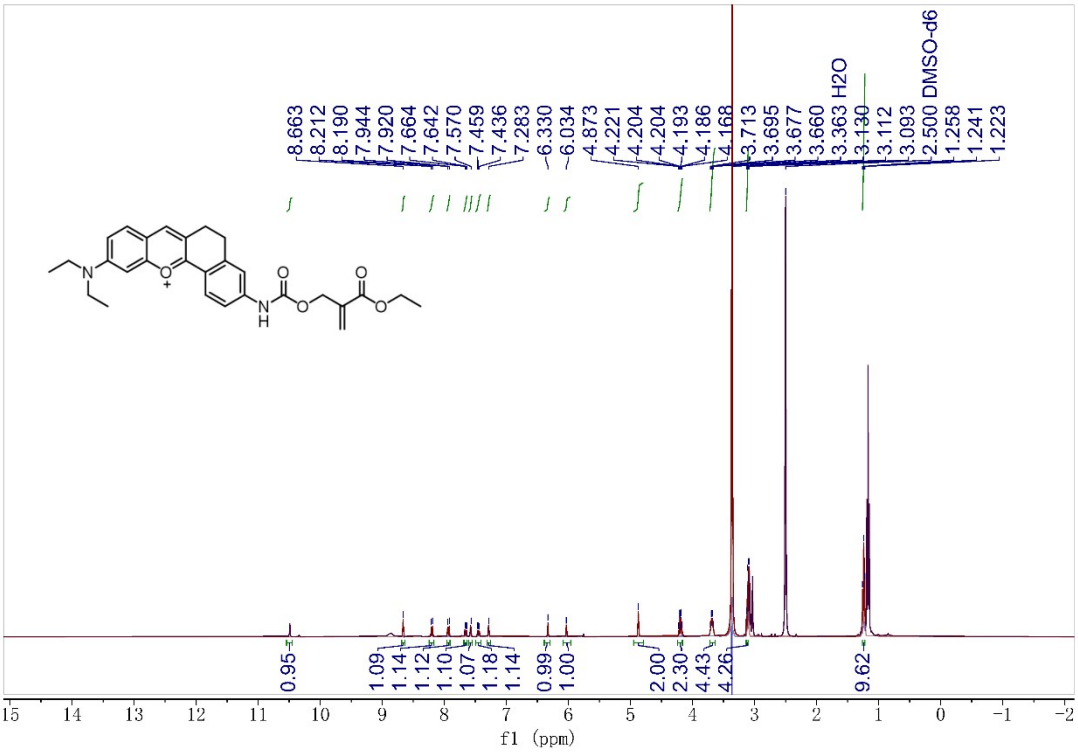
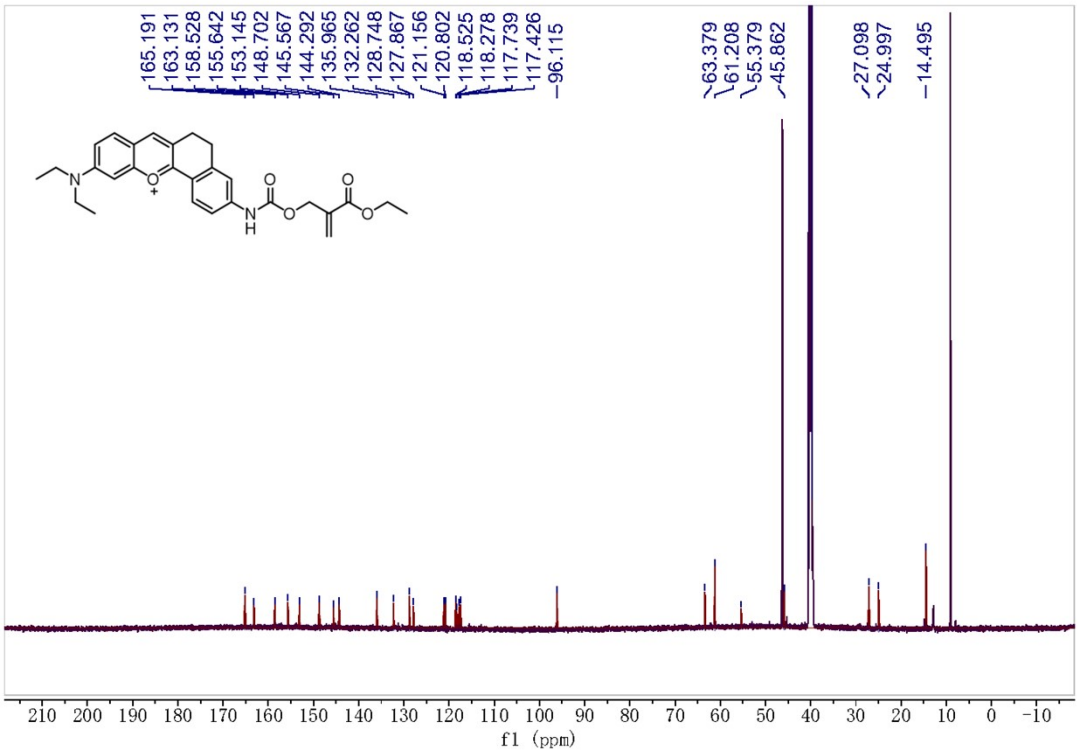


