Unimolecular Binary Half-Adders with Orthogonal Chemical Inputs

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Supporting Information

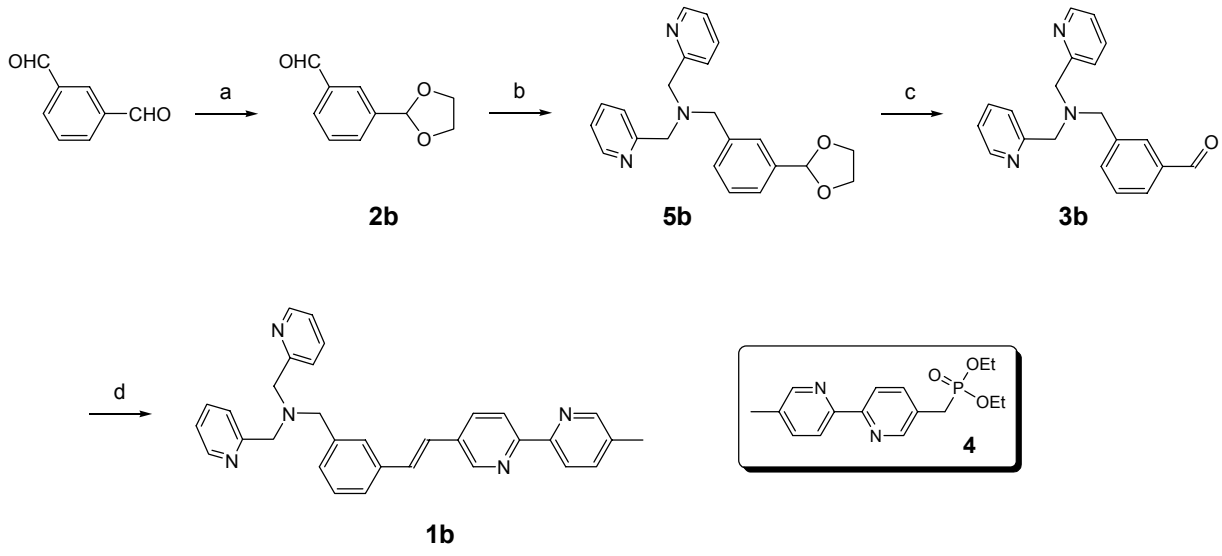
ACRONYMS OF CHEMICALS

$CDCl_3$	chloroform-*d*
$Cd(ClO_4)_2$	cadmium(II) perchlorate
DCM	dichloromethane
DIPEA	diisopropylethylamine
EtOAc	ethyl acetate
HCl	hydrochloric acid
K_2CO_3	potassium carbonate
MeCN	acetonitrile
Na_2CO_3	sodium carbonate
Na_2SO_4	sodium sulfate
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
NaOH	sodium hydroxide
TBAP	tetrabutylammonium perchlorate
THF	tetrahydrofuran
TsOH	*p*-Toluenesulfonic acid
$Zn(OTf)_2$	zinc trifluoromethanesulfonate
$Zn(ClO_4)_2$	zinc perchlorate

MATERIALS AND GENERAL METHODS.

Reagents and solvents were purchased from various commercial sources and used without further purification unless otherwise stated. MeCN (OmniSolv, EMD) was directly used in titration experiments without purification. All reactions were carried out in oven- or flame-dried glassware under argon protections. Analytical thin-layer chromatography (TLC) was performed using pre-coated TLC plates with silica gel 60 F_{254} (EMD) or with aluminum oxide 60 F_{254} neutral. Flash column chromatography was performed using 40-63 μm (230-400 mesh ASTM) silica gel (EMD) or alumina (80-200 mesh, pH 9-10) as the stationary phases. THF was dried by distilling from sodium-benzophenone in a continuous still under argon protection. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, on a Varian Mercury spectrometer. All chemical shifts were reported in δ units relative to tetramethylsilane. $CDCl_3$ was treated with alumina gel prior to use to remove residue acid. High resolution mass spectral data were obtained at the Mass Spectrometry Laboratory at FSU. ESI spectra were obtained on a JEOL AccuTof spectrometer; EI spectra were obtained on a JEOL JMS600H spectrometer. The syntheses of compound **1a** and **4** were reported elsewhere (Zhang, Clark et al. 2008). Spectrophotometric and fluorimetric tritrations were conducted on a Varian Cary 100 Bio UV-Visible Spectrophotometer and a Varian Cary Eclipse Fluorescence Spectrophotometer, respectively.

SYNTHESIS



Scheme S1. Synthesis of compound **1b**. a. ethylene glycol, TsOH (cat.), Dean-Stark, reflux, 4 h, 64%; b. di-(2-picolyl)-amine, $NaBH(OAc)_3$, rt, 6 h, 84%; c. $HCl/THF/H_2O$ = 1/6/7, rt, 14 h; d. NaH, dimethoxyethane, **4**, rt, 14 h, 84% for steps c and d.

COMPOUND 2b. Isophthalaldehyde (268 mg, 2.0 mmol) and ethylene glycol (111 μL, 2.0 mmol) were heated under reflux through a Dean-Stark distilling receiver (5 mL capacity) for 4 h in benzene (15 mL) in the presence of catalytic amount of TsOH. Solvent was removed under vacuum after the reaction was cooled down. The residue was partitioned between DCM and basic water (pH ~ 8-10). After separation, the organic layer was washed twice using distilled water before being dried over Na_2SO_4. The crude product after solvent removal was eluted on a silica column using mixture of hexanes and DCM (gradient from 75/0 hexanes/DCM to 20/80) to afford the pure product (122 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 10.04 (s, 1H), 8.01 (s, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 5.88 (s, 1H), 4.16-4.07 (m, 4H).

