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Supporting Information

Design of Halloysite Nanotube-Based Nanomaterials for Theranostic Applications: Fluorescent Probes and Chemodynamic Activity

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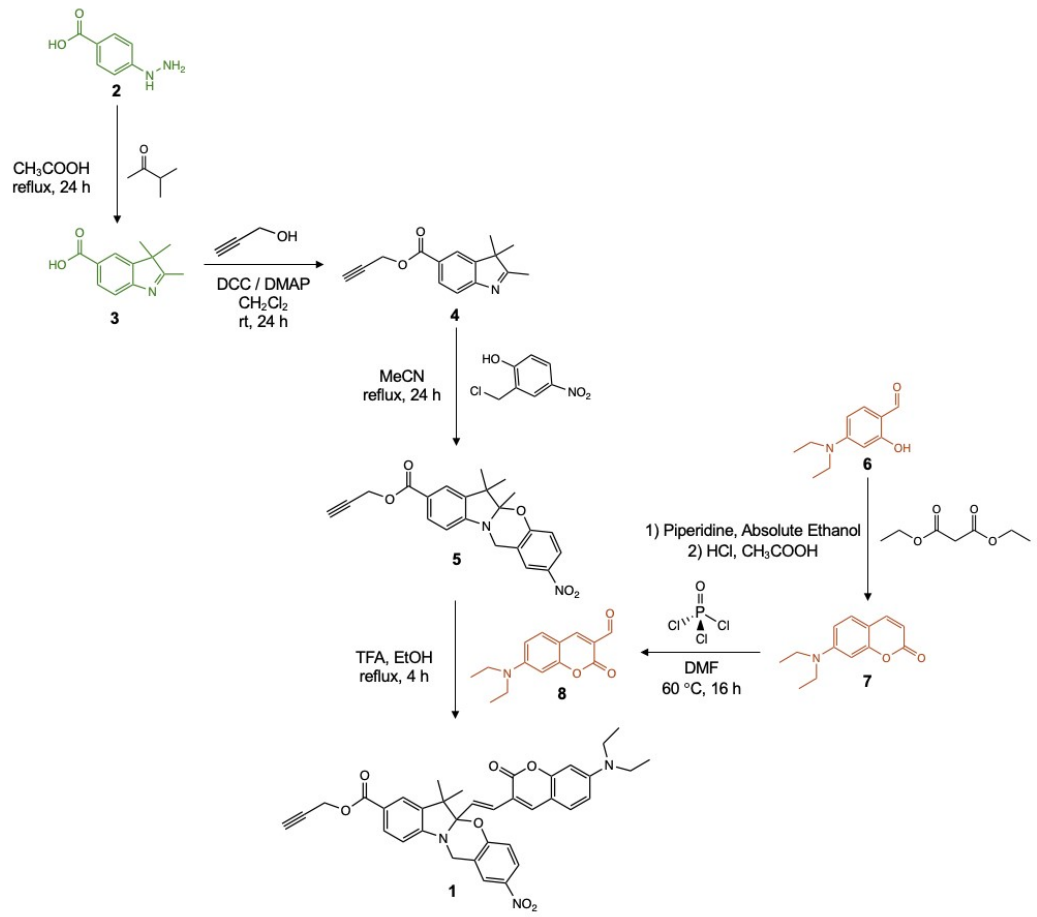

Scheme S1. Synthetic pathway to **1**.

Compound 3.[1] In a 50 mL round bottom flask, 2 g (0.013 mol) of 4-hydrazinobenzoic acid (**2**) were solubilized in 20 mL of glacial acetic acid. Then 2.8 mL of 3-methyl-2-butanone (0.026 mol, 2 eq) were added. The mixture was stirred under argon atmosphere, under reflux for 24 h. After this time, the solvent was evaporated, the pH of the mixture was adjusted to ca. 4 with saturated K_2CO_3 solution, extracted with CH_2Cl_2, and dried with anhydrous $MgSO_4$. The organic phase was filtered and evaporated to obtain **3 (**0.902 g) as a reddish-brown solid with a yield of 34%.

^{1}H NMR (400 MHz, DMSO), δ = 1.265 (6H, s), 2.244 (3H, s), 7.486-7.506 (1H, d, 8 Hz), 7.897-7.921 (1H, dd, 8 and 1.6 Hz), 7.980-7.985 (1H, dd, 1.6 and 0.4 Hz).

^{13}C NMR (400 MHz, DMSO), δ = 15.80, 22.72, 53.92, 119.56, 123.17, 127.79, 130.07, 146.57, 157.86, 167.97, 192.13.

