Supporting Information

for

Tumor Cell Specific and Lysosome-targeted Delivery of Nitric Oxide for Enhanced Photodynamic Therapy Triggered by 808 nm Near-Infrared Light

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1. Chemicals:

All reagents were purchased commercially and used without further purification unless otherwise noted. The compounds Lyso-NINO,[S1] (4-NH_2)-C_6H_4-PO_3H ((4-aminobenzyl)phosphonic acid), [S2] and [Ru(tpy)$^{COOH}Cl_3$](tpy^{COOH} = (2,2':6',2''-terpyridine)-4'-carboxylic acid) [S3,S4] were prepared according to literatures.

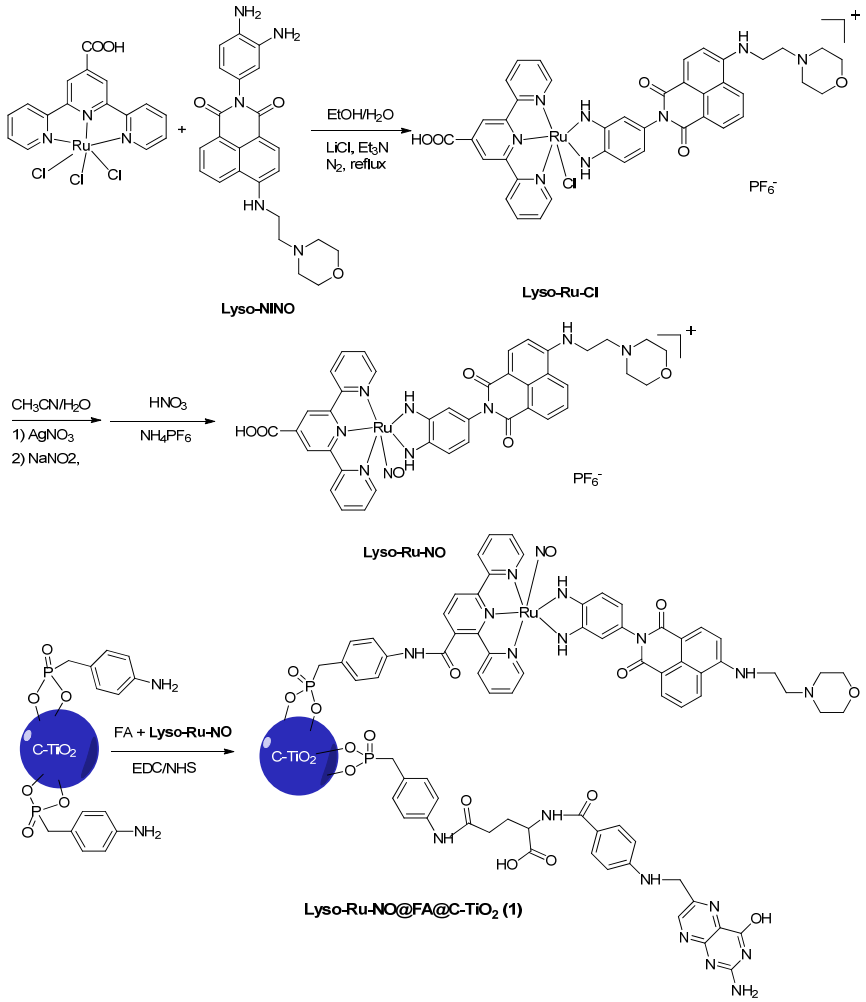
2. General Techniques:

^{1}H NMR spectra were recorded on Bruker AV400 spectrometer (400 MHz). ESI mass spectra were performed on Micromass LCTTM mass spectrometer. Transmission electron microscopy (TEM) was performed on a JEOL JEM-2011 transmission electron microscope operating at 100 kV. Powder X-ray diffraction (XRD) analysis was performed on Bruker D8 ADVANCE X-Ray Diffractomer. XPS data were collected on a Thermo Escalab 250 XPS instrument with a monochromatic Al Kα X-ray source ($h\nu$=1486.6 eV). All binding energies were referenced to the C1s peak (284.6 eV) arising from adventitious carbon. FTIR spectra were recorded on a Shimadzu Fourier transform infrared spectrometer (IRPrestige-21). UV-vis absorption spectra were recorded on a Shimadzu UV-visible spectrophotometer (UV-2600). Fluorescence studies were carried out on a Horiba Fluoromax-4 fluorescence spectrophotometer.

The intensity of 808 nm NIR irradiation on the sample cell was measured using a CEL-NP 2000 intensity meter. The amount of NO released was measured using a NO-sensitive electrode (World Precision Instrument, ISO-NO meter, equipped with a TBR 1025 free radical analyzer for measuring nitric oxide from 0.3 nM to 100 μM.). The tip of the electrode was placed outside the light path. The electrode was accurately calibrated by mixing standard solutions of $NaNO_2$ with H_2SO_4 (0.1 M) and KI (0.1 M), according to the protocol indicated in the manufacturer manual. The amperometric data collected from the electrode was then converted into the corresponding nitric oxide concentration. Fluorescence images were acquired by using a Leica TCS SP5 II inverted microscope with a Leica DMI 6000B confocal scanning system. Flow cytometry (FCM) was performed on a Beckman Coulter flow cytometer (Quanta SC, USA).

3. 3. Methods.

The nanoplatform **(1)** was prepared according to Scheme S1.



Scheme S1 Preparation route for the nanoplatform **(1)**.

Synthesis of [(tpy^{COOH})Ru(Lyso-NINO)(Cl)](PF$_6$)

To a mixture of EtOH-H_2O (40 mL, 3:1, v/v) containing LiCl (100 mg, 2.35 mmol) and Et_3N (0.4 mL), Ru(tpy^{COOH})Cl_3 (145 mg, 0.30 mmol) and Lyso-NINO (155 mg, 0.33 mmol) were added. Then the resulting mixture was heated at reflux for 6 h under N_2 atmosphere. While hot the suspension was filtered through a pad of celite. The resulting clear deep red solution was concentrated to a few milliliters and excess saturated aqueous solution of NH_4PF_6 was added. Then the mixture was stored at 5 °C overnight. The red brown solid precipitate was filtered, washed with cold water and Et_2O, dried in vacuo. Yield: 220.1 mg (74.2 %).