COMPOUND 5b. Compound **2b** (122 mg, 0.68 mmol) and di-(2-picolyl)amine (122 μL, 0.68 mmol) were dissolved in anhydrous 1,2-dichloroethane (2.72 mL). The reaction was stirred at rt for overnight before $NaBH(OAc)_3$ (288 mg, 1.36 mmol) was added. The reaction was stirred for another 6 h before brine (~ 5 mL) was added. The reaction mixture was partitioned between DCM and basic water (pH > 11) and separated. The aqueous layer was extracted for three times using DCM. The DCM fractions were combined and dried over K_2CO_3. After solvent removal the crude product was eluted on an alumina column using a mixture of DCM and EtOAc (gradient from 100/0 DCM/EtOAc to 70/30) to afford the pure product (206 mg, 84%).^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 8.51 (d, J = 4.8 Hz, 2H), 7.69-7.63 (m, 2H), 7.58 (d, J = 7.5 Hz, 2H), 7.50-7.44 (m, 2H), 7.36-7.34 (m, 2H), 7.15-7.11 (m, 2H), 5.81 (s, 1H), 4.13-4.02 (m, 4H), 3.80 (s, 4H), 3.70 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm 159.67, 148.93, 139.23, 137.98, 136.38, 129.60, 128.41, 126.92, 125.20, 122.79, 121.93, 103.70, 65.26, 60.00, 58.40; HRMS (ESI): calcd. ($M+Na^+$) 384.1688, found 384.1682.

COMPOUND 3b. Compound **5b** (206 mg, 0.57 mmol) was dissolved in the mixture (10 mL) of 37% HCl/H_2O/THF = 1/6/7 and stirred at rt for overnight. The solution was partitioned between NaOH (0.1 M) and DCM (3 × 25 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The product was used directly to the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 10.02 (s, 1H), 8.54 (d, J = 4.8 Hz, 2H), 7.94 (s, 2H), 7.77-7.66 (m, 4H), 7.58-7.49 (m, 3H), 7.19-7.14 (m, 2H), 3.83 (s, 4H), 3.79 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm 192.45, 159.36, 149.16, 140.47, 136.64, 136.59, 135.08, 129.98, 129.10, 128.72, 123.03, 122.20, 60.18, 58.06; HRMS (ESI): calcd. ($M+Na^+$) 340.1426, found 340.1426.

COMPOUND 1b. *** Reaction flask was protected from ambient light using aluminum foil; work-up and purification were carried out under illumination of red light bulbs. *** NaH (60% in mineral oil, 18 mg, 0.46 mmol) was added to a solution of compound **3b** (37 mg, 0.12 mmol) in anhydrous 1,2-dimethoxyethane (0.6 mL) in the reaction flask. The suspension was stirred for 8 min. The flask was cooled in an ice bath (0 °C) and was added dropwise the solution of **4** (62 mg, 0.19 mmol) in anhydrous 1,2-dimethoxyethane (0.7 mL). The reaction was stirred at rt for overnight before icy brine was added to quench the reaction. The reaction mixture was partitioned between DCM and NaOH (0.1 M). The organic layer was dried over Na_2SO_4, followed by solvent removal under vacuum. The residue was chromatographed on alumina

gel (DCM/EtOAc from 10/1 to 2/1). The isolated product (47.4 mg, 84%) was precipitated from a DCM solution by addition of hexanes to afford pure *trans*-**1b** (33.5 mg, 59%). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 8.75 (d, J = 2.4 Hz, 1H), 8.56-8.52 (m, 3H), 8.37 (d, J = 7.8 Hz, 2H), 8.30 (d, J = 7.8 Hz, 2H), 7.98 (dd, J = 1.2, 7.8 Hz, 1H), 7.72-7.59 (m, 6H), 7.43-7.34 (m, 3H), 7.26-7.09 (m, 4H), 3.86 (s, 4H), 3.75 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm 159.87, 155.34, 153.59, 149.88, 149.25, 148.27, 139.77, 137.63, 137.00, 136.62, 133.54, 132.93, 130.97, 128.97, 127.42, 125.64, 125.07, 123.04, 122.20, 120.86, 120.76, 60.26, 58.63, 18.57; HRMS (ESI): calcd. ($M+Na^+$) 506.2321, found 506.2312.

ABSORPTION AND FLUORESCENCE SPECTROPHOTOMETRIC STUDIES

An MeCN solution of **1a** (2.0 μM), $Zn(ClO_4)_2$ (15.9 μM), DIPEA (2.0 μM), and TBAP (5 mM) was titrated into a semi-micro quartz spectrophotometer or fluorometer cuvette (Starna®) containing an MeCN solution of **1a** (840 μL, 2.0 μM), DIPEA (2.0 μM), and TBAP (5 mM) at 25 °C (Figures S1-2).

