Supporting information for

Photoregulated Release of Caged Anticancer Drugs from Gold Nanoparticles

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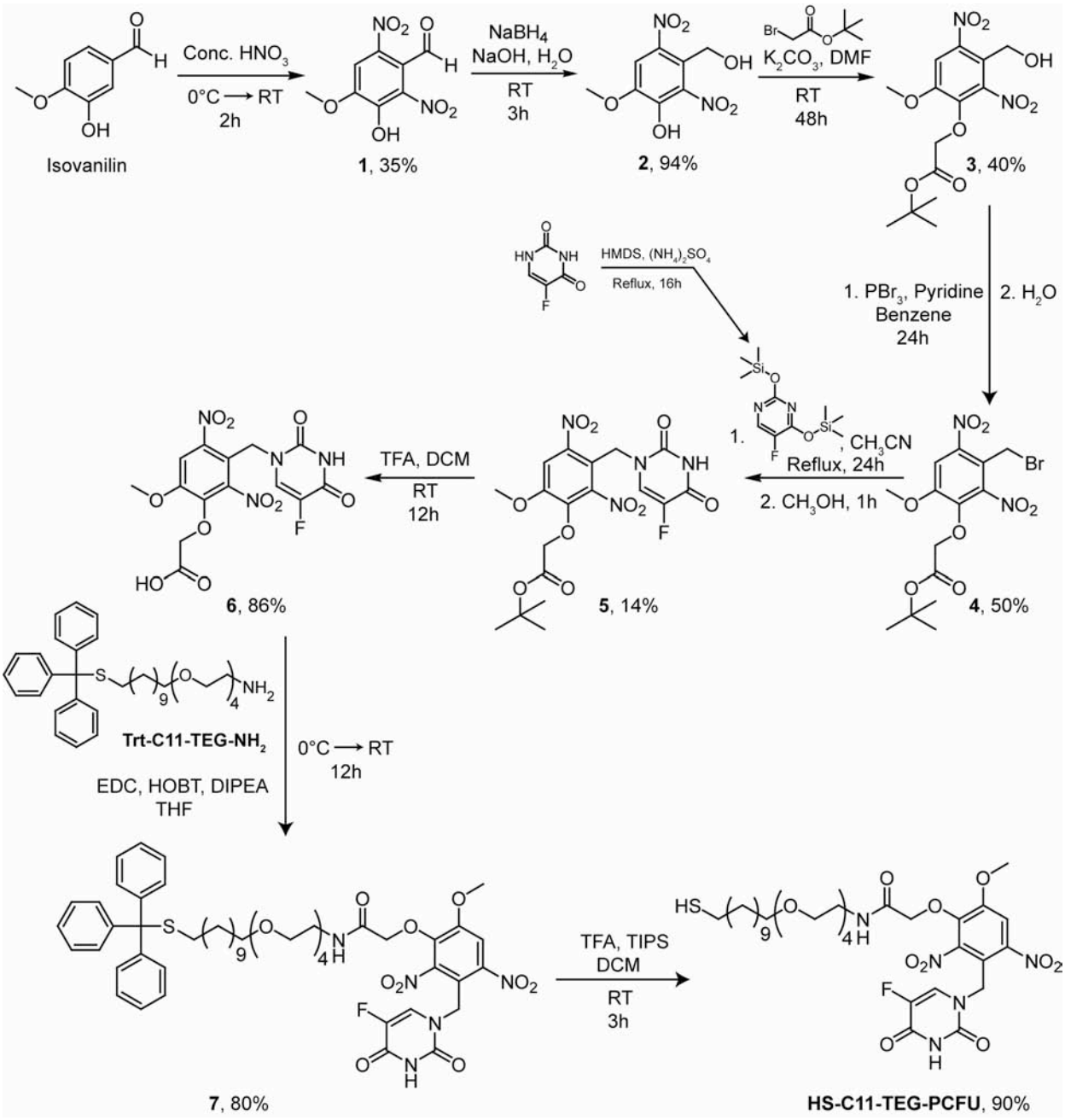
General

All the chemicals were purchased from Sigma-Aldrich or Fischer Scientific, unless otherwise specified. The chemicals were used as received. Dichloromethane (DCM) and tetrahydrofuran (THF) used as a solvent for chemical synthesis were dried according to standard procedures. The yields of the compounds reported here refer to the yields of spectroscopically pure compounds after purification. The zwitterionic ligand (**HS-C11-TEG-ZW**) and the zwitterionic nanoparticle (**AuNPZwit**) were prepared by following our previously reported procedures.[1]

^{1}H NMR spectra were recorded at 400 MHz on a Bruker AVANCE 400 machine. Hewlett-Packard 8452A and Cary 100 Scan UV-Vis spectrophotometer were used to record UV-Vis spectra. The fluorescence from the Alamar blue assay was measured in a SpectraMax M5 microplate spectrophotometer and analyzed by Origin 8 to determine the cell viability. All the cell images were obtained with an Olympus IX51 inverted microscope with the respective modes.



Scheme S1. Synthetic scheme for the preparation of **HS-C11-TEG-PCFU.**

Synthesis of compound 1

Isovanilin (18.3 g, 120 mmol) was placed in a 250 mL round bottom flask. The flask was chilled to 0 °C with an ice bath. Concentrated HNO_3 (69.8%, 40 mL) was then added dropwise to the solid under stirring condition. During the addition period the white solid turns to a dark yellow mixture with the generation of brown NO_2. After complete addition of HNO_3, the mixture was further stirred for 2h at room temperature (RT). The reaction mixture was then transferred into a 200 mL of ice cold water. After filtration, the solid residue (crude product) was collected and recrystallized from water (~1000 mL) to obtain Compound **2** as a yellow needle. Yield 10.2 g (42 mmol, 35%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.48 (s, 1H, –CHO), 7.84 (s, 1H, H_{Ar}), 4.10 (s, 3H, $–OCH_3$).

Synthesis of compound 2

Compound **2** (7.26 g, 30 mmol) was suspended in water (150 mL) and placed in a 250 mL round bottom flask. NaOH pellet (1.2 g, 30 mmol) was added carefully into the suspended solution of compound **2**. The solution became clear in few minutes and turns dark yellow in color. $NaBH_4$ (0.6 g, 15 mmol) was added to the clear solution after 10 min of stirring. The reaction mixture was further stirred at room temperature for 3h. Then, 1(M) HCl was used to adjust the p^H of the solution at ~2. A dark brown solid was formed from the acidic solution. The solid was extracted several times (~3 times) from the reaction mixture using ethyl acetate as a solvent. The organic layers were combined and washed thoroughly with water and brine. After drying over Na_2SO_4, removal of the ethyl acetate under reduced pressure afforded compound **2** pure enough for the next step of reaction. Compound **3** was obtained as a dark brown solid. Yield

6.9 g (28.3 mmol, 94%). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.69 (s, 1H, H_{Ar}), 4.80 (s, 2H, –$PhCH_2O$–), 4.07 (s, 3H, –OCH_3), 2.75 (br, 1H, Benzyl–OH).

