**Electronic Supporting Information** 

## Intracellular Zn(II) induced turn-on fluorescence of L-

## phenylalanine-derived pseudopeptides

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Figure S12: - HRMS (ESI-TOF) of 4+Zn(II).



Figure S13: Scheme for the synthesis of 4.

**Experimental:** 

General methods and instrumentation

<sup>1</sup>H and <sup>13</sup>C-NMR spectra were obtained on a JEOL Resonance-ECZ 500R spectrometer at an operating frequency of 500 MHz (<sup>1</sup>H) and 126 MHz (<sup>13</sup>C) in CDCl<sub>3</sub> or DMSO-d<sub>6</sub> solutions; chemical shifts are given in parts per million (ppm) relative to tetramethyl silane (TMS,  $\partial = 0.00$  ppm) and splitting patterns defined as s (singlet), d (doublet), t (triplet), m (multiplate). High-resolution mass spectra (ESI-HRMS) were recorded on a SCIEX X500R (TOF-MS) mass spectrometer. FT-IR spectra were recorded on an FT-IR 4700 JASCO spectrophotometer using KBr pellet method. UV-visible spectra were recorded on an Agilent Cary 60 single-beam UV-Visible spectrometer, while fluorescence spectra were recorded on a Fluoromax 4CP plus spectrofluorometer with a 10 mm quartz cell at 25 °C. Melting points were measured using a Navyug ISO-9001-2008 melting point apparatus. CD spectra were recorded on a JASCO J-1500 CD Polarimeter at room temperature. Life cell imaging was processed using ZenBlue software from Zeiss, cell viability data were analyzed using Excel, and GraphPad software was used to calculate IC-50.

All chemicals are purchased from a commercial supplier and used without further purification. Lithium hydroxide and *L*-phenylalanine were purchased from spectrochemical grade, 1pyrenecarboxyaldehyde was purchased from Sigma-Aldrich, and sodium borohydride was purchased from SD Fine-Chem limited. Metal salts: Ni(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O, Pb(NO<sub>3</sub>)<sub>2</sub>, Cd(NO<sub>3</sub>)<sub>2</sub>·4H<sub>2</sub>O, Co(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O, Ca(NO<sub>3</sub>)<sub>2</sub>·4H<sub>2</sub>O, Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O, AgNO<sub>3</sub>, NaNO<sub>3</sub>, Zn(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O, and Hg<sub>2</sub>(NO<sub>3</sub>)<sub>2</sub>·2H<sub>2</sub>O were purchased from HI media.

#### Cell culture

RAW 264.7 cells were procured from the National cell Line repository, National Center for Cell Science (NCCS) Pune, Maharashtra India. Cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM)-high glucose, supplemented with 10% fetal bovine serum, 2 mM glutamine,

1% antibiotics in a humidified 5%  $CO_2$  environment at 37 °C Cells were passaged upon 80% confluence.

### **Cell Viability**

RAW 264.7 cells were seeded at a density of 5000 cells per well in 100  $\mu$ L of DMEM. Cells were allowed to grow overnight in the CO<sub>2</sub> incubator. After 12 h, cells were incubated with various concentrations of compound 4 (0, 12.5, 25, 50, 100, and 200  $\mu$ M) for 24 h. Cell viability in various drug concentrations was determined using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method. Briefly, cells were incubated with 10  $\mu$ L of the MTT (5 mg/mL stock) for 2 h. Media was discarded and formazon crystals were dissolved in 100  $\mu$ L of DMSO. Absorbance was measured at 570 nm on an iMarkmicroplate reader from Biorad.