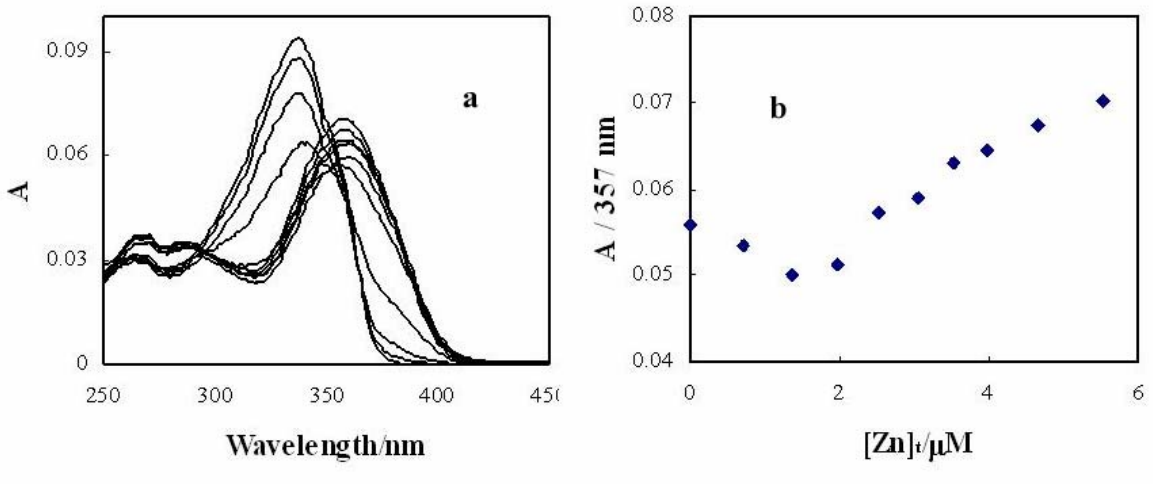


Figure S1. Spectrophotometric titration of **1a** (2.0 μM) with $Zn(ClO_4)_2$ (0 – 5.9 μM) in MeCN (TBAP: 5 mM; DIPEA: 2.0 μM) at 25 °C. (a) Titration spectra; (b) Absorbance at 357 nm vs. $[Zn]_t$/μM.

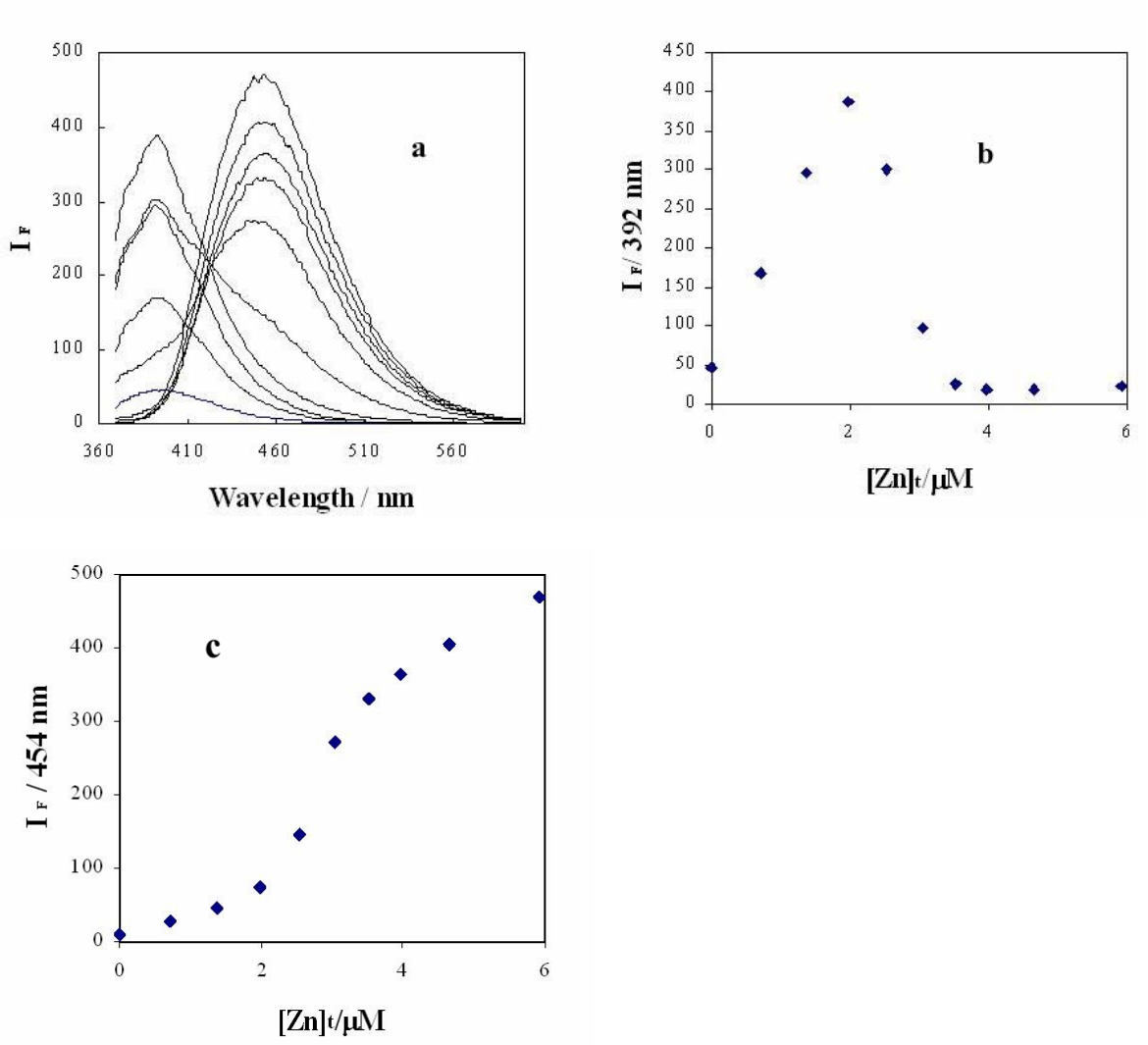


Figure S2. Fluorescence spectra of **1a** (2.0 μM, λ_{ex} = 357 nm) in MeCN (TBAP: 5 mM; DIPEA: 2.0 μM) upon addition of $Zn(ClO_4)_2$ (0 – 5.9 μM) at 25 °C. (a) Titration spectra; Fluorescence intensities at 392 nm (b) and 450 nm (c) versus $[Zn]_t$/μM.