Synthesis of compound 3

Compound **2** (2.8 g, 11.5 mmol) was added to a suspended solution of K_2CO_3 (10.5 g, 76 mmol) in dry DMF (100 mL). The mixture was stirred for 1h and then *tert*-butyl bromoacetate (2.54 g, 13 mmol) was added to the solution. The reaction was continued for 48h at room temperature under stirring condition. After filtration, the filtrate was poured into a large amount of water (~ 300 mL). The aqueous solution was extracted with ethyl acetate for 3 times (~ 150 mL ethyl acetate each time). The ethyl acetate layers were combined and washed thoroughly with water and brine. The organic part was dried over Na_2SO_4. After evaporation of the organic solvent under reduced pressure, the residue (crude product) was charged on a SiO_2 column for purification (eluent: 50% ethyl acetate in hexane v/v). Compound **4** was then obtained as a bright yellow solid. Yield 1.65 g (4.6 mmol, 40%). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.70 (s, 1H, H_{Ar}), 4.79 (s, 2H, –$PhCH_2O$–), 4.72 (d, ^{2}J = 7.32 Hz, 2H, –OCH_2CO–), 3.97 (s, 3H, –OCH_3), 2.69 (t, ^{3}J = 7.44 Hz, 1H, Benzyl–OH), 1.46 (s, 9H, –$C(CH_3)_3$).

Synthesis of compound 4

Compound **3** (1.0 g, 2.8 mmol) was dissolved in benzene (50 mL) and placed in an ice bath. Five drops of dry pyridine was added to the solution. Subsequently, phosphorous tribromide (0.68 g, 2.5 mmol) dissolved in 3 mL of benzene was added dropwise to the reaction mixture. The reaction was stirred for 24h at room temperature. After 24 h, 5 mL of water was added and stirred for a while (~30 min). Then, the solution was further diluted with 300 mL of water and treated with 10 mL of 1(M) HCl. The aqueous reaction mixture was then extracted with ethyl

acetate for 3 times (~ 150 mL ethyl acetate each time). The organic layers were combined and washed thoroughly with water and brine and dried over Na_2SO_4. After removal of the solvent, the residue (crude product) was charged on a SiO_2 column for purification (eluent: dichloromethane). Compound **5** was then obtained as a yellow solid. Yield 0.600 g (1.42 mmol, 50%). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.76 (s, 1H, H_{Ar}), 4.80 (s, 2H, –$PhCH_2Br$), 4.68 (s, 2H, –OCH_2CO–), 3.98 (s, 3H, –OCH_3), 1.46 (s, 9H, –$C(CH_3)_3$). ^{13}C NMR (400MHz, $CDCl_3$): δ 166.5, 151.3, 145.0, 143.2, 142.2, 118.7, 111.0, 83.0, 70.0, 57.1, 28.0, 20.7.

Synthesis of compound 5

Compound **5** was synthesized by following the previously reported procedure of a similar compound.[2] A mixture of 5-fluorouracil (0.100 g, 0.769 mmol) and catalytic amount of ammonium sulfate (0.025 g, 0.19 mmol) was suspended in hexamethyldisilazane (HMDS, 1.238 g, 7.69 mmol). The mixture was heated to reflux for 16h under argon atmosphere. After concentrating the reaction mixture under high vacuum, the residue (2,4-bis(trimethylsilyloxy)-5-fluoropyrimidine) was mixed with compound **4** (0.324 g, 0.769 mmol) in acetonitrile (CH_3CN, 10 mL). The reaction mixture was heated to reflux for 24h under argon atmosphere in dark. After cooling to RT, 5 mL of methanol was added to treat the product. After 1h the solvent was removed under reduced pressure and the residue was loaded on a SiO_2 column for purification (eluent: a gradient eluent of dichloromethane to ethyl acetate). Compound **5** was isolated as a grey solid. Yield 0.050 g (0.106 mmol, 14%). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.05 (br, 1H, –NH_{FU}–), _ 7.70 (s, 1H, H_{Ar}), _ 7.17 (d, ^2J = 5.56 Hz, 1H, H_{FU}), 5.06 (s, 2H, –$PhCH_2N$_), 4.82 (s, 2H, –OCH_2CO–), 4.00 (s, 3H, –OCH_3), 1.46 (s, 9H, –$C(CH_3)_3$).

Synthesis of compound 6

Compound **5** (0.100 g, 0.212 mmol) was placed in a vial under argon atmosphere. Subsequently a mixture of DCM (0.5 mL) and trifluoroacetic acid (TFA, 0.5 mL) was added to the reaction vial. The deprotection reaction was continued at room temperature for 6h. After 6h, the volatile components (solvent, TFA) were distilled off under reduced pressure. The crude product was purified by washing with diethyl ether (10 mL _ 3). After drying under high vacuum a grey color solid was obtained. Yield 0.075 g (0.181 mmol, 86%). ^{1}H NMR (400MHz, DMSO): δ 7.94-7.90 (m, 2H, H_{Ar} and H_{FU}), 5.00 (s, 2H, –$PhCH_2N$_), 4.86 (s, 2H, –OCH_2CO–), 3.99 (s, 3H, –OCH_3). ^{13}C NMR (400MHz, MeOD): δ 171.7, 159.7 (d, J_{CF} = 103.2 Hz), 153.7, 151.2, 146.6, 146.5, 144.3, 141.7 (d, J_{CF} = 927.6 Hz), 130.5 (d, J_{CF} = 137.4 Hz), 116.4, 112.5, 70.8, 57.9, 45.7. MS (ESI-MS) calculated for $C_{14}H_{11}FN_4O_{10}$ 414.05, found 415.2 $[M+H]^+$, 437.2 $[M+Na]^+$.

Synthesis of compound 7

Compound **6** (0.050 g, 0.121 mmol) was dissolved in 20 mL of dry THF and cooled to 0 °C by placing it on an ice bath. Then HOBt·H_2O (0.018 g, 0.121 mmol), DIPEA (0.031 g, 0.242 mmol) and EDC (0.030 g, 0.145 mmol) were added to the solution. The mixture was stirred at 0 °C for 10 min. Subsequently, **Trt-C11-TEG-NH_2**[3] (0.075 g, 0.121 mmol) dissolved in 10 mL of dry DCM was added to the reaction mixture. The reaction mixture was allowed to rise automatically to room temperature. After 12h of stirring, the reaction mixture was concentrated and the residue was directly charged on a SiO_2 column for purification (eluent: a gradient eluent of 0-5% methanol in ethyl acetate v/v). Compound **7** was obtained as a grey color solid. Yield 0.098 g (0.096 mmol, 80%). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.70 (s, 1H, H_{Ar}), 7.40 (m, 6H,

$TrtH_{Ar}$), 7.29-7.18 (m, 10H, $TrtH_{Ar}$ + H_{FU}), 6.84 (br, 1H, –NHCO–), 5.07 (s, 2H, –$PhCH_2N$_), 4.74 (s, 2H, –OCH_2CO–), 4.03 (s, 3H, –OCH_3), 3.67-3.52 (m, 16H, –CH_2O– + –OCH_2–), 3.44 (t, ^3J = 6.82 Hz, 2H, –CH_2N–), 2.12 (t, ^3J = 7.32 Hz, 2H, –CH_2S–), 1.55-1.21 (m, 18H, –CH_2–).