## Live cell imaging microscopy

 $1 \times 10^5$  cells per well were seeded in a 6-well plate. Cells were allowed to grow overnight. Cells were treated with 20 µM ZnNO<sub>3</sub> (prepared in 1X PBS) for 30 minutes in a CO<sub>2</sub> incubator. Cells were washed thrice with 1X PBS (2 mL each) followed by incubation with the probe (50 µM) (5µL in 1mL ethanol) for 30 minutes at 37 °C in the medium. Cells were washed twice with PBS (2 mL each) followed by image acquisition at Zeiss Cell discoverer 7 microscopes for live imaging ( $\lambda_{ex}$ = 349 and  $\lambda_{em}$  = 420 nm) at the Central Discovery Center (CDC) facility at the Banaras Hindu University.

## General methods for measurements

UV-Vis and fluorescence measurements: The modulation in the emission and absorption spectra of the designed probe 4 was studied using various environmentally and physiologically important alkali-alkaline earth and transition metal ions. A stock solution of 4 (10  $\mu$ M) for UV-visible and

fluorescence studies was prepared in EtOH: water (8:3, v/v at room temperature). Stock solutions for the various metal ions (Na(I), Co(II), Ca(II), Ni(II), Cu(II), Cd(II), Ag(I), Zn(II), Hg(II), Pb(II)) were prepared by dissolving their respective nitrate salts in distilled water, (10 mM). Titration experiments were carried out by using 3.0 mL of the stock solution of **4** in a quartz cuvette (4 mL, 1 cm path length) to which the solution of the corresponding metal ion was added gradually with the help of a micropipette. Fluorescence measurements were carried out at the maximum excitation wavelength of 349 nm and the maximum emission wavelength of 470 nm, while the absorbance measurements were carried out in the wavelength range of 200-800 nm.

## Synthesis of compound 1: (2,5-dioxopyrrolidin-1-yl ((benzyloxy)carbonyl)-Lphenylalaninate)<sup>1</sup>

N-Cbz-*L*-phenylalanine (2.993 g, 10 mmol) and N-hydroxy succinimide (1.150 g, 10 mmol) was dissolved in dry THF at 0°C stirring till the formation of clear solution Dicyclohexylcarbamide (DCC) (2.266 g, 11 mmol) previously dissolved in dry THF was added dropwise and the resultant solution was again stirred at 0-5 °C for 3-4 h. Dicyclohexylurea formed as a solid side product was filtered off and the solution was vacuum concentrated to dryness. Recrystallization using 2-propanol afforded the pure product. Yield (3.0 g, 7.5 mmol, 86.7%).

# Synthesisofcompound2:dibenzyl((2S,2'S)-((1,3-phenylenebis(methylene))bis(azanediyl))bis(1-oxo-3-phenylpropane-1,2-diyl))dicarbamate

The N-hydroxysuccinimide ester of N-Cbz-*L*-phenylalanine (3 g, 7.5 mmol) was dissolved in anhydrous DME (10 mL) with cooling in an ice bath. The diamine *m*-xylylenediamine (0.511 g, 3.75 mmol) previously dissolved in dry DME was added dropwise to the above solution. The

reaction mixture was stirred for 18 h at room temperature and then heated for 6 h at 50-60 °C. The white solid formed was filtered and washed with cold methanol and water. Yield = 4.8 g (6.8 mmol, 90%) M.P. 174-176 °C, FT-IR: Wavenumber [KBr, cm<sup>-1</sup>] 701, 743, 1043, 1241, 1288, 1455, 1538, 1653, 1693, 2945, 3034, 3059, 3088, and 3303.<sup>1</sup>H NMR (600 MHz, DMSO-d<sub>6</sub>)  $\delta$  8.53 (t, *J* = 6.0 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.33 – 7.19 (m, 19H), 7.10 (s, 1H), 7.05 (dd, *J* = 7.6, 1.7 Hz, 2H), 4.99 – 4.90 (m, 4H), 4.33 – 4.20 (m, 6H), 3.02 (dd, *J* = 13.7, 4.7 Hz, 2H), 2.80 (dd, *J* = 13.7, 10.3 Hz, 2H), <sup>13</sup>C NMR (151 MHz, DMSO-d<sub>6</sub>)  $\delta$  171.9, 156.4, 139.6, 138.5, 137.5, 129.7, 128.7, 128.5, 128.2, 127.9, 126.7, 125.9, 65.7, 56.8, 42.5, 40.45, 38.0. HRMS (ESI-TOF)<sup>+</sup> calculated [M+H]<sup>+</sup> m/z 699.3183, found [M+H]<sup>+</sup> m/z 699.3162.