An MeCN solution of **1a** (2.0 μM), $Cd(ClO_4)_2$ (15.9 μM), DIPEA (2.0 μM), and TBAP (5 mM) was titrated into a semi-micro quartz spectrophotometer or fluorometer cuvette (Starna®) containing an MeCN solution of **1a** (840 μL, 2.0 μM), DIPEA (2.0 μM), and TBAP (5 mM) at 25 °C (Figures S3-4).

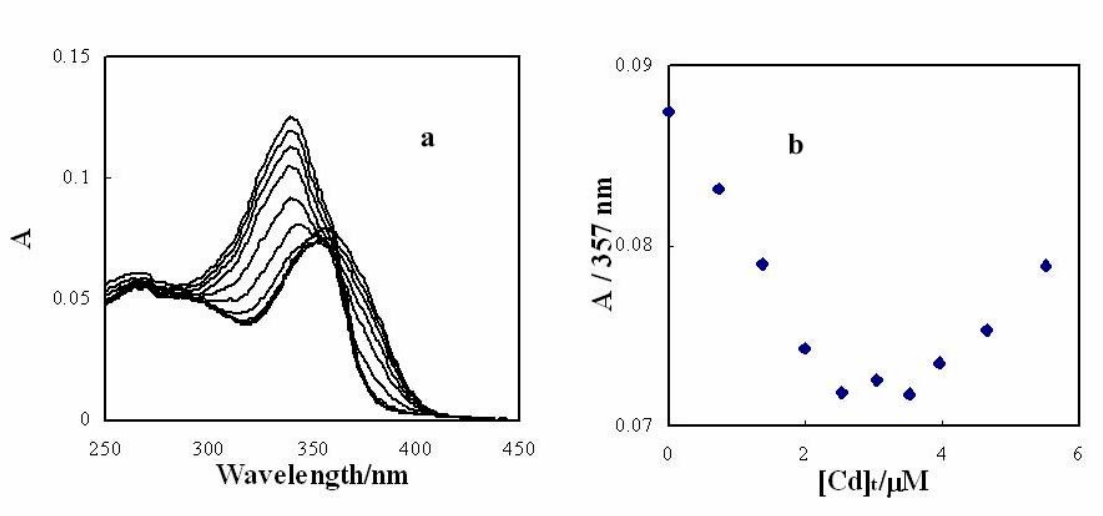


Figure S3. Spectrophotometric titration of **1a** (2.0 μM) with $Cd(ClO_4)_2$ (0 – 5.5 μM) in MeCN (TBAP: 5 mM; DIPEA: 2.0 μM) at 25 °C. (a) Titration spectra; (b) Absorbance at 357 nm versus $[Cd]_t$/μM.

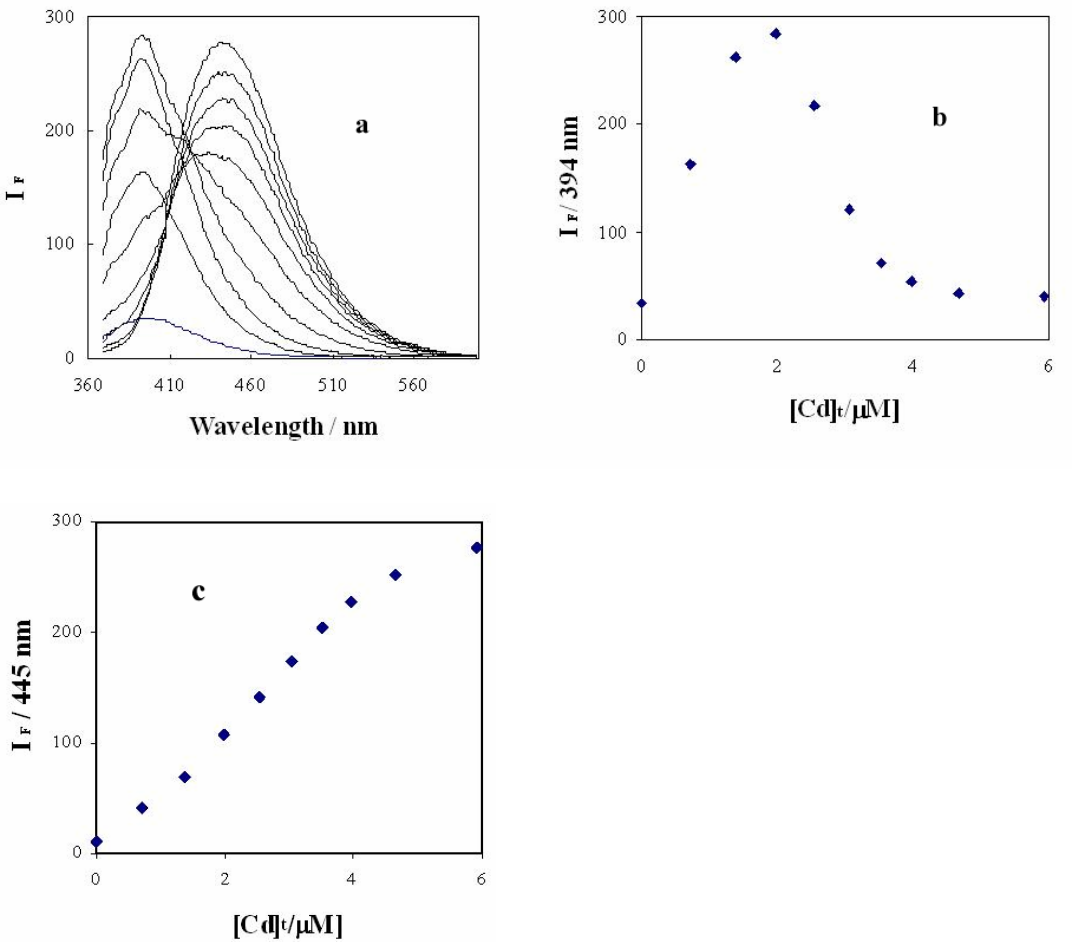


Figure S4. Fluorescence spectra of **1a** (2.0 μM, λ_{ex} = 357 nm) in MeCN (TBAP: 5 mM; DIPEA: 2.0 μM) upon addition of $Cd(ClO_4)_2$ (0 – 5.9 μM) at 25 °C. (a) Titration spectra; Fluorescence intensities at 394 nm (b) and 445 nm (c) versus $[Cd]_t$/μM.