Compound 4.[2] A solution of **3** (800 mg, 4.0 mmol), propargyl alcohol (300 µL, 4.7 mmol), DCC (810 mg, 4.0 mmol) and DMAP (480 mg, 4.0 mmol) in CH_2Cl_2 (20 mL) was stirred at ambient temperature for 16 h. The resulting precipitate was filtered off and washed with CH_2Cl_2. The filtrate was distilled off under reduced pression to give an orange solid. This residue was purified by column chromatography [SiO_2, hexane/EtOAc (3:1, v/v)] to afford **4** (690 mg) as a yellow solid with a yield of 72%.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 1.335 (6H, s), 2.320 (3H, s), 2.520-2.532 (1H, t, 2.4 Hz), 4.930-4.936 (2H, d, 2.4 Hz), 7.559-7.579 (1H, d, 1.2 Hz), 8.064-8.089 (1H, dd, 8 and 1.6 Hz).

^{13}C NMR (400 MHz, $CDCl_3$), δ = 15.74, 22.86, 33.96, 52.41, 53.92, 74.95, 77.96, 119.74, 122.93, 126.10, 130.46, 145.82, 158.11, 165.99, 192.03.

Compound 5.[2] A solution of **4** (630 mg, 2.61 mmol) and 2-chloromethyl-4-nitrophenol (612 mg, 3.26 mmol) in MeCN (50 mL) was heated under reflux for 24 h. After cooling down to room temperature, the solvent was distilled off under reduced pressure and the residue was purified by column chromatography [SiO_2: hexane/EtOAc (4:1, v/v)] to afford **5** (443 mg) as a white solid with a yield of 43%.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 1.211 (3H, s), 1.577 (3H, s), 1.605 (3H, s), 2.480-2.491 (1H, t, 2.0 Hz), 4.680 (2H, s), 4.871-4.877 (2H, d, 2.4 Hz), 6.583-6.604 (1H, d, 8.4 Hz), 6.745-6.768 (1H, d, 9.2 Hz), 7.811-7.814 (1H, d, 1.2 Hz), 7.874-7.907 (1H, dd, 12.4 and 5.2 Hz), 7.964-7.993 (1H, dd, 9.2 and 2.4 Hz), 8.085-8.091 (1H, d, 2.4 Hz).

Compound 7.[3] 4-Diethylaminosalicylaldehyde (**6**) (2 g, 10.3 mmol) was dissolved in absolute ethanol (30 mL). Then diethylmalonate (3.0 mL, 20.0 mmol) and piperidine (1 mL) were added and the resulting solution was stirred for 6 h under reflux conditions. Ethanol was evaporated under reduced pressure, and to the resulting mixture concentrated HCl (20 mL) and glacial acetic acid (20 mL) were added to hydrolyze the reaction. The suspension was left to stir at room temperature for 6 h. Then it was poured into 100 mL of ice water. NaOH was added to modulate pH of the solution to ~5, and a pale precipitate formed immediately. The mixture was filtered, washed with water, dried, then recrystallized with toluene to give **7** (664 mg) in 30% yield.

Compound 8.[3] **A**nhydrous DMF (4 mL) was added dropwise to $POCl_3$ (430 μL, 4.60 mmol) at 50 °C and stirred for 45 min to yield a red solution. This solution was combined with a portion of **7** (330 mg, 1.50 mmol) that was dissolved in 5 mL of anhydrous DMF to yield a scarlet suspension. The mixture was stirred at 60 °C for 15 h and then poured into 100 mL of ice water. HCl solution (18%, 30 mL) was added, and the reaction was heated under reflux for 6 h and then poured into 100 mL of ice water. NaOH solution was added to adjust the pH of the mixture to yield large amount of precipitate. The crude product was filtered, thoroughly washed with water, dried to give **8** in 81.2% yield.
^{1}H NMR (400 MHz, $CDCl_3$), δ = 1.241-1.277 (6H, t, 7.2 Hz), 3.453-3.506 (4H, q, 7.2 and 14 Hz), 6.485-6.491 (1H, d, 2.4 Hz), 6.625-6.653 (1H, dd, 8.8 and 2.4 Hz), 7.402-7.724 (1H, d, 8.8 Hz), 8.254 (1H, s), 10.127 (1H, s)