Synthesis of HS-C11-TEG-PCFU

The trityl protected thiol ligand (compound **7**, 0.098 g, 0.096 mmol) was dissolved in dry DCM. The solution was purged with argon and an excess of TFA (0.25 mL) was added. During the addition period of TFA the color of the solution was turned to yellow. Subsequently, triisopropylsilane (TIPS, 0.075 mL) was added to the reaction mixture and the color of mixture slowly recovered to colorless. The reaction mixture was allowed to stir at room temperature for 3 h. The volatile components (solvent, TFA and TIPS) were distilled off under reduced pressure. The pale yellow residue was further purified by washing with diethyl ether (15 mL _ 4). After drying under high vacuum a grey color solid was obtained. Yield 0.067 g (0.086 mmol, 90%). ^{1}H NMR (400MHz, $CDCl_3$): δ 9.19 (br, 1H, –NH_{FU}–) δ 7.70 (s, 1H, H_{Ar}), _ 7.22 (d, ^2J = 5.56 Hz, 1H, H_{FU}), 6.88 (br, 1H, –NHCO–), 5.06 (s, 2H, –$PhCH_2N$_), 4.74 (s, 2H, –OCH_2CO–), 4.04 (s, 3H, –OCH_3), 3.68-3.52 (m, 16H, –CH_2O– + –OCH_2–), 3.44 (t, ^3J = 6.94 Hz, 2H, –CH_2N–), 2.51 (q, ^4J = 7.4 Hz, 2H, –C H_2S–), 1.55-1.25 (m, 18H, –CH_2–). ^{13}C NMR (400MHz, $CDCl_3$): δ 166.63, 156.6 (d, J_{CF} = 105.7 Hz), 152.7, 148.9, 145.8, 145.4, 142.8, 140.6 (d, J_{CF} = 951.08 Hz), 127.5 (d, J_{CF} = 134.4 Hz), 114.8, 110.8, 72.7, 71.5, 70.5, 70.4, 70.3, 69.9, 69.5, 57.3, 44.1, 39.0, 34.8, 34.0, 30.6, 29.9, 29.5, 29.0, 28.4, 26.1, 24.7, 23.5. MS (ESI-MS) calculated for $C_{33}H_{50}FN_5O_{13}S$ 775.31, found 776.5 $[M+H]^+$, 798.5 $[M+Na]^+$, 814.5 $[M+K]^+$. HRMS (FAB-HRMS) calculated for $[C_{33}H_{50}FN_5O_{13}S+ H]^+$ 776.3188, found 776.3168 $[M+H]^+$.

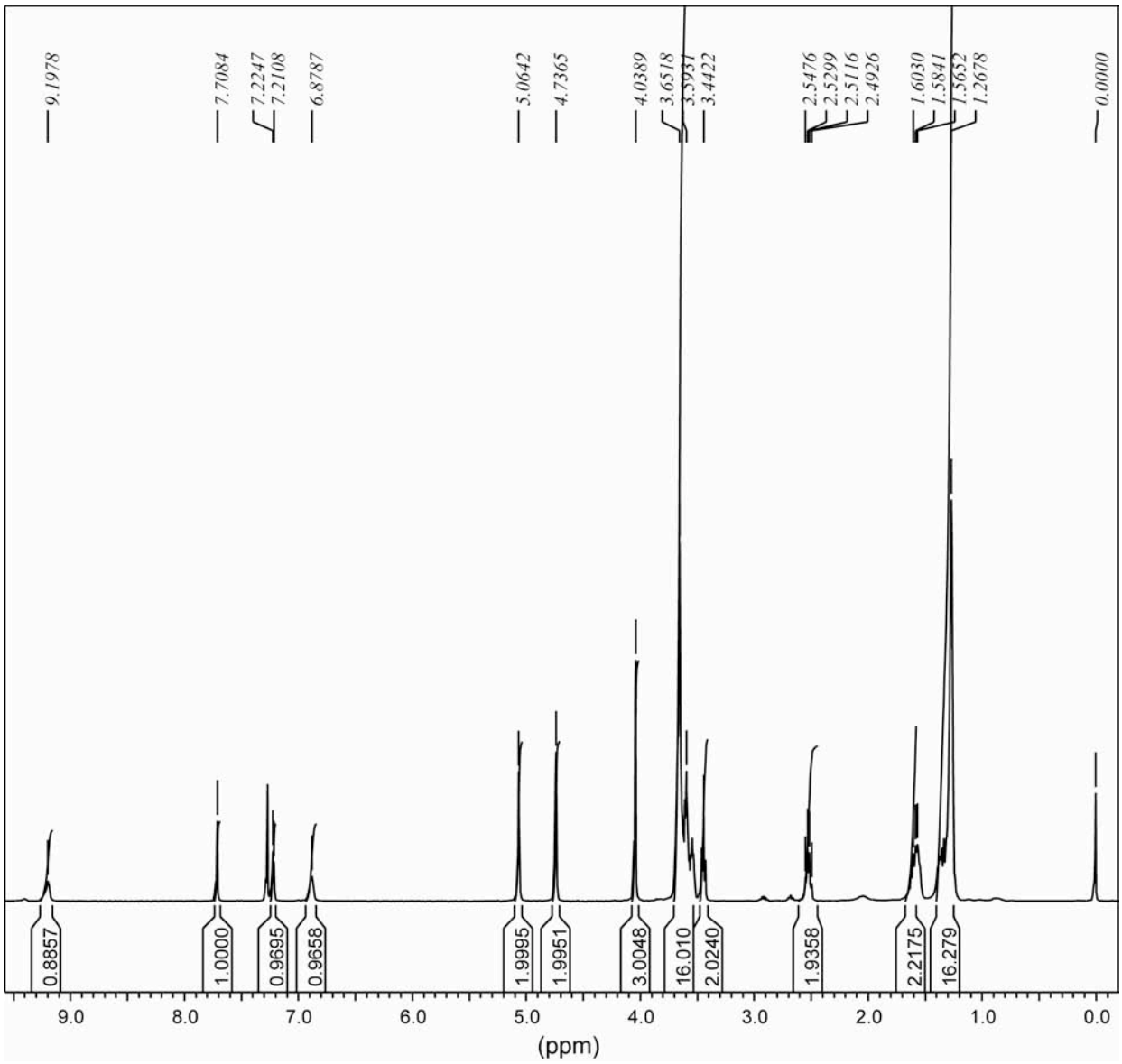


Figure S1. 400MHz ^{1}H NMR spectrum of **HS-C11-TEG-PCFU** in $CDCl_3$.