An MeCN solution of **1b** (2.0 μM), $Zn(ClO_4)_2$ (15.9 μM), DIPEA (2.0 μM), and TBAP (5 mM) was titrated into a semi-micro quartz spectrophotometer or fluorometer cuvette (Starna®) containing an MeCN solution of **1a** (840 μL, 2.0 μM), DIPEA (2.0 μM), and TBAP (5 mM) at 25 °C (Figures S5-6).

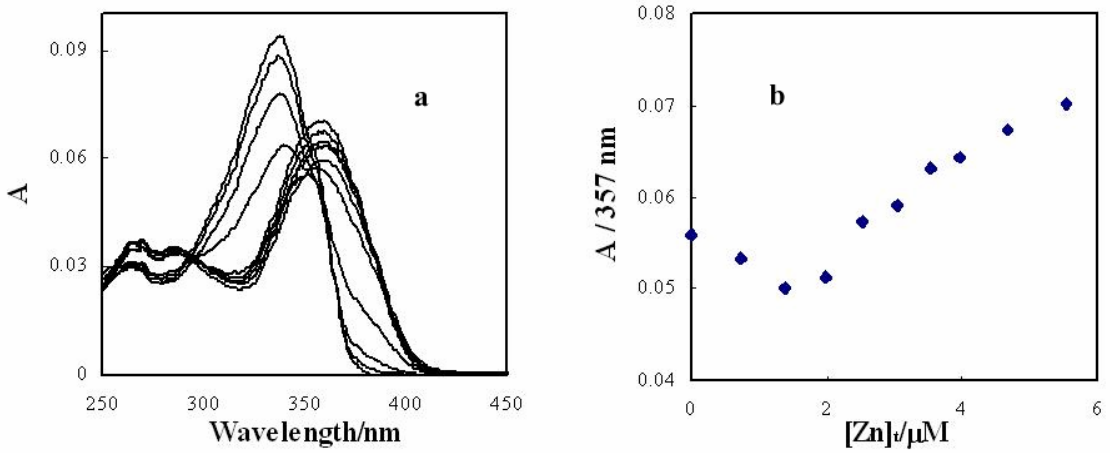


Figure S5. Spectrophotometric titration of **1b** (2.0 μM) with $Zn(ClO_4)_2$ (0 – 5.5 μM) in CH_3CN (TBAP: 5 mM; DIPEA: 2.0 μM) at 25 °C. (a) Titration spectra; (b) Absorbance at 357 nm versus $[Zn]_t$/μM.