^{1}H NMR (DMSO-d_6): 2.63-2.69 (m, 2H), 3.54-3.60 (m, 8H), 6.83 (d, J = 8.5 Hz, 1H), 6.89-7.70 (m, 1H), 7.03-7.08 (m, 1H), 7.46-7.50 (m, 3H), 7.68-7.85 (m, 4H), 8.04-8.05 (m, 2H), 8.22 (d, J = 8.2 Hz, 1H), 8.39 (d, J = 7.1 Hz,1H), 8.69-8.81 (m, 3H), 9.02-9.09 (m, 2H), 14.35 (s, 1H) ppm.

ESI-MS: *m/z,* [M-PF_6]$^+$: calcd. 843.1, found 843.1.

Synthesis of [(tpy^{COOH})Ru(Lyso-NINO)(NO)](PF$_6$)$_3$

[(tpy^{COOH})Ru(Lyso-NINO)(Cl)](PF$_6$) (110 mg, 0.11 mmol) and an excess of $AgNO_3$ (40 mg, 0.24 mmol) were taken in 30 mL of CH_3CN-H_2O (1:1, v/v) and heated at reflux for 2 h. The color of the solution changed gradually from red to violet. The solution was cooled to room temperature and the precipitated AgCl was separated by filtration through a sintered glass frit. An excess of $NaNO_2$ (103.5 mg, 1.5 mmol) was added to the filtrate and the mixture was heated under reflux for 6 h. After cooling to room temperature, the violet solution was reduced to 10 mL under vacuum, 2.0 mL of HNO_3 (2.0 mol·L^{-1}) was directly added dropwisely into the violet solution at 273 K under stirring condition, A deep-red solid product was formed on addition of saturated aqueous NH_4PF_6 solution (5.0 mL). The precipitate was filtered off immediately, washed with cold water and Et_2O, and then dried in vacuo. Yield: 85.6 mg (61.2 %).

^{1}H NMR (DMSO-d$_6$): 2.63-2.73 (m, 2H), 3.53-3.62 (m, 8H), 6.83 (d, *J* = 8.5 Hz, 1H), 6.89-6.95 (m, 1H), 7.05-7.08 (m, 1H), 7.46-7.49 (m, 3H), 7.68-7.85 (m, 4H), 8.02-8.04 (m, 2H), 8.22 (d, *J* = 8.4 Hz, 1H), 8.39 (d, *J* = 7.6 Hz,1H), 8.70 (d, *J* = 8.2 Hz,1H), 8.75-8.80 (m, 2H), 9.05-9.07 (m, 2H), 14.35 (s, 1H) ppm. **ESI-MS:** *m/z* [M-3PF$_6$-2H$^+$-NO]$^+$: calcd 806.2, found 806.2. m/z [M-3PF$_6$-2H$^+$+H$_2$O]$^+$: calcd 854.2, found 854.1.

Synthesis of {C-TiO$_2$ NPs}

Glucose (0.14 g) was dissolved in 60 mL of ethanol to form a clear solution, to which a 2.0 mL of $Ti(OC_4H_9)_4$ (0.018 mol) was dropwise added. After vigorous stirring for 10 min, the suspensions were transferred into autoclaves and kept at 200 °C for 4 h. After reaction, the autoclaves were cooled naturally in air, and the suspensions were isolated by filtration and washed with water.

Synthesis of the nanoplatform (1)

In the typical process, 9.3 mg of (4-aminobenzyl) phosphonic acid (0.05 mmol) was dissolved in 1.0 mL of water at pH 9. Meanwhile, 10.0 mg of C-TiO_2 was sonicated in 4.0 mL of water. Subsequently, the (4-aminobenzyl)phosphonic acid solution was added to the stirred C-TiO_2 dispersion. The mixture was left stirring overnight under dark. The resulting dispersion was centrifuged at 10,000 rpm for 10 min and washed twice with water. The supernatant was decanted and the obtained NH_2@C-TiO_2 NPs were re-dispersed in water.

$[(tpy^{COOH})Ru(DAMBO)(NO)](PF_6)_3$ (100 mg, 0.08 mmol) and FA (5.0 mg, 0.01mmol) were dissolved in 5.0 mL DMF, activated by an EDC/NHS solution for 30 min. Following that, 50.0 mg of NH_2@C-TiO_2 NPs was added to react for 12 h at room temperature. The excess reagents were removed as supernatant by centrifugation at 10,000 rpm for 10 min, and the precipitate was washed thrice with DMF and deionized water. Finally, the nanoplatform **(1)** thus obtained were re-dispersed in water.

Light triggered NO release.

The nanoplatform **(1)** (1.0 mg/mL) was suspended in saline solution (150 mM) in a quartz cuvette under gentle stirring using a magnetic stirring bar. Following that, NO release was initiated by irradiation of the sample cell with an 808 nm NIR laser. The intensity of 808 nm NIR irradiation on the sample cell was measured by using a CEL-NP 2000 intensity meter. The amount of NO released was measured using a NO-sensitive electrode (World Precision Instrument, ISO-NO meter, equipped with a TBR1025 free radical analyzer for measuring nitric oxide from 0.3 nM to 100 μM.). The tip of the electrode was placed outside the light path. The electrode was accurately calibrated by mixing standard solutions of $NaNO_2$ with H_2SO_4 (0.1 M) and KI (0.1 M), according to the protocol indicated in the manufacturer manual. The amperometric data collected from the electrode was then converted into the corresponding NO concentration.

NO quantum yield measurement.

An 808nm NIR laser was used for NO quantum yields measurement. Light intensity was determined before each photolysis experiments by an actinometry meter (measured intensity of ~ 10 mW). The solution of nanoplatform **(1)** was placed in a 1.0 cm-path-length quartz cuvette, 1.0 cm away from the light source. The solution was prepared to ensure sufficient absorbance (>90 %) at the irradiation wavelength and agitated periodically during the photolysis experiment. NO quantum yields (Φ) were calculated based on NO concentrations, obtained by NO meter measurement. The calculated values were plotted versus time. These plots were linear, with a negative slope, for the first 20-25% of the reaction. The extrapolated quantum yield at t = 0 (y intercept) was taken as Φ_{NO} for the photolabilization of NO from the nanoplatform **(1)** solution.

Reaction Oxygen Species (ROS) detection.