# Synthesis of compound 3: (2S,2'S)-N,N'-(1,3-phenylenebis(methylene))bis(2-amino-3-phenylpropanamide)

Compound **2** (4.8 g, 6.8 mmol) was added to HBr/Acetic acid (33%) (12 mL) and stirred at r.t. until CO<sub>2</sub> evolution stopped. After this, adding diethyl ether to the solution led to the formation of a white precipitate, which was dissolved in distilled water and extracted with chloroform. Then a solid NaOH pellet was added to the solution to achieve a pH = 12 that was then saturated with NaCl and extracted with chloroform (10 mL x 3). The organic phase was dried over anhy. MgSO<sub>4</sub> and concentrated using a vacuum evaporator to get a white solid. Yield = 2.5 g (5.8 mmol, 85%), M.P. 60-62 °C, FT-IR: Wavenumber [KBr, cm<sup>-1</sup>] 705, 1032, 1254, 1452, 1547, 1661, 2365, 2850, 2923, 3025, 3059, 3381 and 3502,<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.60 (s, 2H), 7.34 – 7.14 (m, 16H), 4.43 (d, *J* = 5.8 Hz, 4H), 3.66 (dd, *J* = 9.1, 4.0 Hz, 2H), 3.31 (dd, *J* = 13.8, 3.8 Hz, 2H), 2.75 (dd, *J* = 13.7, 9.3 Hz, 2H),<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  167.8, 136.9, 133.3, 132.2, 129.8, 128.6, 126.9, 119.3, 117.4, 43.5, 40.9. HRMS (ESI-TOF)<sup>+</sup> calculated [M+H]<sup>+</sup> m/z 431.2447, found [M+H]<sup>+</sup> m/z 431.2471.

Synthesis of compound 4: ((S)-2-(((E)-4-(diethylamino)-2-hydroxybenzylidene)amino)-N-(3-(((S)-2-(((Z)-4-(diethylamino)-2-hydroxybenzylidene)amino)-3-

### phenylpropanamido)methyl)benzyl)-3-phenylpropanamide)

Compound **3** (0.431 g; 1 mmol) was dissolved in methanol (10 mL) and to the clear solution *N*,*N*<sup>-</sup> diethylamino salicylaldehyde (0.386 g, 2 mmol) in methanol (5 mL) was added. The reaction mixture was stirred for 5 h at 65 °C. The reaction mixture was vacuum dried, and the residue was washed with diethyl ether. The crude product was crystallized from DCM /acetonitrile by slow evaporation of the solvent to give 0.700 g (0.89 mmol, 90%) of a light brown solid. M.P. 218-220 °C, FT-IR: Wavenumber [KBr, cm<sup>-1</sup>] 786, 825, 1014, 1078, 1190, 1133, 1238, 1345, 1525, 1615, 2867, 2932, 2973 and 3311, <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.71 (s, 2H), 7.23 – 7.10 (m, 8H), 7.01 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.50 (t, *J* = 6.1 Hz, 2H), 6.15 – 6.06 (m, 4H), 4.43 – 4.31 (m, 4H), 3.98 (dd, *J* = 8.6, 3.7 Hz, 2H), 3.33 (q, *J* = 7.3 Hz, 10H), 3.11 (dd, *J* = 13.4, 8.6 Hz, 2H), 1.15 (t, *J* = 7.0 Hz, 12H), <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  171.7, 166.4, 163.1, 151.7, 138.5, 137.6, 133.6, 130.0, 129.2, 128.4, 126.8, 126.6, 108.0, 103.6, 97.6, 74.8, 44.6, 43.2, 41.1, 31.7, 12.7. HRMS (ESI-TOF)<sup>+</sup> calculated [M+H]<sup>+</sup> m/z 781.4263, found [M+H]<sup>+</sup> m/z 781.4223.