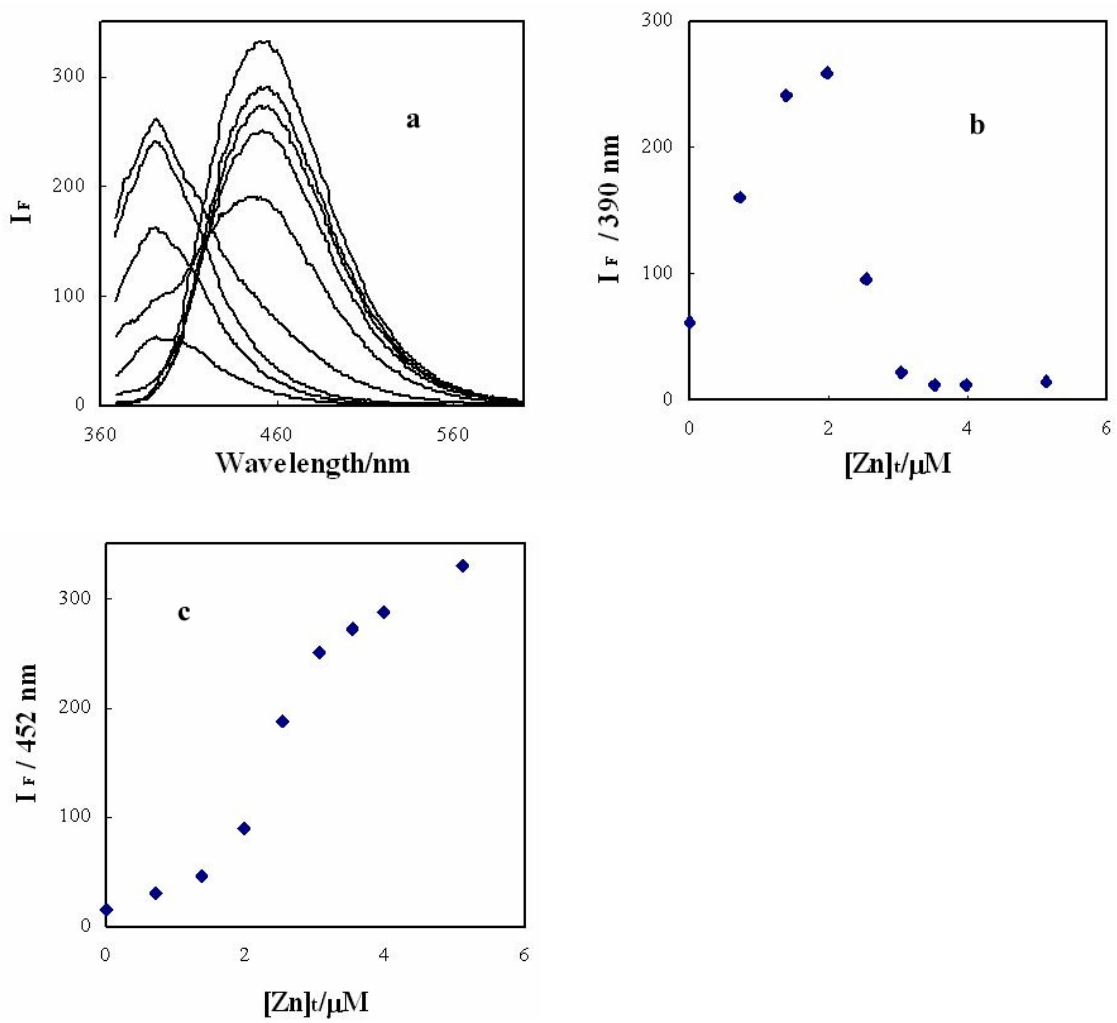


Figure S6. Fluorescence spectra of **1b** (2.0 μM, λ_{ex} = 357 nm) in MeCN (TBAP: 5 mM; DIPEA: 2.0 μM) upon addition of $Zn(ClO_4)_2$ (0 – 5.1 μM) at 25 °C. (a) Titration spectra; Fluorescence intensities at 390 nm (b) and 452 nm (c) vs. $[Zn]_t$/μM.

An MeCN solution of **1b** (2.0 μM), $Cd(ClO_4)_2$ (15.9 μM), DIPEA (2.0 μM), and TBAP (5 mM) was titrated into a semi-micro quartz spectrophotometer or fluorometer cuvette (Starna®) containing an MeCN solution of **1b** (840 μL, 2.0 μM), DIPEA (2.0 μM), and TBAP (5 mM) at 25 °C (Figures S7-8).

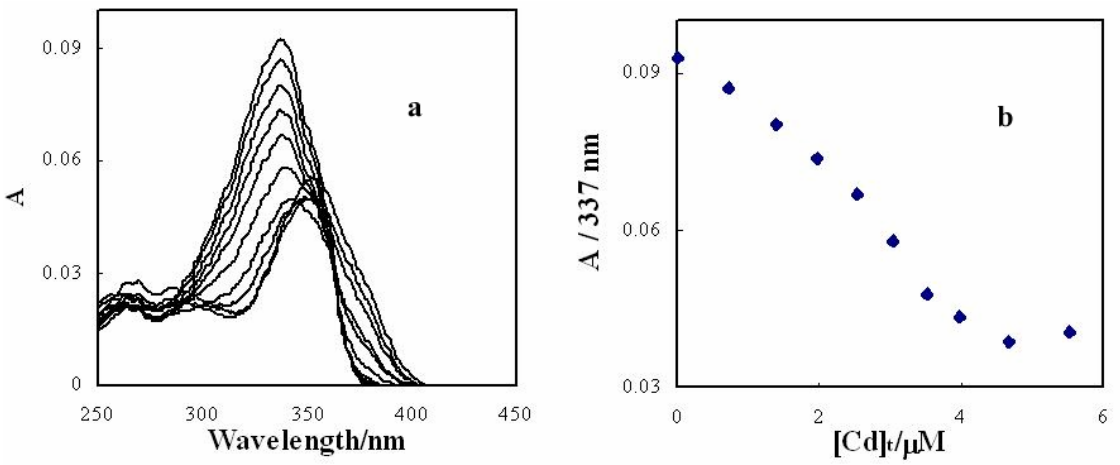


Figure S7. Spectrophotometric titration of **1b** (2.0 μM) with $Cd(ClO_4)_2$ (0 – 5.5 μM) in MeCN (TBAP: 5 mM; DIPEA: 2.0 μM) at 25 °C. (a) Titration spectra; (b) Absorbance at 337 nm vs. $[Cd]_t$/μM.