Nanoplatform **(1)** (3.0 mg) or C-TiO_2 NPs (3.0 mg) were added to a quartz cuvette containing 3.0 mL of 5.0 μM DCFH-DA aqueous solution. The solution was then irradiated by an 808 nm NIR laser (200 mW/cm^2), the solution was analyzed by fluorescence spectrophotometer with 10 min intervals. The generation of ROS was determined from the emission peak at 525 nm.

Singlet Oxygen ($^1O_2$) quantum yields measurement:

The production efficiency of $^1O_2$ induced by the nanoplatform **(1)** under 808 nm irradiation was evaluate by a steady-state method using DPBF as the $^1O_2$ indicator and methylene blue (MB) as the standard (ΦΔ = 0.52). Singlet oxygen quantum yields (Φ_Δ) were determined through monitoring the oxidation of 1,3-diphenylisobenzofuran (DPBF).[S5] Briefly an oxygen-saturated solution of nanoplatform (**1**) containing 30 μM DPBF was prepared in the dark and irradiated with an 808 nm laser at a power of 600 mW/cm^2 in an interval of 30 s. DPBF oxidation was monitored by UV-Vis-NIR spectrophotometer. The Φ_Δ values were obtained by the relative method using methylene blue (MB) in DMF (Φ_Δ = 0.52) as the standard and calculated with eq. 1

$$\Phi_{\Delta\,(x)} = \Phi_{\Delta\,(std)}\,(S_x / S_{std})\,(F_{std} / F_x) \qquad (1)$$

where subscripts x and std designate the sample and MB, respectively, S stands for the slope of plot of the absorbance of DPBF (at 418 nm) vs. irradiation time. F stands for the absorption correction factor, which is given by $F = 1 - 10^{-OD}$ (OD represents the optical density of sample and MB at 808 nm).

Singlet oxygen quantum yields (Φ_Δ) of 0.284, 0.267, 0.227 and 0.225 were obtained under pH of 4.0, 6.0, 7.4 and 8.0, respectively.

Cell culture.

Human cervical carcinoma cells (HeLa cells), and human breast cancer cells (MCF-7 cells) were obtained from Shanghai Institutes for Biological Sciences (SIBS), Chinese Academy of Science (CAS, China). HeLa cells and MCF-7 Cells were cultured in Roswell Park Memorial Institute medium (RPMI-1640, Thermo, USA) and Dulbecco′s Modified Eagle Medium (DMEM, Thermo, USA) at 37 °C under 5% CO_2 atmosphere, supplemented with 10% (v/v) fetal bovine serum (Gibco, USA) and 1% (v/v) penicillin/streptomycin (Thermo, USA).

MTT assay.

All the cells were seeded on a 96-well plate with a density of 5×10^4 cells per well and incubated in a humidified 5% CO_2 atmosphere for 24 h. The cell culture medium were removed and washed with PBS. Following that, different concentrations of the nanoplatform **(1)** (0, 10, 20, 50, 100, 200 μg/mL) suspended in cell culture medium were added and incubated further for a period of 12 or 24 h at 37 °C in a humidified 5% CO_2 atmosphere. MTT (20 μL, 5.0 mg/mL) solution was added to each well. After 4 h of incubation at 37 °C, the cell culture medium was removed and the formazan crystals were lysed with 150 μL of DMSO. The absorbance was then measured at 490 nm using a microplate reader (Multiskan MK3, USA).

808 nm NIR irradiation experiments: After incubation of the cells with different concentrations of the nanoplatform **(1)**, {Ru-NO@FA@C-TiO_2 NPs}, and {Ru-lyso-NO@FA@TiO_2 NPs} for 4 h, light irradiation was applied (808 nm, 600 mW/cm^2, 10 min), and the cells were incubated for another 1 h. Subsequently, the same procedures, as described above, were performed to obtain the final absorbance measurement at 490 nm using a microplate reader.

Confocal laser scanning microscopy.

Fluorescence imaging was performed with a Leica DMI 6000B confocal scanning system. A 405 nm laser was used as the excitation source and the corresponding emissions were collected in the wavelength range of 420–490 nm. HeLa and MCF-7 cells were seeded on a plastic-bottomed μ-dish of diameter 35 mm, with a density of 10^4 cells and maintained at 37 °C in 5% CO_2 atmosphere for 24 h. The cells were then treated with the nanoplatform **(1)** (50 μg/mL) for 2 h. After incubation, the cells were washed twice with PBS and subjected to confocal fluorescence microscopy analysis.

Real-time intracellular NO detection experiments: After incubating the cells with the nanoplatform (**1**) solution (50 μg/mL) in the cell culture medium for 4 h, the cells were washed twice with PBS, treated with DAF-FM-DA (5.0 μM), and then incubated for 30 min. After the incubation period, the cells were washed twice with PBS and imaged with serum-free medium in the absence or presence of light irradiation (808 nm, 200 mW/cm^2, 3 min). Excitation was carried out with lasers at λ = 405 nm or 488 nm, and emissions were recorded in the wavelength range of 420–490 nm or 500–550 nm, respectively.

Co-localization experiments: the cells were incubated with the nanoplatform (**1**) solution (50 μg/mL) or {Ru-NO@FA@C-TiO_2 NPs} in the cell culture medium for 4 h or 8 h, the cells were washed twice with PBS, treated with Lyso-Tracker Red (5.0 μM), and then incubated for 30 min. After the incubation period, the cells were washed twice with PBS and imaged with serum-free medium. Excitation was carried out with lasers at λ = 405 nm or 543 nm, and emissions were recorded in the wavelength range of 420–490 nm or 570–620 nm, respectively.

Flow Cytometry (FCM).

For receptor-directing binding experiments, HeLa and MCF-7 cells were incubated with nanoplatform **(1)** solution (50 μg/mL) in cell culture medium for 2 h at 37 °C. Similarly, for the competitive binding experiments, HeLa cells were pre-incubated with free folic acid (50 μg/mL) for 30 min and then further incubated with the nanoplatform (**1**) solution (50 μg/mL) for 2 h at 37 °C. All the cells were washed twice with PBS and harvested by trypsinization, followed by centrifugation at 1,500 rpm for 6 min. The precipitate thus obtained was re-suspended in PBS and analyzed using a flow cytometer.