## Synthesis of complex 1+Zn(II)

Compound **4** (0.780 g; 1 mmol) was dissolved in methanol (10 mL) and a clear solution of Zinc Nitrate hexahydrate (0.297 g; 1 mmol) in methanol (5 mL) was added. The reaction mixture was stirred for 3-4 h at rt. precipitate was filtered was washed with diethyl ether. 0.700 g (0.89 mmol, 90%) of a light green solid compound was formed. FT-IR: Wavenumber [KBr, cm<sup>-1</sup>] 784, 823, 1013, 1093, 1187, 1247, 1354, 1520, 1608, 2865, 2930, and 2973, 1H NMR (500 MHz, DMSO-D6)  $\delta$  7.87 (s, 2H), 7.13 (dt, J = 26.8, 7.4 Hz, 12H), 6.88 (dd, J = 19.9, 8.0 Hz, 4H), 6.07 (d, J = 8.7 Hz, 2H), 4.24 – 4.03 (m, 6H), 3.35 – 3.18 (m, 6H), 3.13 (dd, J = 13.6, 5.8 Hz, 4H), 2.91 (dd, J

= 13.5, 8.2 Hz, 2H), 0.99 (t, J = 6.7 Hz, 12H). 3C NMR (126 MHz, DMSO-D6) δ 171.70, 165.62, 165.11, 134.50, 130.36, 129.29, 129.17, 127.34, 126.44, 104.18, 45.12, 44.79, 42.82, 40.47, 40.29, 40.13, 39.96, 39.80, 39.63, 39.46, 13.39, 13.27. HRMS (ESI-TOF)<sup>+</sup> (C<sub>48</sub>H<sub>57</sub>N<sub>6</sub>O<sub>4</sub>Zn)calculated [M+3H]<sup>+</sup> m/z 843.3576, found [M+3H]<sup>+</sup> m/z 843.3620.



Figure S14: - Comparative IR spectra of 4 and 4+Zn(II).



Figure S15: UV-Visible spectrum of 4 (10 µM) in EtOH : water (8:2, v/v, r.t.).



Figure S16: UV-Visible absorbance spectra of 4 (10  $\mu$ M) in the presence of various metal ions (10 equiv., 10mM) in EtOH : water (8:2, v/v, r.t.)



**Figure S17:** Fluorescence spectra of 4 (10  $\mu$ M) before and after the addition of Zn(II) ions (10 equiv., 10 mM) in EtOH : water (8:2, v/v, r.t.).



**Figure S18:** Fluorescence spectra of **4** (10  $\mu$ M) in the presence of various anions (10 equiv., 10mM) in EtOH : water (8:2, v/v, r.t.).



**Figure S19:** Fluorescence lifetime decay curves for 4 (10  $\mu$ M) and 4+Zn(II) (after the addition of 10 equiv. of Zn(II) (10 mM in distilled water)) on excitation of 350 nm in EtOH : water (8:2,v/v, r.t.).



**Figure S20: (a)** Job plot spectra for the complexation of **4** (10  $\mu$ M in EtOH : water, 8:2, v/v, r.t.) with Zn(II). (b) Effect of the addition of different metal ions on the intensity increase of the emission spectra of the **4**: Zn(II) (10 equiv. of Zn(II) (10 mM) and 10 equiv. of metal (10 mM)).



**Figure S21:-** Circular Dichroism spectra for neat **4** and for the 4+Zn(II) complex (10  $\mu$ M, pure ethanol, r.t.).