Fig. S5. Imaging VDPs in living cells. (A) Fluorescence images of HepG2 cells. HepG2 cells were pretreated with or without PAO (10 μM) for 30 min, and then stained with **VDP-red** (5 μM) for 10 min. Bright field (top panel) and fluorescent field (bottom panel) images were shown. (B) The cells were incubated with varying time with **VDP-red** (5 μM) for 20 min. Scale bars: 20 μm.

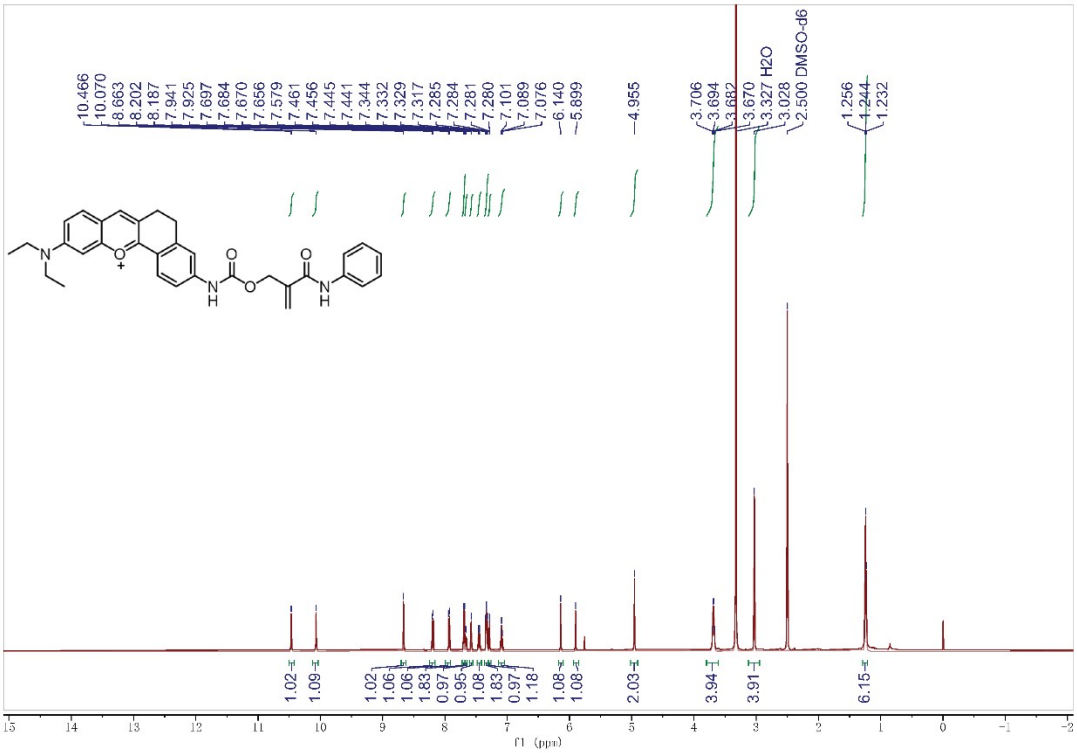


V. Supporting Figures

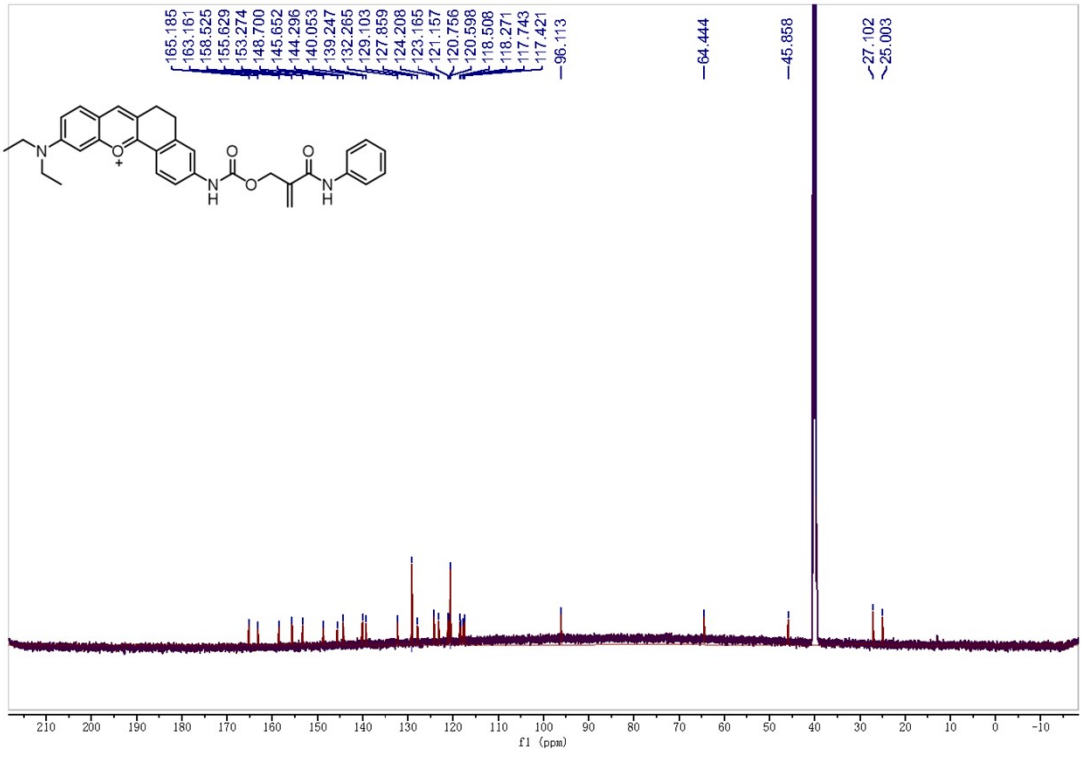


^{1}H NMR (400 MHz, DMSO-d_6) of compound **1**.

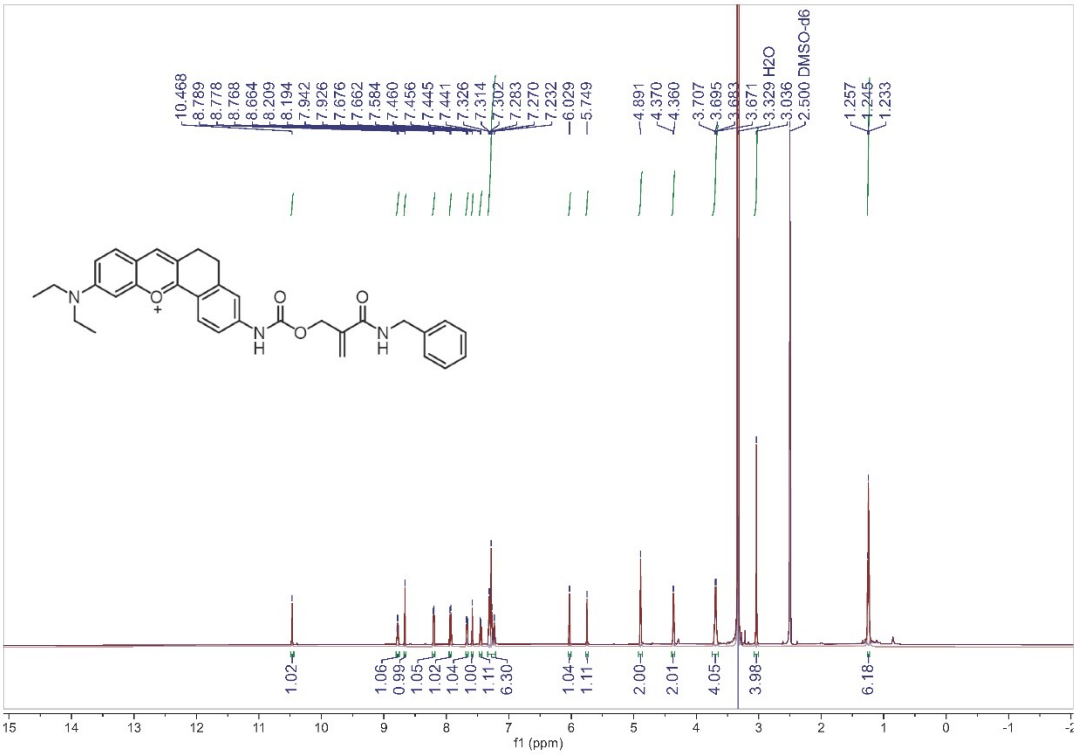
^{13}C NMR (151 MHz, DMSO-d_6) of compound **1**.