For intracellular ROS detection experiments: HeLa cells were incubated with nanoplatform **(1)** solution (100 μg/mL) in cell culture medium for 4 h at 37 °C, respectively. The cells were washed twice with PBS, treated with DCFH-DA (10 μM) and then incubated for 20 min. After visible light (808nm, 600 mW/cm^2, 5min, 10min, 15min) irradiation, the cells were washed twice by PBS and detached by trypinization, followed by centrifugation at 1,500 rpm for 6 minutes. The precipitate thus obtained was re-suspended in PBS and analyzed using a flow cytometer.

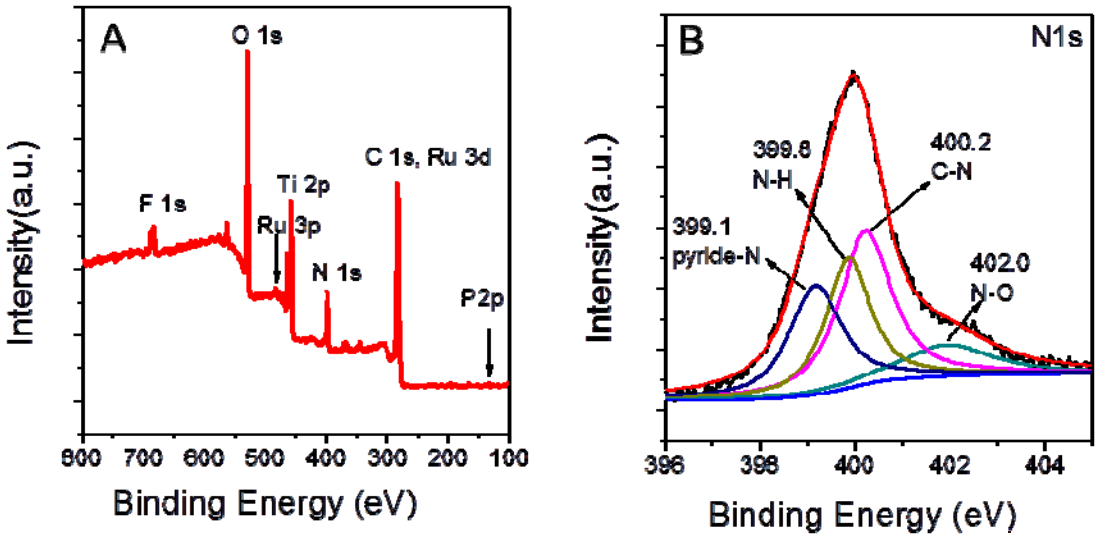


Figure S1 XPS survey (A), and N1s high resolution scan spectra (B) of nanoplatform (1).

The XP survey spectrum revealed signatures of C, F, N, O, P, Ru, and Ti (Fig. S1A). The high resolution N1s XP spectrum of nanoplatform (**1**) showed one broad nitrogen signal that was deconvoluted into several components as indicated in Figure S1B. The N1s peak at 402.0 eV was assignable to the nitrogen atom of nitrosyl.[S6]

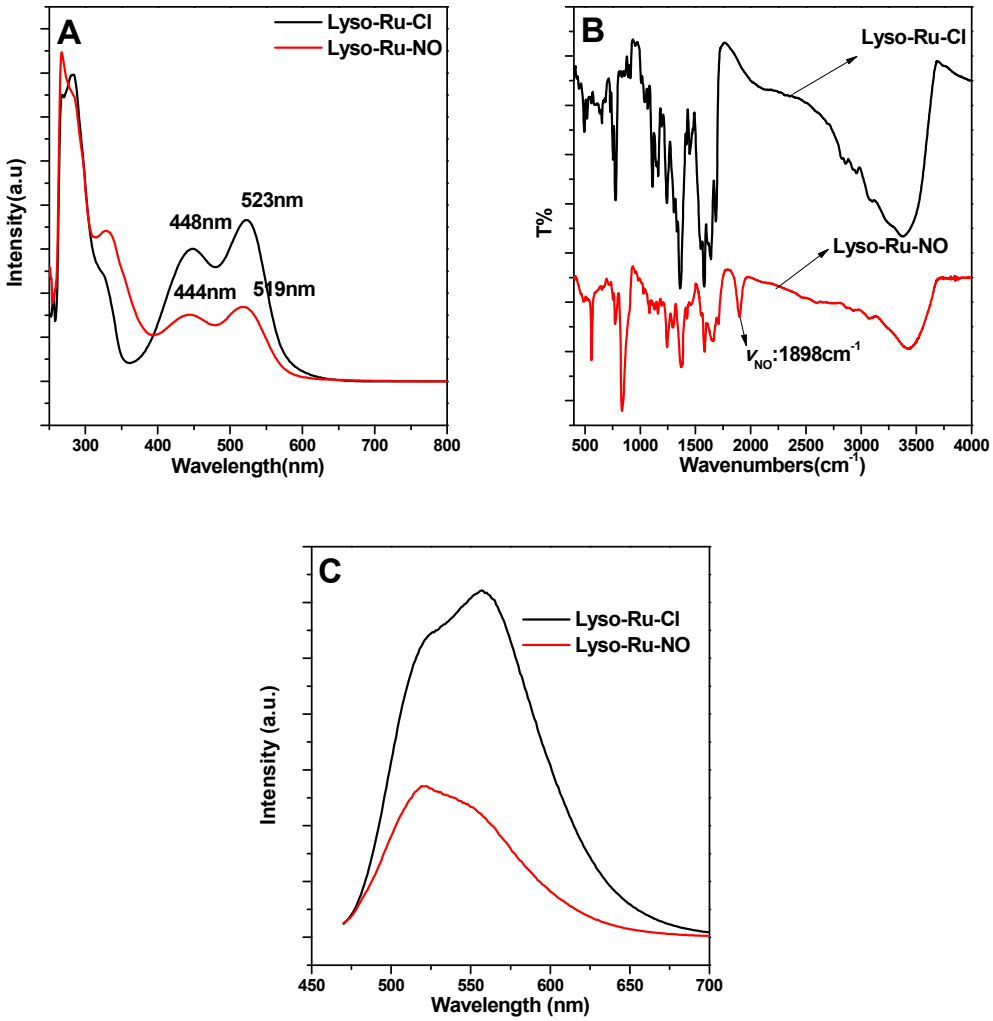


Figure S2. (A) UV-vis spectra of [Ru(tpy^{COOH}) (Lyso-NINO)(NO)]$^{3+}$(red), and [Ru(tpy^{COOH}) (Lyso-NINO)Cl]$^{+}$ (black) in DMF solution. (B) FT-IR spectra of [Ru(tpy^{COOH}) (Lyso-NINO)(NO)]$^{3+}$(red), and [Ru(tpy^{COOH}) (Lyso-NINO)Cl]$^{+}$ (black). (C) Fluorescence spectra of [Ru(tpy^{COOH}) (Lyso-NINO)(NO)]$^{3+}$(red), and [Ru(tpy^{COOH}) (Lyso-NINO)Cl]$^{+}$ (black) in DMSO solution.