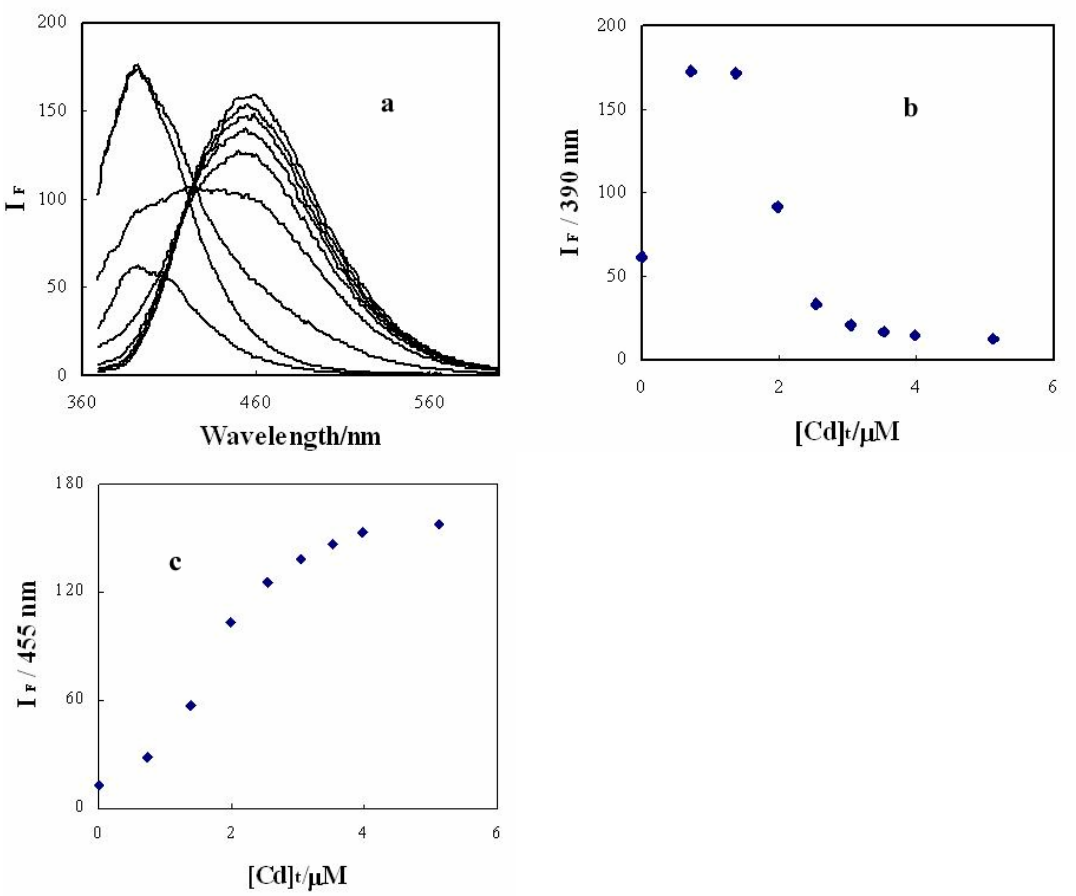


Figure S8. Fluorescence spectra of **1b** (2.0 μM, λ_{ex} = 357 nm) in MeCN (TBAP: 5 mM; DIPEA: 2.0 μM) upon addition of $Cd(ClO_4)_2$ (0 – 5.1 μM) at 25 °C. (a) Titration spectra; Fluorescence intensities at 390 nm (b) and 455 nm (c) vs. $[Cd]_t$/μM.

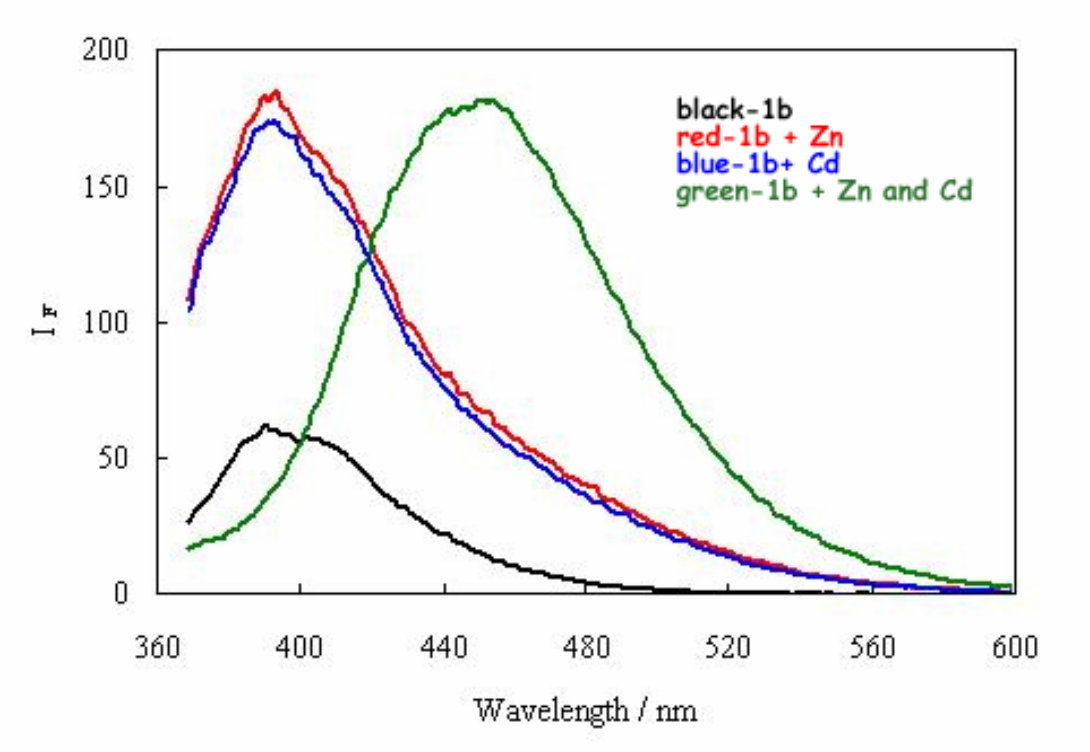


Figure S9. Fluorescence spectra (λ_{ex} = 357 nm) of **1b** (2.0 μM) in MeCN (TBAP: 5 mM; DIPEA: 2.0 μM) in the presence of different metal ion at 0.7 eq. (1.4 μM each) input combinations at 25 °C.

HALF-ADDER RESET

Resetting of half-adder **1a** was attempted using different conditions. Chelating resin (Chelex 100 sodium form), a DMSO solution of EDTA in conjunction with DIPEA or granular K_2CO_3 as proton scavengers were used to remove Zn^{2+} and Cd^{2+} from their complexes of **1a** to "reset" the half-adder to the initial unbound state. Under all conditions, the fluorescence of the metal complexes of **1a** in MeCN was reduced to the level of unbound **1a**. However, restoration of fluorescence in either emission band required more metal ions than 1 equiv. used in the first cycle. Our explanation at this point is that the proton scavengers needed to neutralize EDTA in MeCN also removed certain amount of metal ion from the solution, therefore effectively decreased the affinity of **1a** to Zn^{2+} and Cd^{2+}. Under current level of investigation, the EDTA/K_2CO_3 combination afforded the most reproducible results where 2.0 equiv. Zn^{2+} and 1.8 equiv. Cd^{2+}, respectively, were added as quanta in the second cycle instead of 1 equiv. of metal ions used in the first cycle.