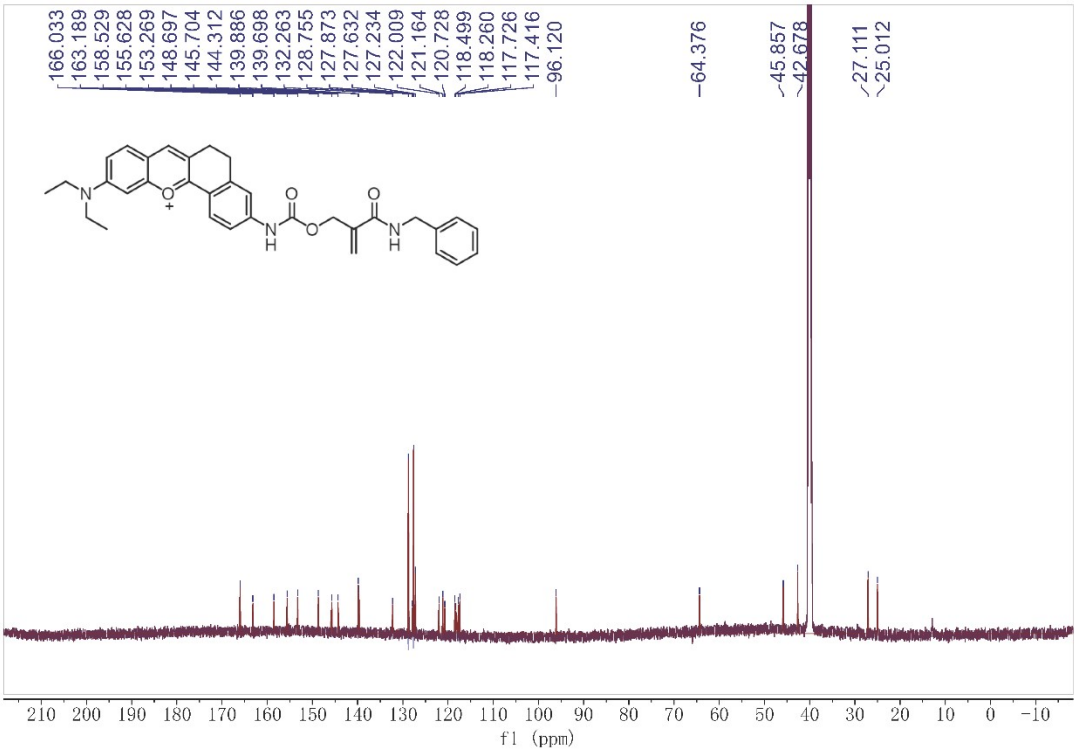
^{1}H NMR (400 MHz, DMSO-d_6) of compound **2**.