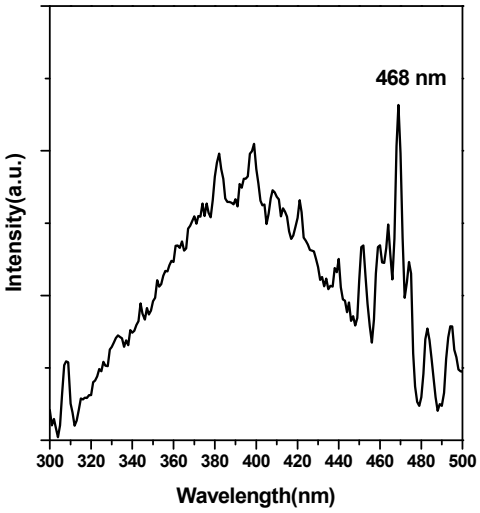


***Figure S3*.** Photoluminescence spectra of the nanoplatform **(1)**. Ex: 280 nm.

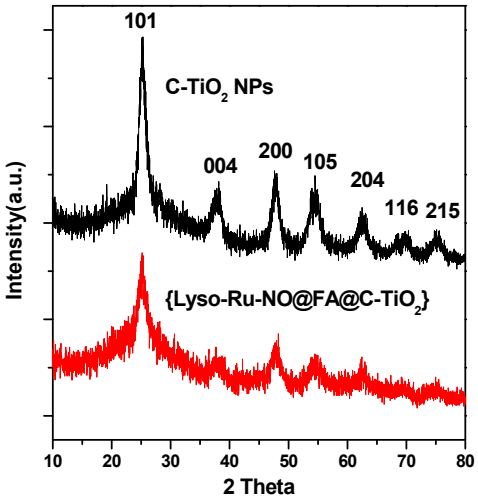


Figure S4. PXRD patterns of nanoplatform **(1)** (red line), and C-TiO_2 NPs (black line).

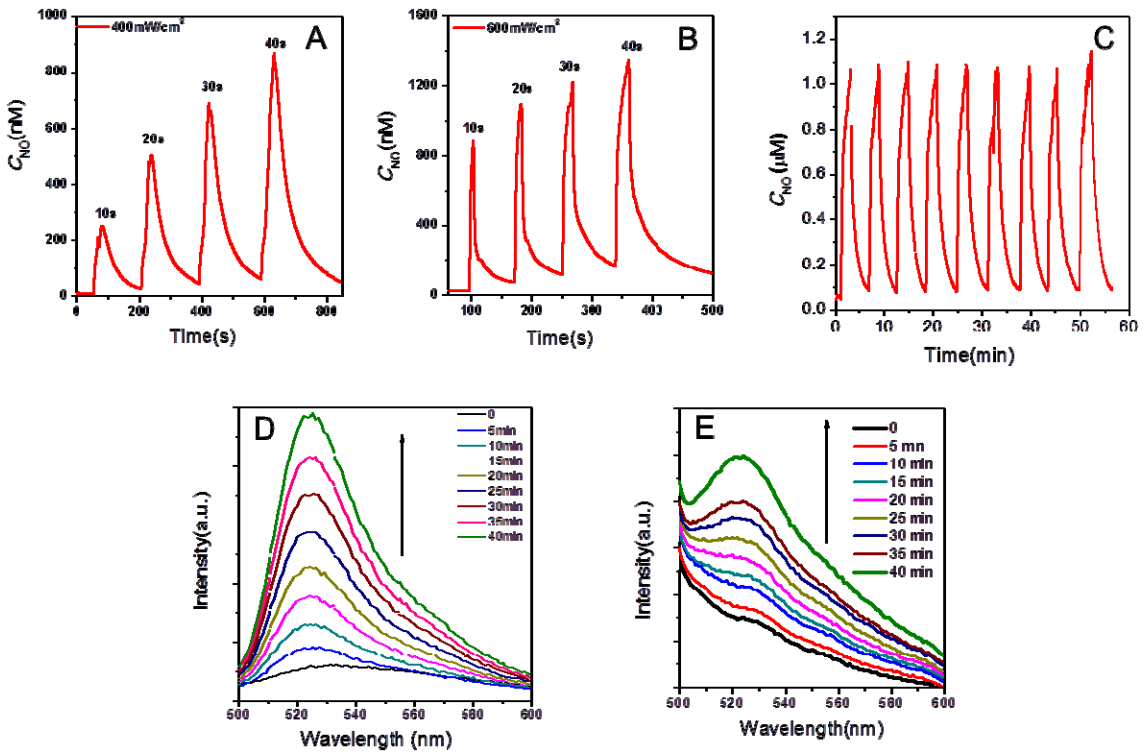


Figure S5. NO flux released from 1.0 mg/mL nanoplatform (**1**) in anaerobic saline solution upon illumination with 808 nm NIR light at the intensity of 400 mW/cm^2 (A) and 600 mW/cm^2 (B) for the time periods (in seconds) as indicated. (C) NIR light-induced NO release from 1.0 mg/mL nanoplatform (**1**) suspended in aerobic saline solution by periodic 808 nm light illumination (600 mW/cm^2). (D) Fluorescence intensity changes of DCFH DA (10 μM) solution in the presence of 1.0 mg/mL nanoplatform (**1**) (D) and C-TiO_2 NPs (E) irradiated by 808 nm NIR light (200 mW/cm^2) at every 5 minutes.