Compound 1.[2] A solution of **5** (204 mg, 0.5 mmol), **8** (147 mg, 0.6 mmol) and TFA (250 μL) in EtOH (20 mL) was heated under reflux for 15 h. After cooling down to ambient temperature, the solvent was distilled off under reduced pressure and the residue was purified by column chromatography [SiO_2, hexane/EtOAc (3:1, v/v)] to afford **1** (251 mg) as a green solid in a yield of 79.1%.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 1.195-1.261 (12H, m), 2.481-2.493 (1H, t, 4.8 Hz), 3.390-3.443 (4H, q, 7.2 and 14 Hz), 4.646- 4.661 (2H, d, 6 Hz), 4.877-4.882 (2H, d, 2 Hz), 6.469-6.674 (1H, d, 2 Hz), 6.557-6.585 (1H, dd, 8.8 and 2.4 Hz), 6.617-6.627 (1H, d, 4.0 Hz), 6.648-6.657 (1H, d, 3.6 Hz), 6.885-6.907(1H, m, 8.8 Hz), 6.942 (1H, s), 7.227-7.249 (1H, d, 8.8 Hz), 7.513 (1H, s), 7.814- 7.817 (1H, d, 1.2 Hz), 7.890-7.914 (1H, dd, 8 and 1.2 Hz), 7.978-7.984 (1H, d, 2.4 Hz), 8.007-8.013 (1H, d, 2.4 Hz)

^{13}C NMR (400 MHz, $CDCl_3$), δ = 12.46, 18.48, 26.62, 29.69, 40.92, 44.88, 49.75, 52.03, 74.67, 78.13, 96.93, 103.91, 107.96, 108.46, 109.23, 115.33, 117.87, 119.87, 121.51, 123.20, 124.16, 125.06, 129.13, 131.20, 131.27, 138.50, 140.88, 141.64, 151.06, 151.26, 155.96, 158.89, 160.67, 165.75

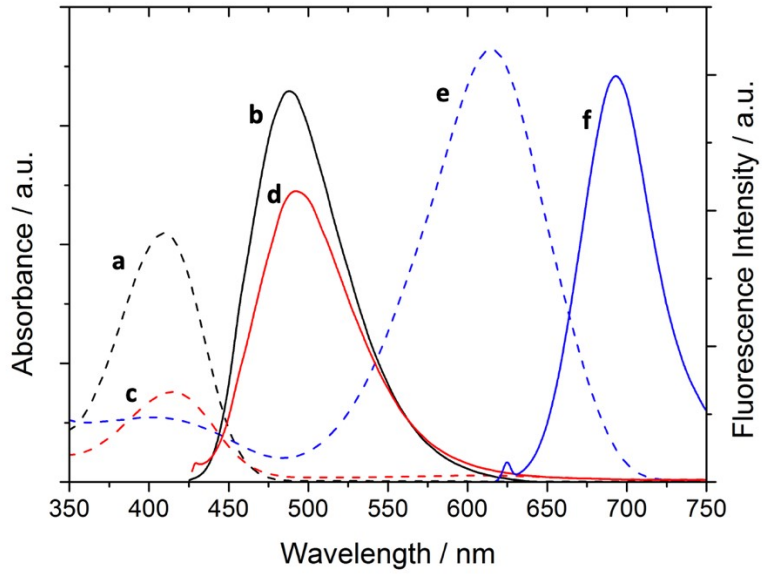

Figure S.1. Absorption (dash lines) and emission (straight lines) spectra in different solvents of compound **1** (3×10^{-5} M, 298.15 K): MeCN (a and b), H_2O/MeCN (1:1) (c and d), HCl/MeCN (1:1) (e and f).

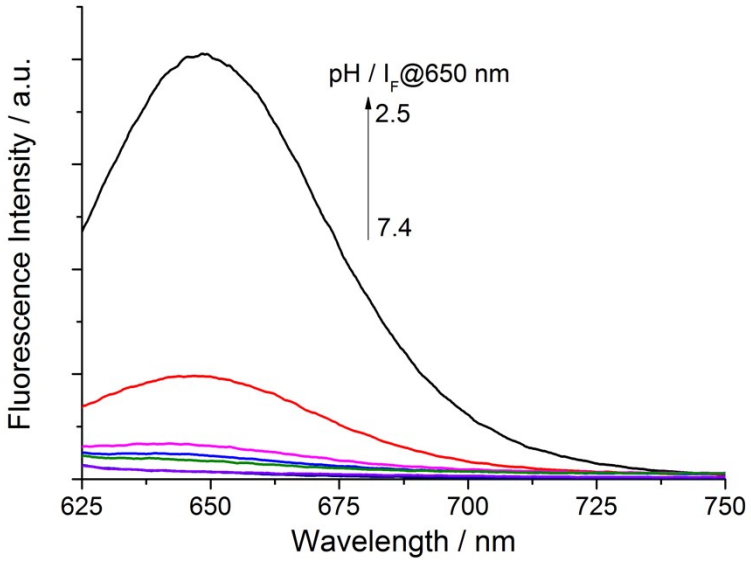

Figure S.2. Emission spectra of HNTs-**1** dispersion (0.25 mg mL^{-1}) at different pH in the presence of Pluronic 123 at 298.15 K.