Procedure: To the sample of **1a** (2.0 μM) in MeCN (TBAP: 5 mM; DIPEA: 2.0 μM) in the presence of Zn^{2+} and Cd^{2+} (2.0 μM each) was added 1.0 μL EDTA solution (2.156 mM in DMSO) and K_2CO_3 (110 mg). The metal ion stock solutions ($Zn(ClO_4)_2$: 671.4 μM in MeCN; $Cd(ClO_4)_2$: 717.1 μM in MeCN) of specified quantities (see Caption of Figure S10) were directly added to the sample to obtain the second cycle of half-adder results.

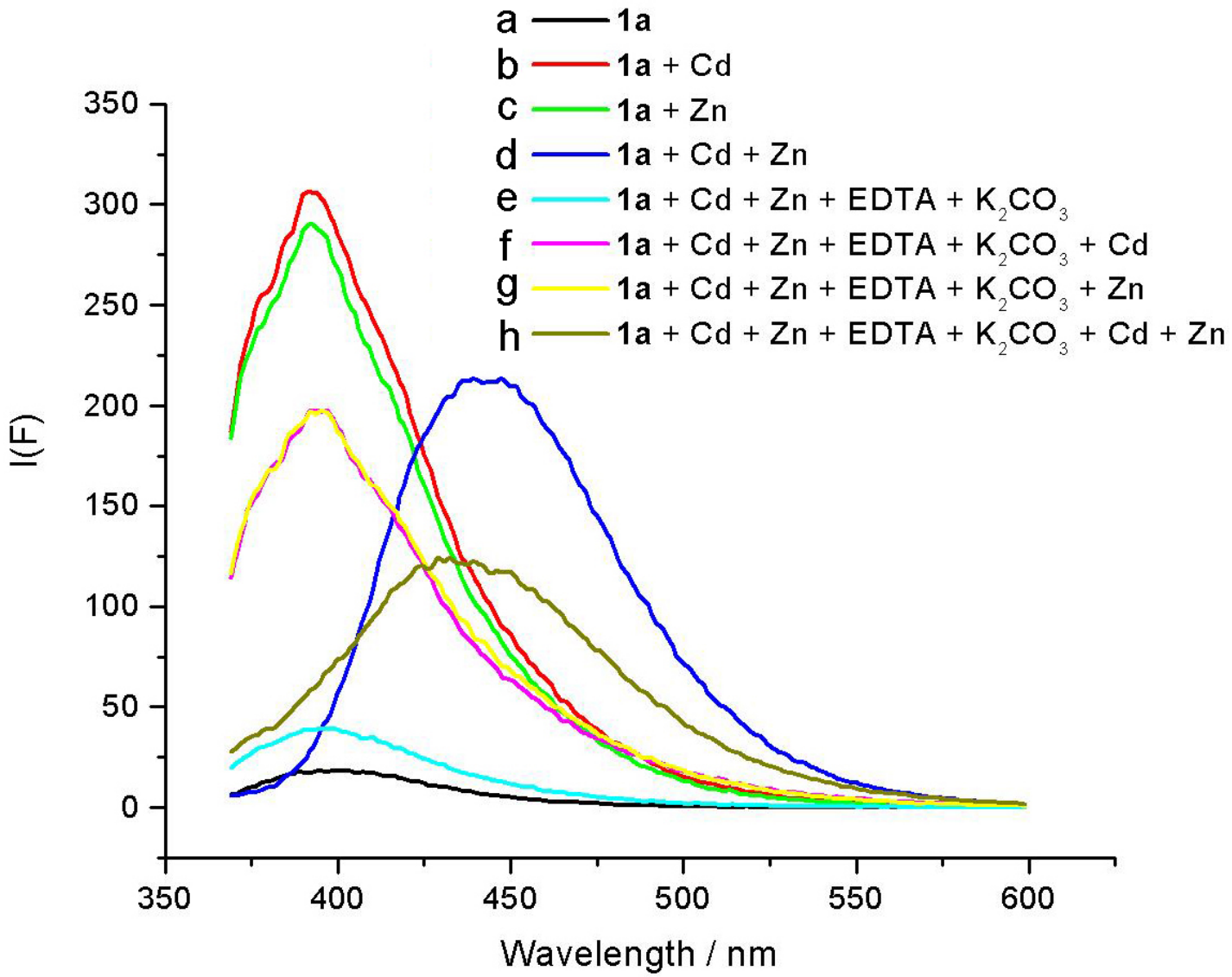


Figure S10. Fluorescence spectra (λ_{ex} = 357 nm) of **1a** (2.0 μM) in MeCN (TBAP: 5 mM; DIPEA: 2.0 μM) in the presence of different metal ion input combinations and/or EDTA/K_2CO_3. a) **1a** alone, b) **1a** with 1 equiv. Zn^{2+}, c) **1a** with 1 equiv. Cd^{2+}, d) **1a** with 1 equiv. Zn^{2+} and 1 equiv. Cd^{2+}, e) sample 'd' (1120 μL) with 0.9 equiv. EDTA and 110 mg K_2CO_3, f) sample 'e' with 2.0 equiv. Zn^{2+}, g) sample 'e' with 1.8 equiv. Cd^{2+}, h) sample 'e' with 2.0 equiv. Zn^{2+} and 1.8 equiv. Cd^{2+}.

Reference:

Zhang, L., R. J. Clark, et al. (2008). "A Heteroditopic Fluoroionophoric Platform for Constructing Fluorescent Probes for Zinc Ion with Large Dynamic Ranges." Chem. Eur. J.: In Press.