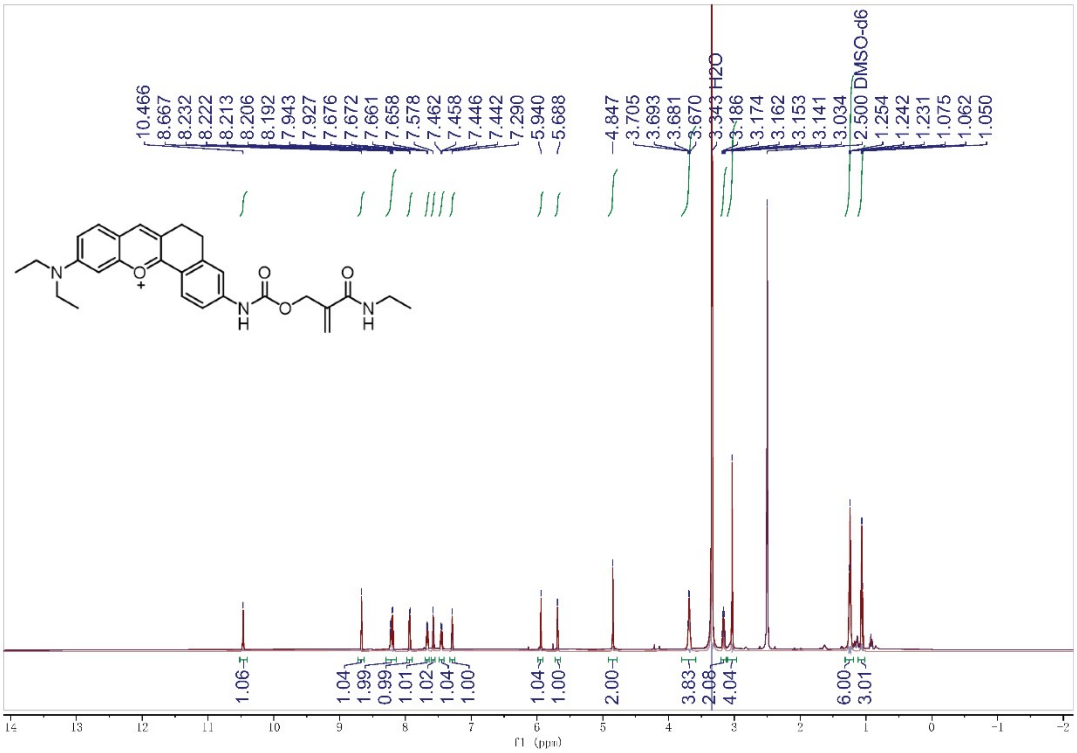
^{13}C NMR (151 MHz, DMSO-d_6) of compound **2**.



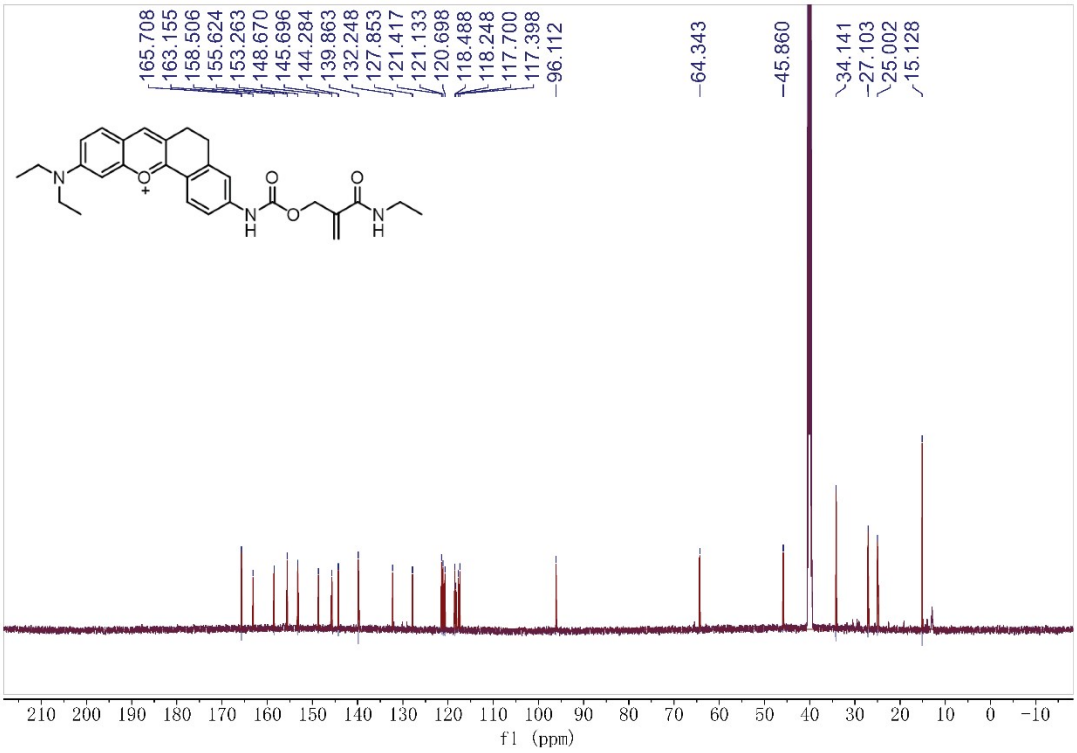
^{1}H NMR (400 MHz, DMSO-d_6) of compound **VDP-red**.