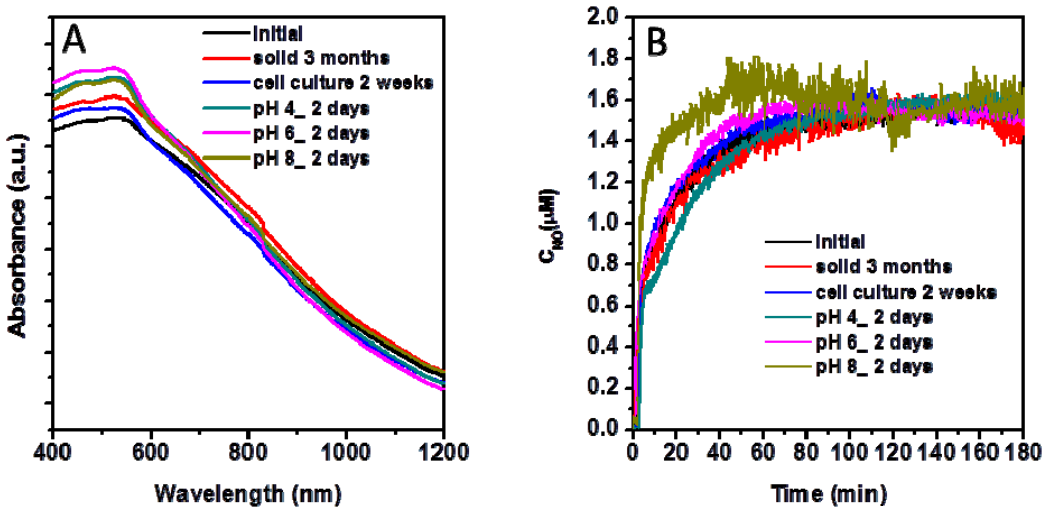


Figure S6. **Stability test of the nanoplatform (1).** (A) Light-induced NO release from 1.0 mg/mL nanoplatform (**1**) suspended in saline solution by constant light illumination (808 nm, 200 mW/cm^2). Black line: nanoplatform tested initially; red line: after 3 months-storage in the dark as solid; blue line: 3 months-storage in the dark as solid and further keeping in cell culture for 2 weeks in the dark; green line: 2 days storage in acidic saline solution (pH = 4.0) in the dark. Pink line: 2 days storage in acidic saline solution (pH = 6.0) in the dark. Dark yellow line: 2 days storage in acidic saline solution (pH = 8.0) in the dark. (B) Diffuse reflectance UV-vis spectra of nanoplatform (**1**). Black line: nanoplatform tested initially; red line: after 3 months-storage in the dark as solid; blue line: 3 months-storage in the dark as solid and further keeping in cell culture for 2 weeks in the dark; green line: 2 days storage in acidic saline solution (pH = 4.0) in the dark. Pink line: 2 days storage in acidic saline solution (pH = 6.0) in the dark. Dark yellow line: 2 days storage in acidic saline solution (pH = 8.0) in the dark. Cell culture was composed of RPMI 1640 medium/fetal bovine serum (V:V = 9:1).

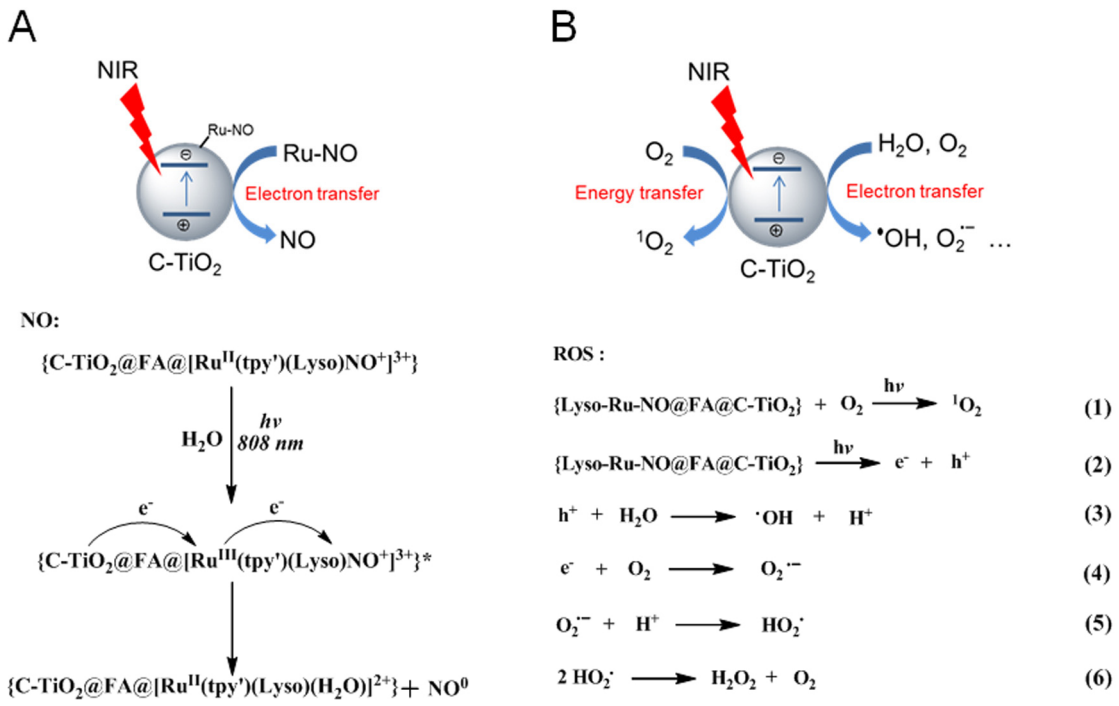


Figure S7. Plausible photochemical pathways for NO release (A) and ROS generation (B) from the nanoplatform (**1**) under 808 nm laser irradiation.

Ruthenium nitrosyls derived from polypyridine ligand are photolabile, and release of NO upon their exposure to light excitation is often accompanied by the replacement of NO with solvent molecule, e. g. H_2O, in the coordination sphere of the ruthenium ion (P. K. Mascharak, *Coord. Chem. Rev.* 2008, **252**, 2093; *Acc. Chem. Res.* 2008, **41**, 190.). In order to extend the light responsive of the ruthenium nitrosyl, Lyso-Ru-NO, to longer wavelength, the Lyso-Ru-NO was then covalently attached to the NIR light responsive C-TiO_2 nanoparticles. Consequently, NIR light-generated electron transfers from the C-TiO_2 moiety to the NO donor (Lyso-Ru-NO) leads to NO release from nanoplatform (**1**) (Figure S7A).