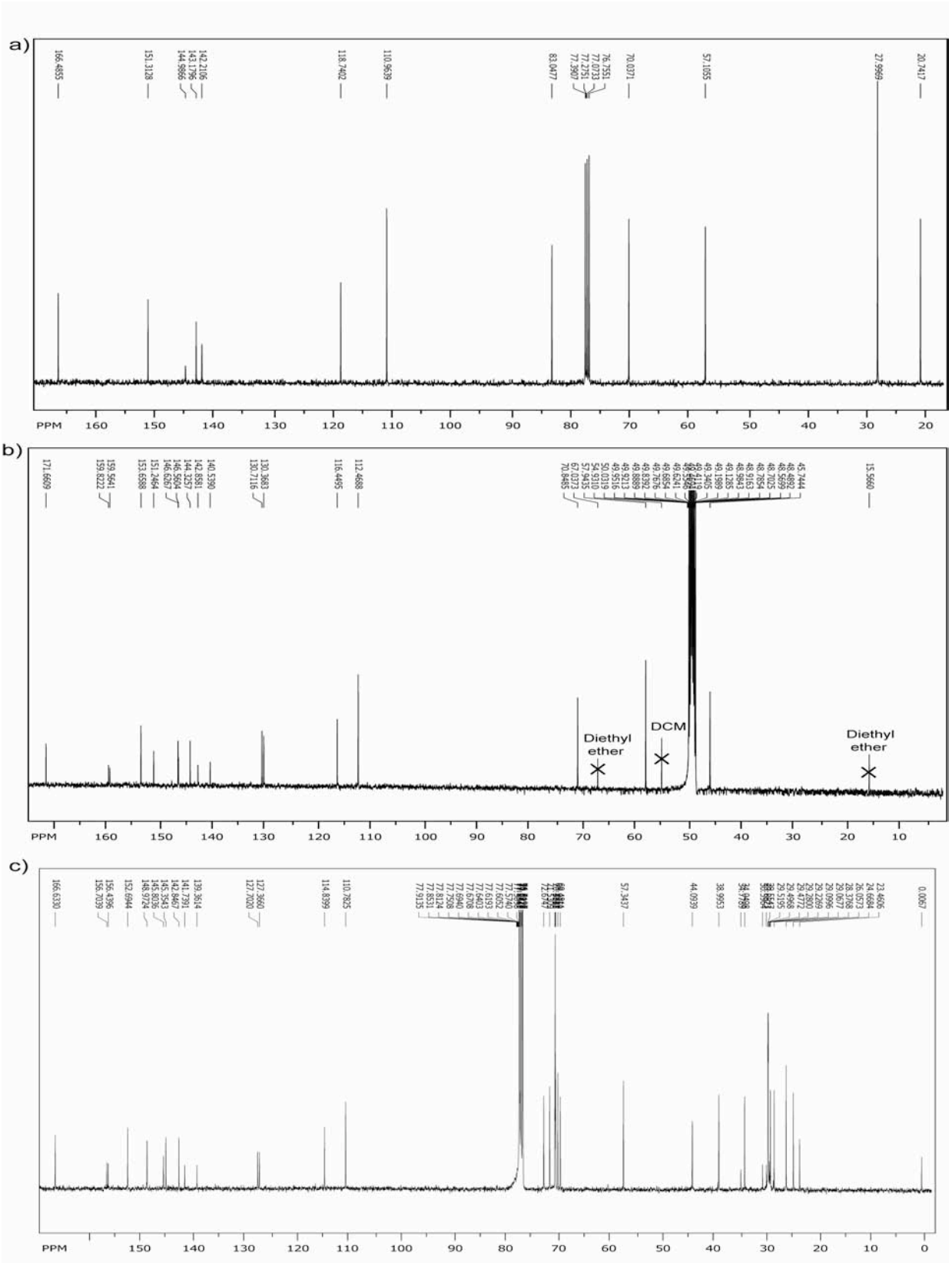


Figure S2. 400MHz ^{13}C NMR spectrum of a) Compound **4**, b) compound **6** and c) **HS-C11-TEG-PCFU**.

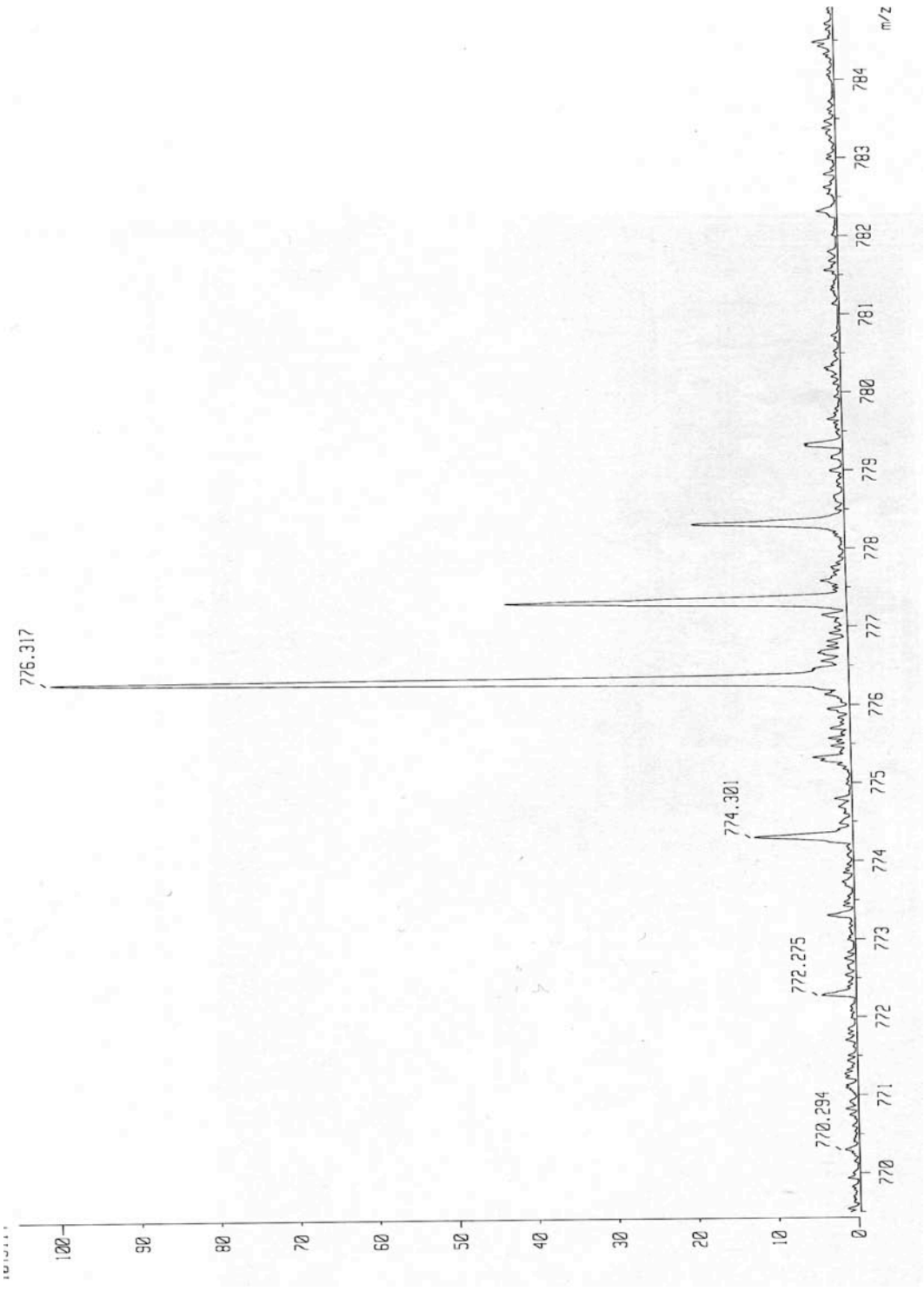


Figure S3. FAB-HRMS spectrum of **HS-C11-TEG-PCFU**.