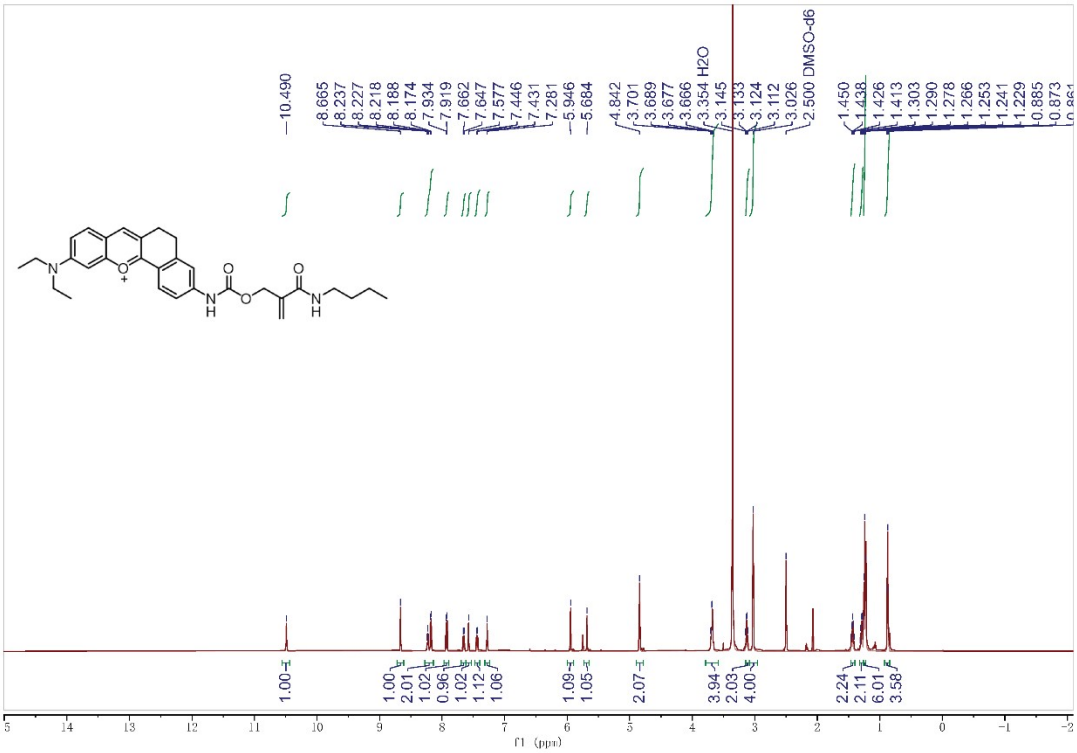
^{13}C NMR (151 MHz, DMSO-d_6) of compound **VDP-red**.



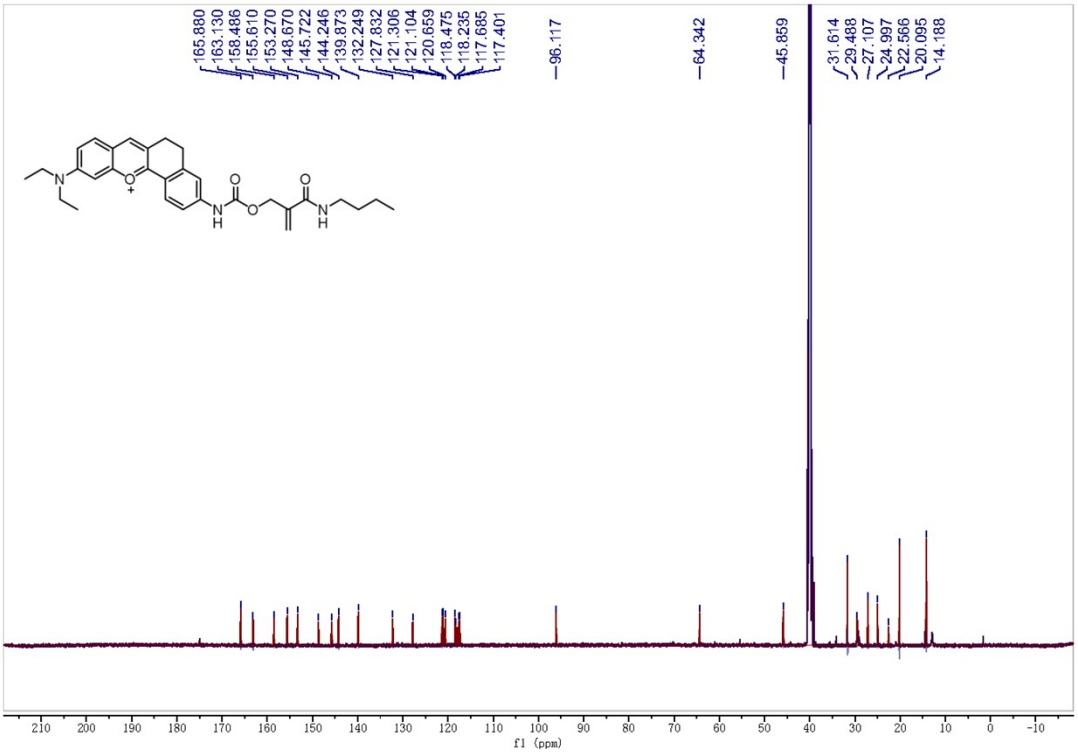
^{1}H NMR (400 MHz, DMSO-d_6) of compound **4**.