About the generation of reactive oxygen species (ROS) from TiO_2 and its derivatives, it is well-known that photoexcitation of TiO_2 in an aqueous solution results in the formation of various ROS such as singlet oxygen ($^1O_2$), hydroxyl (·OH) and peroxy ($\cdot HO_2$) radicals, superoxide anions ($O_2^{-\cdot}$), and hydrogen peroxide (H_2O_2) (W. Macyk, *J. Am. Chem. Soc*. 2006, **128**, 15574; J. Li, *Acs Nano*. 2015, **9**, 2584; Y. H. Su, *PhysChemChemPhys* 2013, **15**, 4844.). Carbon doping may generate new hybrid states in the band gap of TiO_2, which renders C-TiO_2 NPs with significant absorbance in long wavelength region. The major reactions that result in the formation of ROS upon 808-nm light illumination of the nanoplatform (**1**) are shown as simplified eqs. 1-6 (Figure S7B).

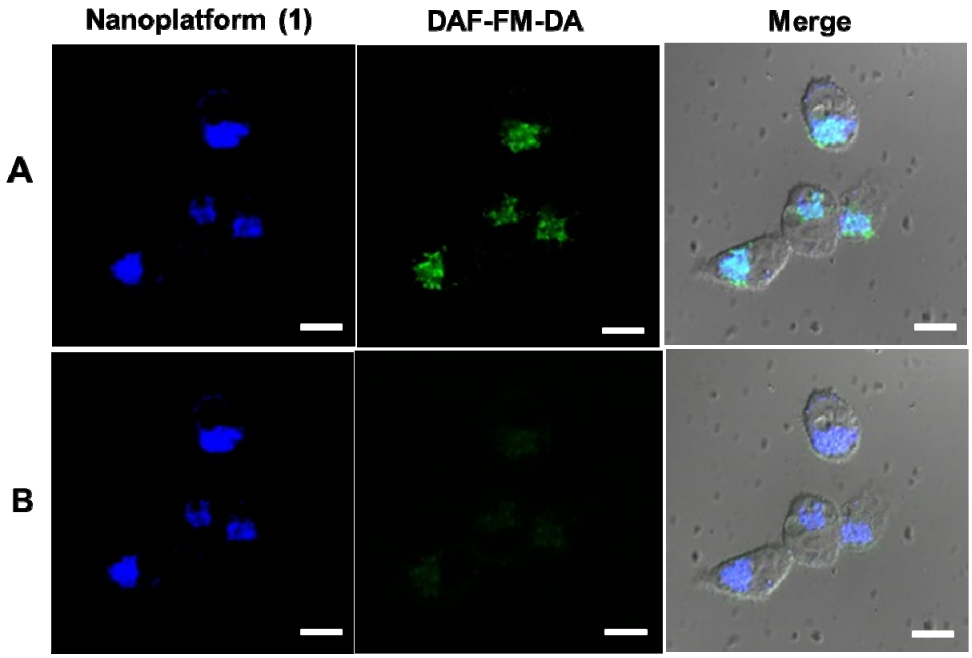


Figure S8. Confocal microscopy images of HeLa cells treated with nanoplatform **(1)** (50 μg/mL) and DAF-FM DA (5 μM) after (A) and before (B) 808 nm laser irradiation (3 min). The blue and green images were obtained for excitation at 405 and 488 nm, and recording the corresponding fluorescence in the range of 420–490 nm, and 500–550 nm, respectively. (Scale bars = 20 μm).

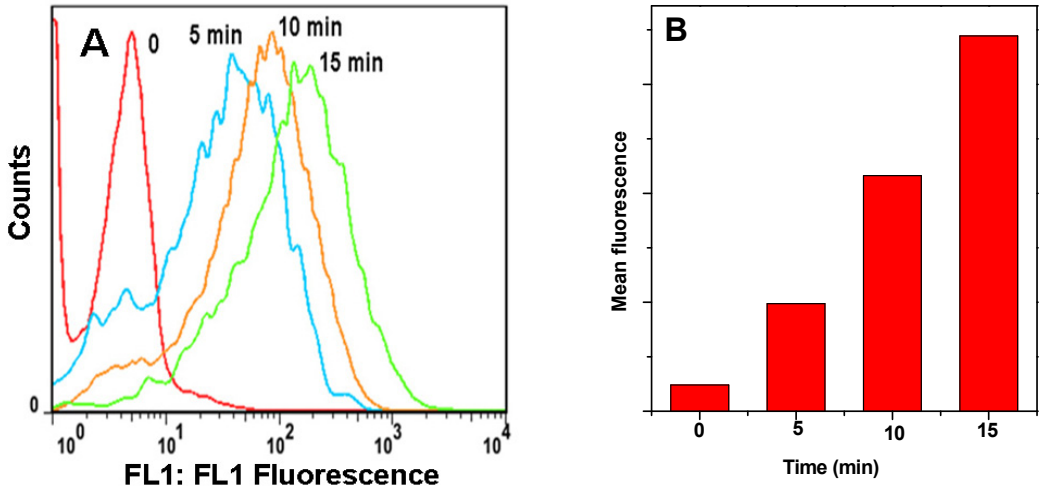


Figure S9. (A) Intracellular ROS generation was detected in HeLa cells treated with the nanoplatform **(1)** (50 μg/mL) under 808 nm laser irradiation. The level of intracellular ROS was measured by FACS Calibur flow cytometry using ROS fluorescent probe DCFH-DA (5 μM). (B) Mean fluorescence of DCF with different illumination time.