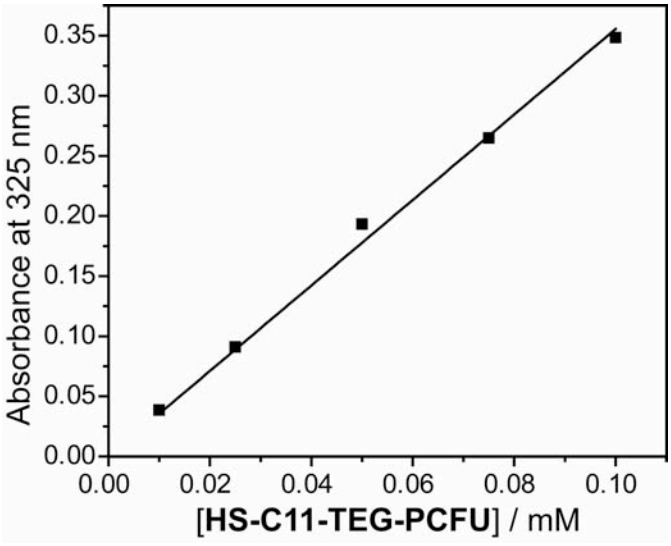
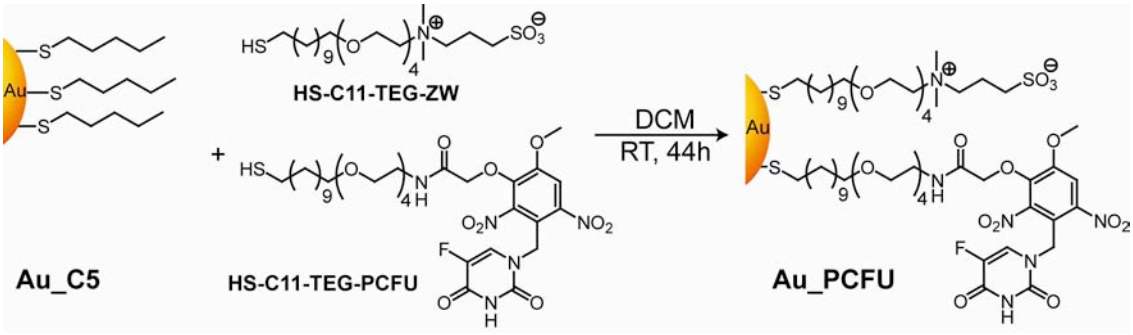


Figure S4. The plot of absorbance against concentration of **HS-C11-TEG-PCFU** dissolved in acetonitrile-water (9:1 v/v). The straight line represents the best fitting of the data according to the Beer-Lambert Law. An extinction coefficient of 3.55 mmole dm^{-3} cm^{-1} (_ =325 nm) was estimated based on the fitted data.



Scheme S2. Place exchange reaction for the preparation of gold nanoparicles.

Procedure for construction of gold nanoparticle (Au_PCFU)

Gold nanoparticle (**Au_PCFU**) was prepared through place-exchange reaction of 1-pentanethiol protected 2 nm gold nanoparticle (**Au_C5**). As shown in Scheme S2, nanoparticle was decorated with two functionally distinctive ligands (H**S-C11-TEG-PCFU** and **HS-C11-TEG-ZW**). To decorate the nanoparticle, place exchange reaction of **Au_C5** was carried out with a mixture of corresponding thiol ligands according to the general procedure reported by Murray *et al.* (Scheme S2). In a typical reaction, a mixture of **HS-C11-TEG-PCFU** (22.5 mg)

and **HS-C11-TEG-ZW** (22.5 mg) in DCM (3 mL) was added carefully to a solution of **Au_C5** (15 mg nanoparticle dissolved in a 2 mL of dry DCM). The mixture was purged with argon for 5 min and was allowed to stirrer for 44h. During this period all particles precipitated, indicating the transformation of nanoparticle surface functionality. The precipitated particle was then collected by centrifugation and washed five times with dry DCM (12 mL) to remove the excess free ligand. The dark color residue was dissolved in a small amount of D_2O and kept open in dark for 12 h to remove the volatile components. ^1H NMR spectra in D_2O was then recorded in a 400 MHz Bruker machine. The nanoparticle was stable in solution for months and was stored in miliq water at 4 °C.