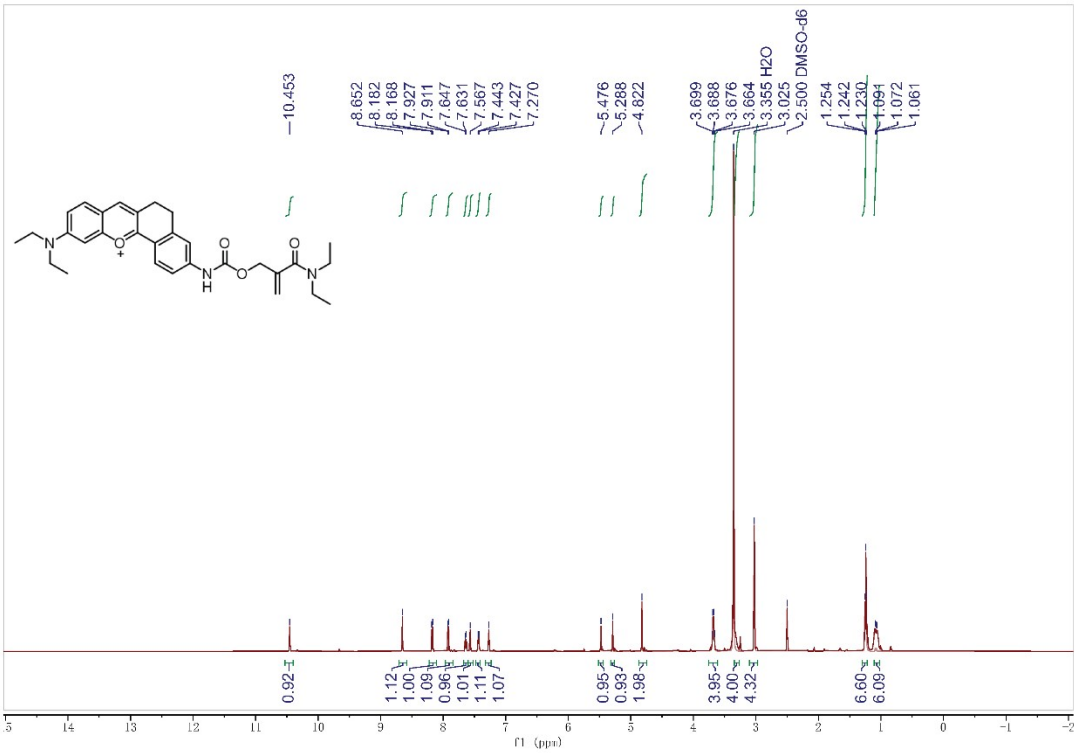
^{13}C NMR (151 MHz, DMSO-d_6) of compound **4**.