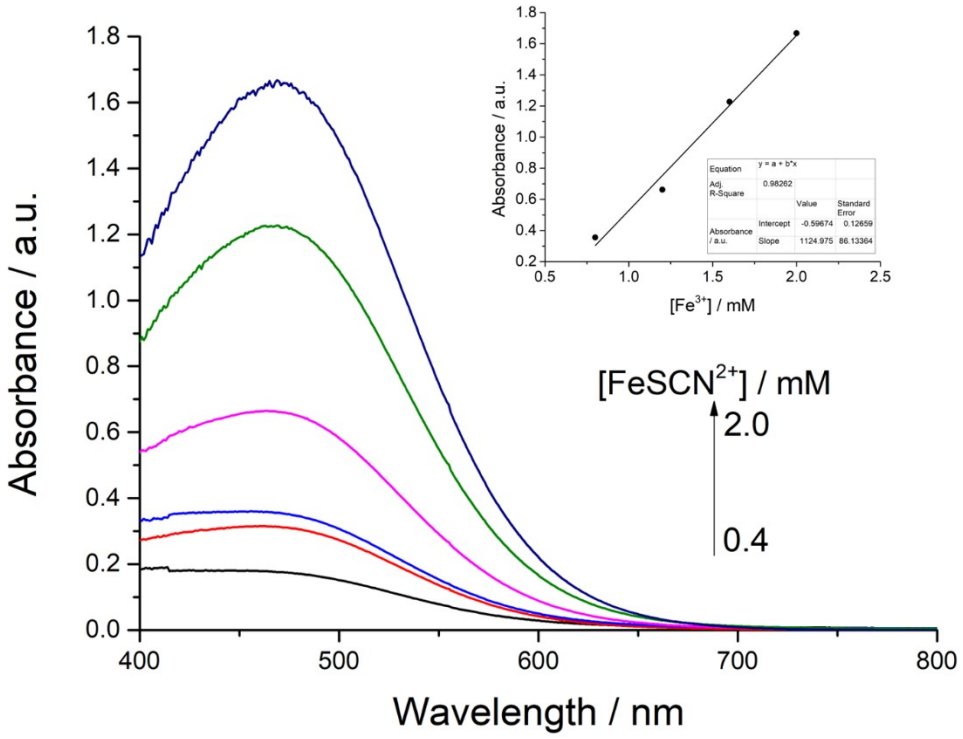

Figure S.3. Absorption spectra of the calibration curve using thiocyanate method. The inset shows the calibration curve.

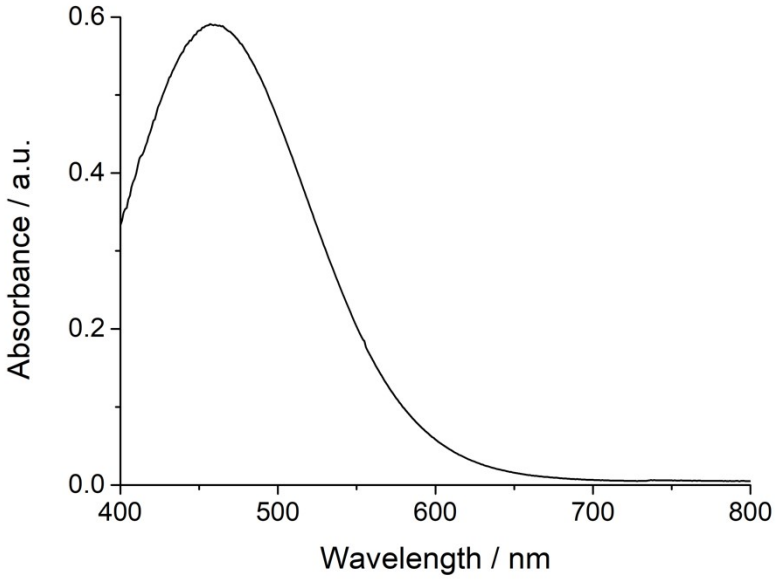

Figure S.4. Absorption spectra of the unknown solution treated with thiocyanate, from HNTs-**1**@Fe_3O_4 nanomaterial treated with aqua regia.