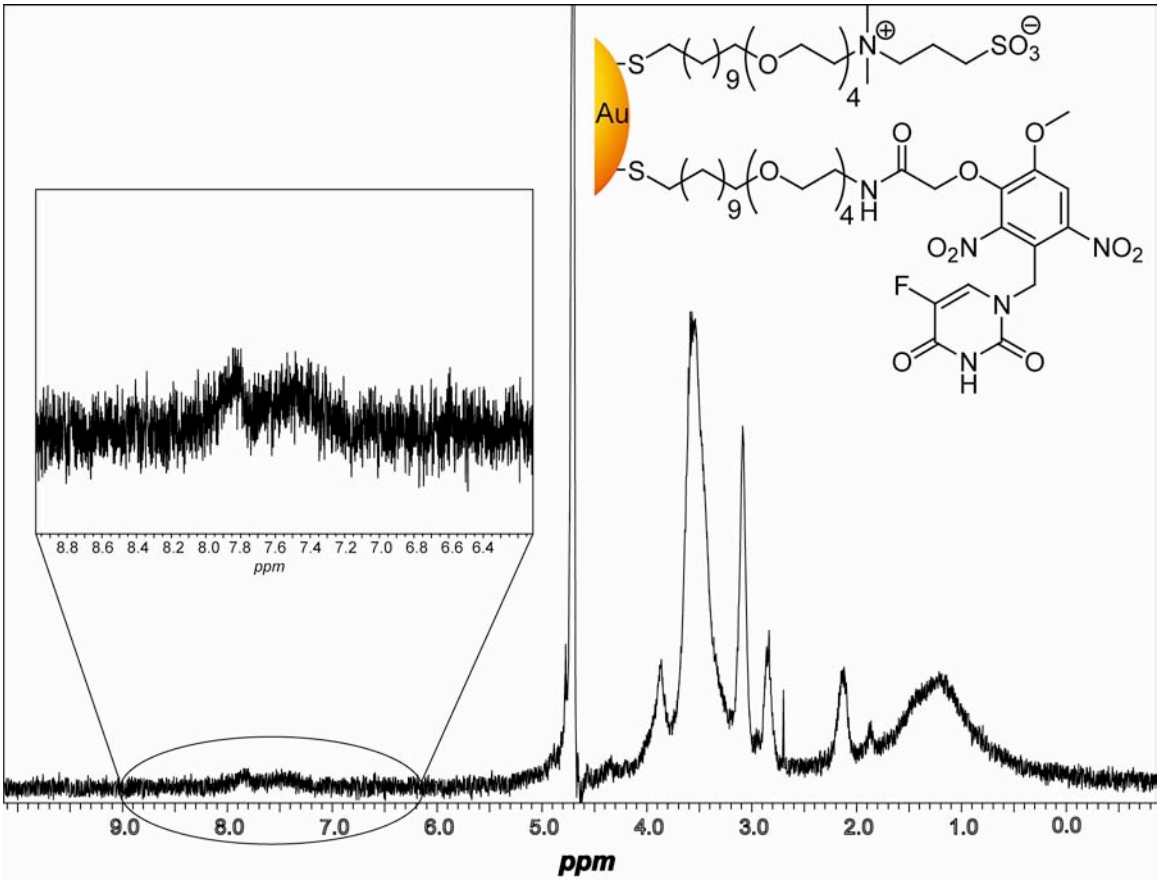


Figure S5. 400 MHz ^{1}H NMR spectrum of **Au_PCFU** in D_2O solvent. Substantial broadening of the proton signals as compared with the ligand precursor indicates proper surface capping and absence of free ligands. The inset shows the magnified aromatic region, which indicates the presence of aromatic proton photoclevable linker and the 5-FU group.

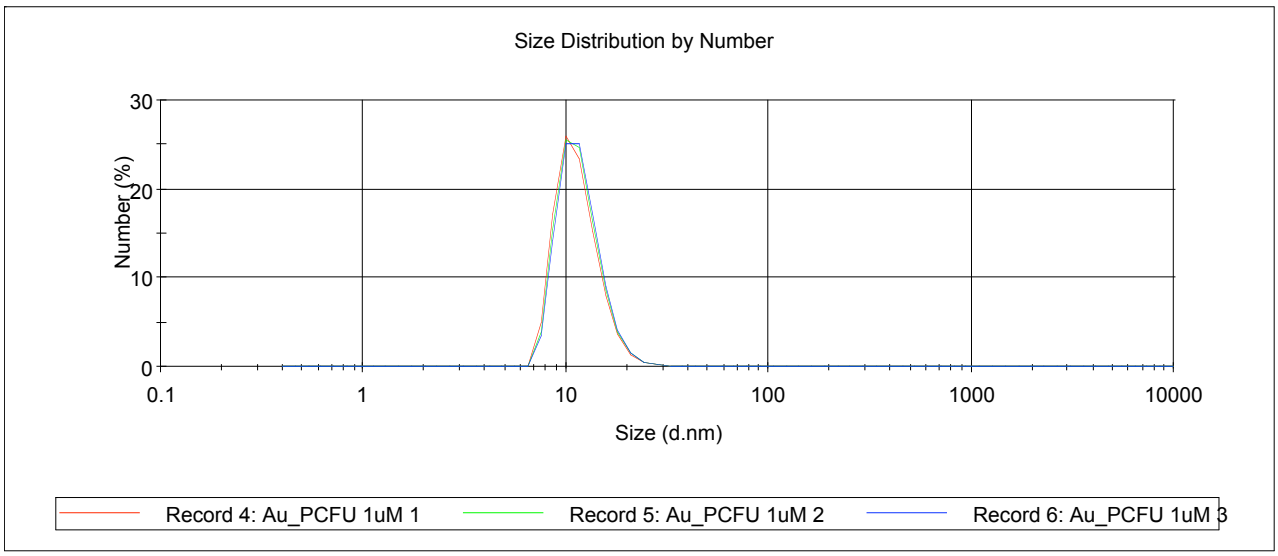


Figure S6. Hydrodynamic diameter of **Au_PCFU** measured by DLS (1μM solution in miliq water).

Determination HS-C11-TEG-PCFU ligand number per particle

UV-Vis spectrum of **Au_PCFU** was obtained after diluting the solution with miliq water. The absorption spectrum of **Au_PCFU** was compared with the absorption spectrum of **AuNPZwit** (Figure S7a). **Au_PCFU** and **AuNPZwit** shared an absorption band corresponding to the surface plasmon resonance of gold nanoparticle at 520 nm. However, **Au_PCFU** showed a difference in absorption behavior in UV region of the spectra (200-400 nm). This difference represents the presence of **HS-C11-TEG-PCFU** ligand in the **Au_PCFU** nanoparticle surface. The conclusion was drawn on the basis of the fact that the **HS-C11-TEG-PCFU** ligand spectrum shown in Figure S7a resembles with the difference spectrum of **Au_PCFU** and **AuNPZwit** (shown in Figure S7b). The difference spectrum obtained by subtracting one absorbance from other was used to calculate the number of **HS-C11-TEG-PCFU** ligand per particle. The absorbance at 325 nm from difference spectrum was used to deduce **HS-C11-TEG-PCFU** concentration by Beer-Lambert Law where the molar extinction coefficient of **HS-C11-TEG-PCFU** was 3.55 mmole dm^{-3} cm^{-1} at 325 nm (see Figure S4). The number of **HS-C11-TEG-**

PCFU ligand present in a single nanoparticle surface was then determined by the ratio of **HS-C11-TEG-PCFU** to cluster concentrations. The estimated number of **HS-C11-TEG-PCFU** ligand per particle was 17.