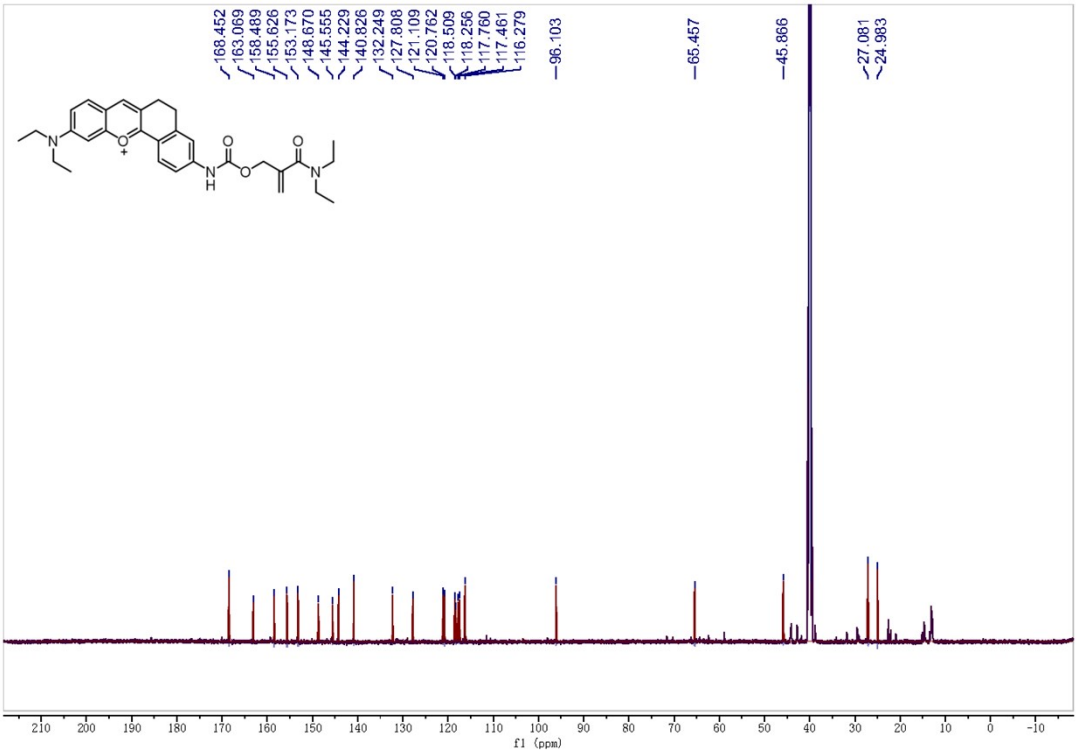
^{1}H NMR (400 MHz, DMSO-d_6) of compound **5**.



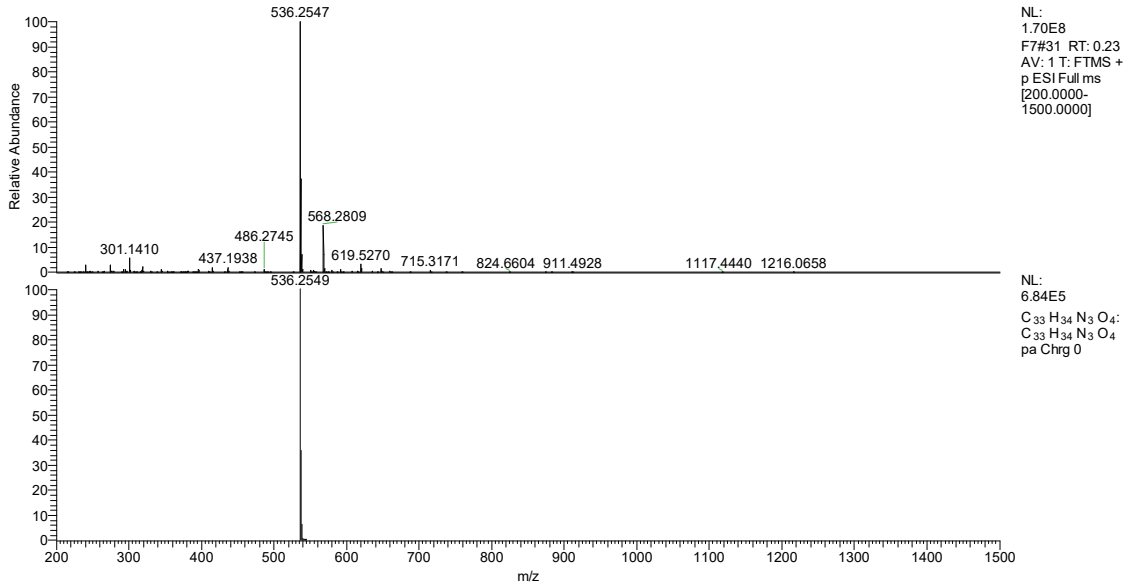
^{13}C NMR (151 MHz, DMSO-d_6) of compound **5**.



^{1}H NMR (400 MHz, DMSO-d_6) of compound **6**.



^{13}C NMR (151 MHz, DMSO-d_6) of compound **6**.



ESI-Mass spectrum of **VDP-red** (ESI-MS).

VI. References

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