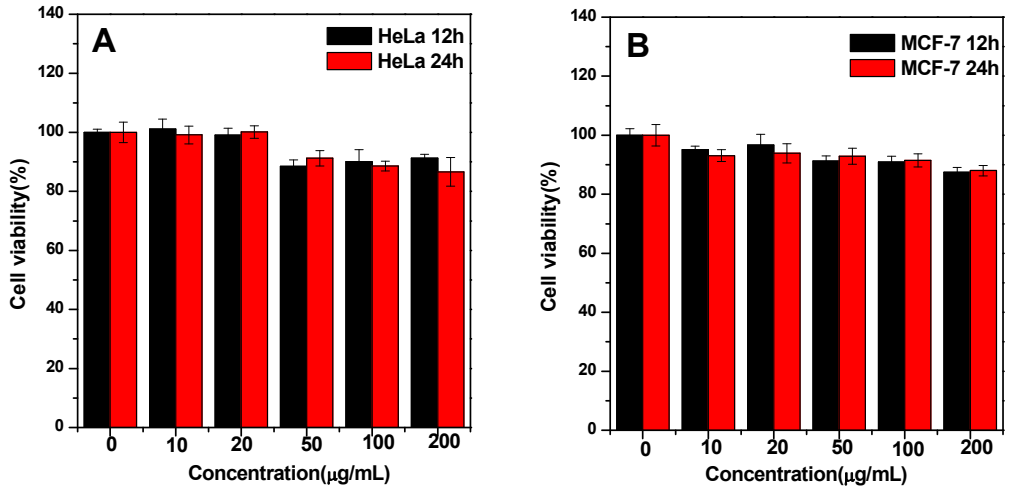


Figure S10. Cytotoxicity assays of HeLa (A), and MCF-7 cells (B) treated with the {C-TiO_2 NPs} concentration ranging from 0 to 200 μg/mL for incubation of 12 h and 24 h, respectively.

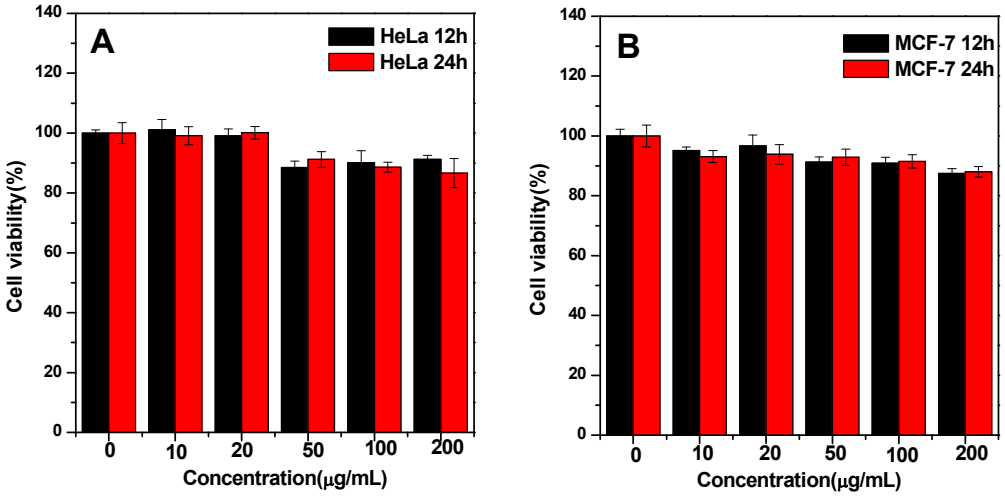


Figure S11. Cytotoxicity assays of HeLa (A), and MCF-7 cells (B) treated with the nanoplatform **(1)** of concentration ranging from 0 to 200 μg/mL for incubation of 12 h and 24 h, respectively.

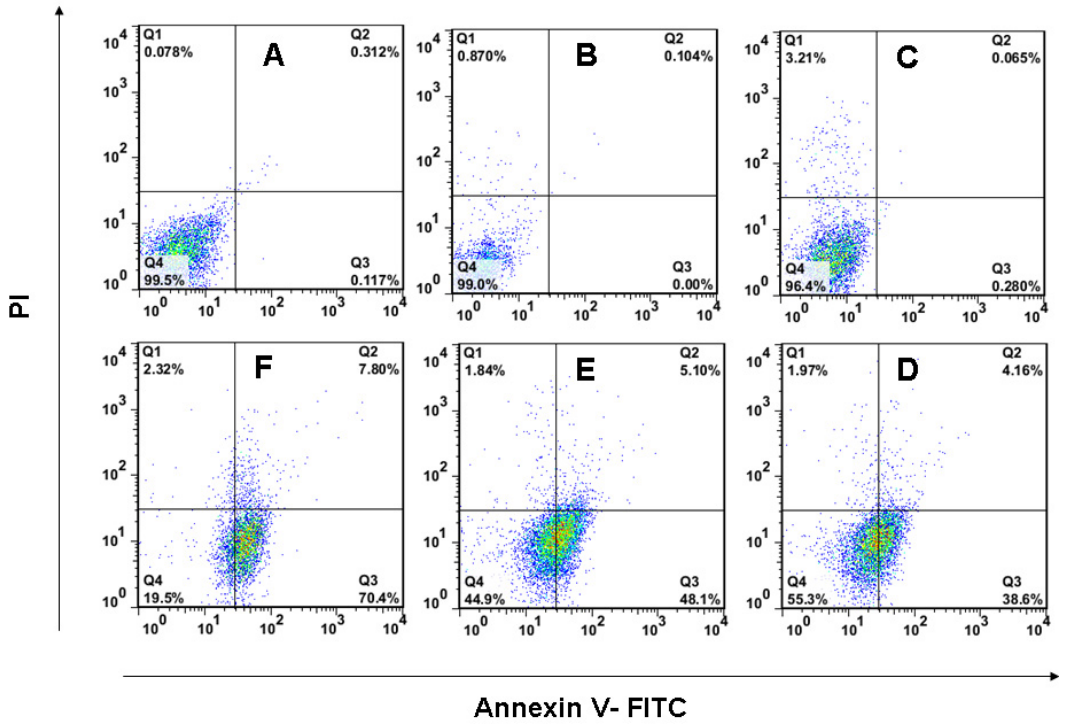


Figure *S12*. Flow cytometric analysis for early and late apoptotic cells. (A) Control HeLa cells. (B) HeLa cells were irradiated by an NIR laser (808 nm, 600 mW/cm^{-2}, 10 min) in the absence of the nanoplatform. (C) HeLa cells were treated with 100 μg/mL of the nanoplatform **(1)** and incubated with 4 h without NIR irradiation. From (D-F): HeLa cells were treated with the nanoplatform **(1)** in the concentration of 20 (D), 50 (E), 100 (F) μg/mL, incubated with 4 h, irradiated by an NIR laser (808 nm, 600 mW/cm^2, 10 min), and then followed by incubation of 1h, respectively.

References:

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