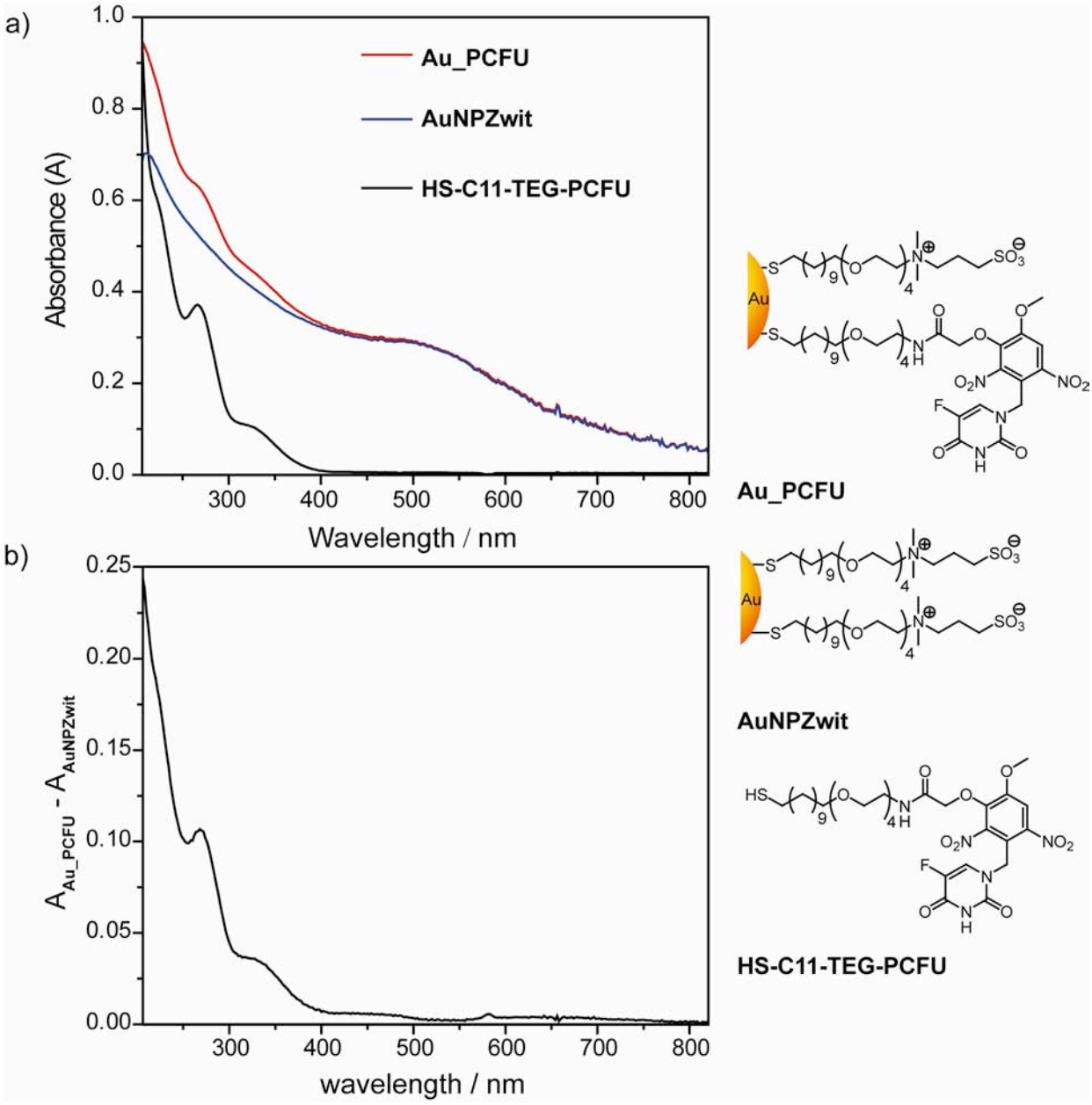


Figure S7. a) UV-Vis spectrum of **Au_PCFU** (in water), **AuNPZwit** (in water) and **HS-C11-TEG-PCFU** (in 9:1 v/v acetonitrile-water). b) Difference spectrum of **Au_PCFU** and **AuNPZwit** obtained by subtracting one from other.

Photochemical reaction of Au_PCFU and HS-C11-TEG-PCFU

Photochemical reaction of **Au_PCFU** was performed using a 1.25 μM solution in miliq water. As the free thiol ligand **HS-C11-TEG-PCFU** was insoluble in water, we carried out the photochemical reaction of **HS-C11-TEG-PCFU** using a 30 μM solution in acetonitrile-water (9:1 v/v). A solution of the compound under investigation was irradiated using a handheld UV lamp (λ = 365 nm) in a 1 cm path length quartz cuvette. UV-Vis absorption spectra at various time intervals were recorded using a UV-Vis spectrophotometer. UV-Vis spectral changes during the time course of photochemical reaction were reported in the in Figure S8. These changes in the absorption spectra typically reflect the breakage of the photolabile benzyl-N / $PhCH_2$-N bond and the generation of nitrosobenzaldehyde group concomitant with FU release from the ligand shell. Furthermore, the presence of isosbestic points in the absorption profiles indicates that reaction proceeds with no side products.

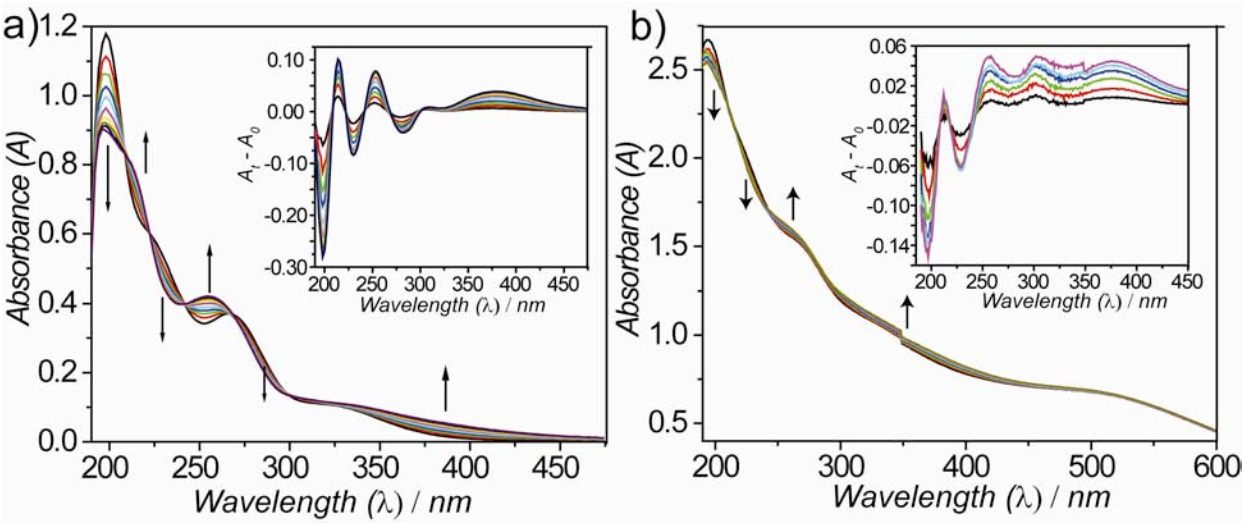


Figure S8. Overlaid UV-Vis spectral changes upon irradiation with UV light (_ = 365 nm) of: a) **HS-C11-TEG-PCFU** and b) **Au_PCFU**. Insets: the time differential absorption profiles.

Analysis of photoreleased product (5-FU) from the Au_PCFU nanoparticle surface

A 2.5 μM aqueous solution of **Au_PCFU** was kept in 7 different glass vials. Each vial was irradiated using a handheld UV lamp (λ = 365 nm) for different duration of time viz. 0, 2, 4, 6, 10, 15, 20 min. Subsequently, to characterize the product of photolysis the nanoparticle residue was separated from the product (5-FU) solution using a MWCO membrane filter. For this purpose, the irradiated solutions were spin filtered by using a 50,000 KDa MWCO filter (Microcon 50, Millipore). The flow through was directly used to determine the identity of the photoreleased product. The concentration of 5-FU in the flow through was deduced by Beer-Lambert Law (Extinction coefficient of 5-FU= 7.07 mmole dm^{-3} cm^{-1} at λ =265 nm). The maximum number of 5-FU released from a single nanoparticle was then determined by the ratio of 5-FU (after 20 min light exposure) to nanoparticle concentrations.

Photochemical reaction under alternating periods of light and dark

A 2.5 μM aqueous solution of **Au_PCFU** kept in a glass vial was exposed to alternating periods of light (handheld UV lamp, λ = 365) and dark (no light). After each exposure small portions were dispensed from the solution and the photoreleased product was analyzed by the above described procedure.