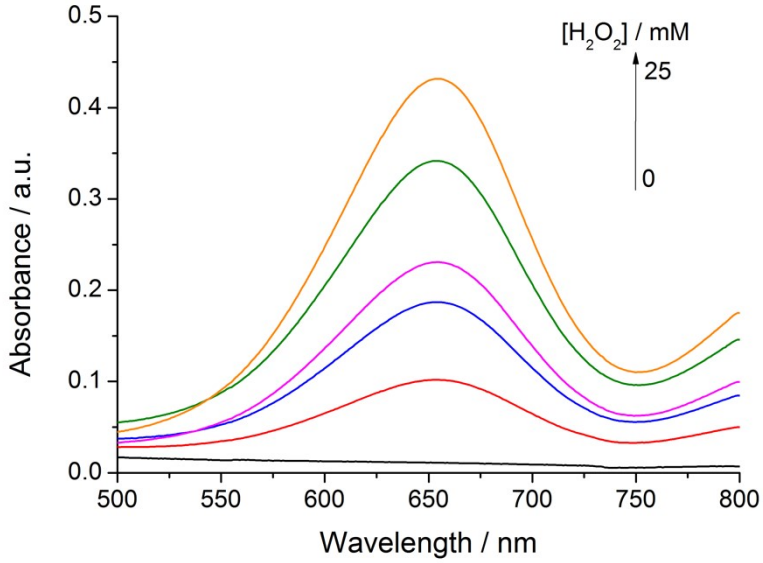

Figure S.5. UV−*vis* spectra of TMB (1.5 mM) treated with HNTs-**1**@Fe_3O_4 nanomaterial and different H_2O_2 concentrations (0.0, 2.5, 5.0, 7.5, 12.5, 25.0 mM) after 30 min of incubation.

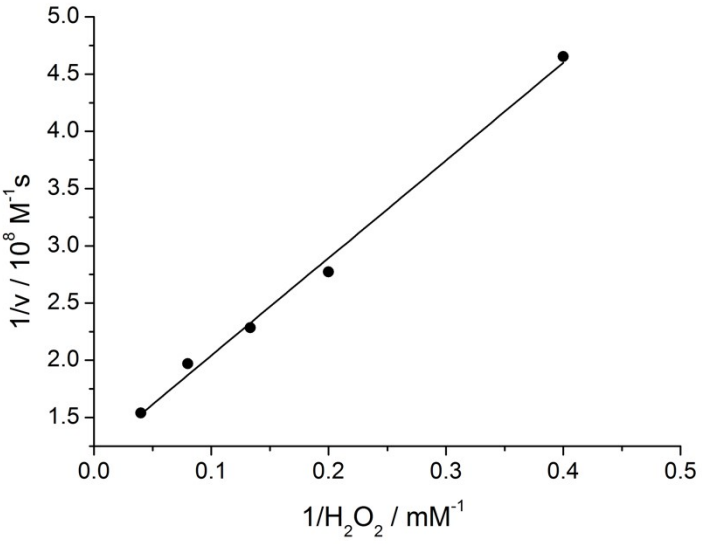

Figure S.6. Lineweaver–Burk plotting for HNTs-**1**@Fe_3O_4 with H_2O_2 as a substrate.

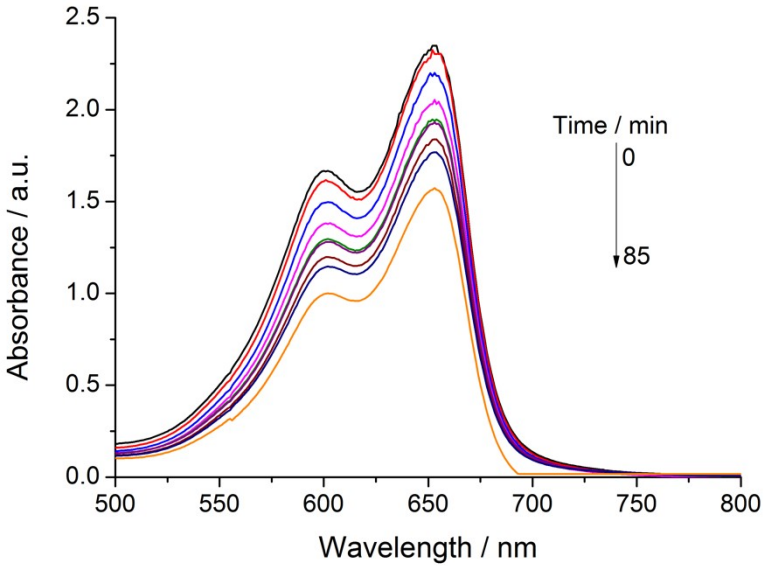

Figure S.7. Degradation process of MB (50 μM) with time in the presence of HNTs-**1**@Fe_3O_4 dispersions (0.1 mg mL^{-1}) without H_2O_2.

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