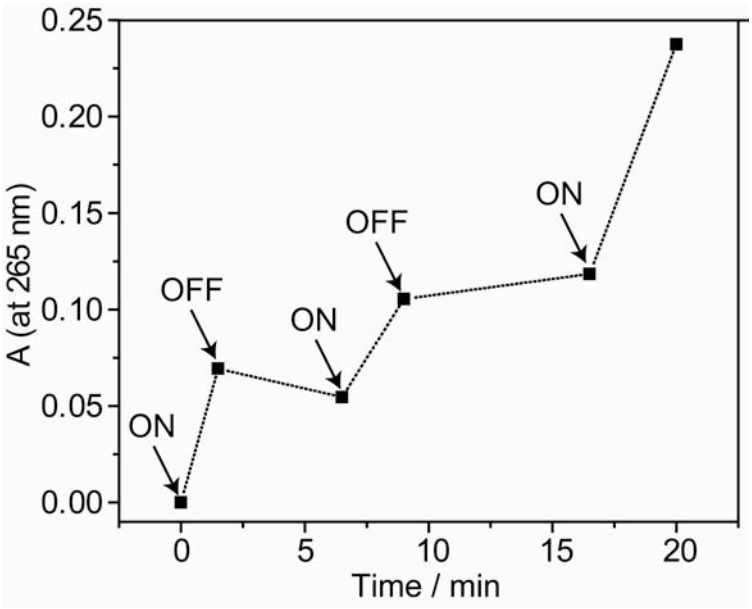


Figure S9. Progress of 5-FU formation represented by the change in absorbance at 265 nm in light and dark conditions. "On" indicates the beginning of light irradiation and "off" indicates the beginning of dark (no light) condition.

Cell culture

Breast cancer cell line (MCF-7) was cultured at 37 °C under a humidified atmosphere of 5% CO_2. The cells were grown in low glucose Dulbecco's Modified eagle's Medium (DMEM, 4.0 g/L glucose) supplemented with 10% fetal bovine serum and 1% antibiotics (100 U/ml penicillin and 100 µg/ml streptomycin). The cells were maintained continuously in the culture media and

subcultured every 3-4 days. Unless otherwise stated, MCF-7 cells were seeded at 20K cells/well in 200 μL media in a 96-well plate for 24 h before the experiment and allowed cell attachment.

Cell culture experiments

I) Prior perform the experiment, the old culture media was aspirated and the cold PBS was used to wash the cell for one time. Then, the **Au_PCFU** dispersed in the 200 μL culture media were added into cells. The concentrations ranging from 0 μM to 5 μM were used to perform concentration dependent cell viability and 1 μM were used to perform time-dependent drug release study. Then, the cells suspended with **Au_PCFU** culture media were submitted to UV light (λ = 365 nm) for 20 min for concentration dependent cell viability and 1 min, 6 min and 15 min for time-dependent drug release study. The cells were subsequently incubated in cell culture incubator for 96 h. Then, the **Au_PCFU** solution was taken out and washed 3x with PBS buffer. The cell viability was determined by the Alamar blue assay. The experiments were performed in triplicate.

II) For the control experiments, cells were first exposed with 20 min of UV light (_ = 365 nm). Thereafter, the medium was aspirated. The cold PBS was used to wash the cell for one time. Then, the **Au_PCFU** dispersed in the extracellular media were added into cells. The concentrations up to 5 μM for **Au_PCFU** were used to perform the concentration dependent cell viability study. In addition, we also performed experiment without UV irradiated condition to monitor the effect of only **Au_PCFU** to the cell viability. The experiments were

carried out by incubating the cells with 1 μM of **Au_PCFU**. After 96h of incubation, the cell viability was determined by Alamar blue assay.

Cell Viability Assay

The cell viability was assessed by using Alamar blue assay according to the manufacturer's protocol (Invitrogen Biosource, USA). In a typical experiment, after thoroughly washing the cells 3x with PBS buffer, the cells were treated with 220 μL 10% Alamar blue solution. Subsequently, the cells were incubated at 37 °C under a humidified atmosphere of 5% CO_2 for 3 h. After 3 h of incubation, 200 μL of solution from each wells was taken out and placed in a 96-well black microplate. Red fluorescence, resulting from the reduction of Alamar blue solution, was valued (excitation/emission: 535/590) on a SpectroMax M5 microplate reader (Molecular Device) to determine the cell viability.

Optical and fluorescence imaging of live and dead cells

MCF-7 cells suspended in 1.5 mL media were seeded at 80K cells/dish in 35mm glass bottom dish and kept for 24 h before the experiment to allow cell attachment. The experiments were carried out by the procedure noted above, but the condition used in this experiment was 5 μM in 1.5 mL culture media. After 96 h of incubation, live cell stain assay was performed using calcein AM (from Molecular Probes) according to the manufacturer supplied standard protocols. All images were obtained with an Olympus IX51 inverted microscope with green fluorescence channel to visualize live cells. All images were taken at 20x magnification.

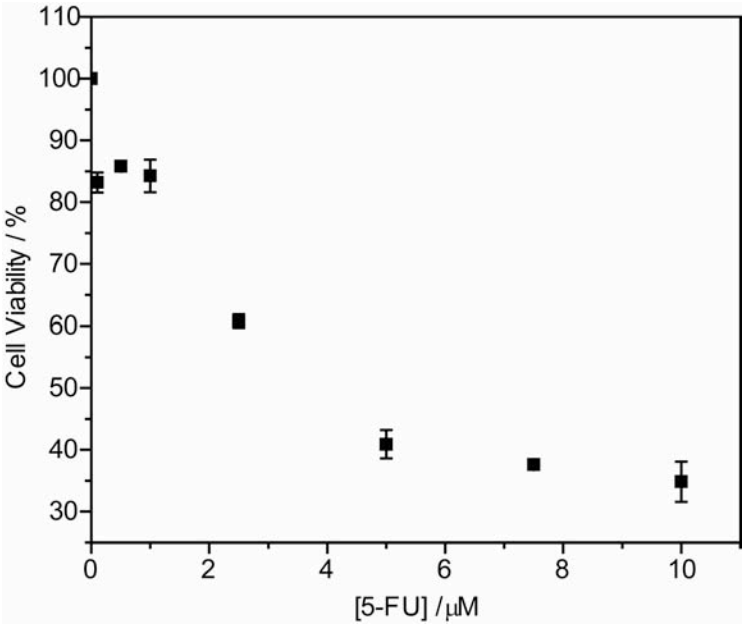


Figure S10. The cytotoxicity of different concentration of 5-FU measured by Alamar blue assay. In the typical experiment cells were first exposed with 20 min of UV light (_ = 365 nm). Thereafter, the medium was aspirated and the cold PBS was used to wash the cell for one time. 5-FU dispersed in the extracellular media was then added into cells. The concentrations up to 10 μM were used to perform the concentration dependent cell viability study. After 96h of incubation, the old media was taken out and the cells were washed 3 times with PBS buffer. The cell viability was then determined by the Alamar blue assay.

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1. Kim, C. K.; Ghosh, P.; Pagliuca C.; Zhu, Z. J.; Menichetti, S.; Rotello, V. M. *J. Am. Chem. Soc*. **2009,** 131, 1360-1361.

2. Zhang, Z.; Hatta, H.; Ito, T.; Nishimoto, S. *Org. Biomol. Chem*. **2005**, *3*, 592-596.

3. Chompoosor, A.; Han, G.; Rotello, V. M. *Bioconjugate Chem.* **2008**, 19, 1342-1345.