**Figure S22:** Emission intensity of 4 with Zn(II) (10 equiv., 10mM) on adding various competitive anions (10 equiv., 10mM) in EtOH: water (8:2, v/v, r.t.). ( $\lambda_{exc} = 349$  nm)



**Figure S23:** Benesi-Hildebrand plot for the determination of the binding constant between **4** and Zn(II) ions in EtOH: water (8:2, v/v, r.t.).



**Figure S24:** Effect of Zn(II) concentration on the enhancement in the fluorescence signal of 4 ( $10^{-11}$  to  $10^{-3}$  M) in EtOH : water (8:2, v/v, r.t.).



**Figure S25:** - Fluorescence sensitivity of **4** in the presence of a different concentration of Zn(II)  $(1 \times 10^{-9} \text{ to } 9 \times 10^{-9} \text{ M})$  ions in EtOH : water (8:2, v/v, r.t.).

## Determination of the quantum yield.

Standard used: Quinine sulfate salt (QS); QS in 0.5 M sulfuric acid has  $\phi_f = 0.546$  (at 25 °C)

A 10  $\mu$ M solution of quinine sulfate was prepared in 0.5 M H<sub>2</sub>SO<sub>4</sub>, and the absorbance maximum of the solution was recorded at 345 nm, Abs = 0.305. The emission spectrum was also recorded with  $\lambda_{exc.}$  = 345 nm; the fluorescence emission was integrated in the 365-627 nm range to be  $1.681 \times 10^8$  a.u.

Two 10  $\mu$ M solutions of 4 and 4+Zn(II) (10 equiv.) were prepared in in EtOH : water (8:2, v/v, r.t.), and the absorbance maximum of the solutions at 349 nm was measured to be Abs.= 0.321 for 4 and Abs.= 0.380 for 4+Zn(II). The emission spectrum was also recorded with  $\lambda_{exc.}$ = 349 nm for 4 and 4+Zn(II). The fluorescence emission of 4 was integrated in the 357-675 nm range giving a value of 1.96×10<sup>7</sup> a.u. while the fluorescence emission of 4 after the addition of Zn(II) was integrated in the 356-666 nm range giving a value of 3.72×10<sup>7</sup> a.u.

The following formula was used for calculating quantum yield:

 $\Phi_{\rm s} = \phi_{\rm rf.} \ I_{\rm s}/I_{\rm rf.} \ A_{\rm rf}/A_{\rm s}$ 

Where  $\Phi_s$  is the fluorescence quantum yield of the sample,  $\phi_{rf}$  is the fluorescence quantum yield of the standard reference,  $I_s$  and  $I_{rf}$  are the integrated emission intensities of the sample and the standard reference respectively,  $A_{rf}$  and  $A_s$  are the absorbance of the standard reference and the sample at the excitation wavelength, respectively, and  $n_s$  and  $n_{rf}$  are the refractive indexes of the corresponding solutions of sample and reference.

The ratio of the refractive solvent indexes  $\eta_s/\eta_{rf}$  was considered one.

Table S1: - Quantum yield of 4 (neat) and with the addition of Zn(II) ions.

Entry	Quantum yield (\$)
Neat 4	0.059
4+Zn(II)	0.095

Table S2: - Compariso	on of the limit of detect	tion found in the present	work with the reported
values for some Zn(II)	chemosensors in some	e of the literature.	

S.No.	Sensor	Mechanism	LOD	References
		CLIEF		
1	1	CHEF	6.82 nM	This work
	2	CLIEF	1.64	2
2	2	CHEF	164 nM	2
3	3	ratiometric	72 nM	3

4	4	-	5.36µM	4
5	5	CHEF	0.027 nM	5
6	6	PET	49nM	6
7	7	-	30nM	7
8	8	Ratiometric	200nM	8
9	9	CHEF	236nM	9
10	10	PET	23.6nM	10
11	11	CHEF	37.13nM	11
12	12	CHEF	9.0 nM	12



**Figure S26:** - (a) DFT optimized structure of **4** having E conformation on one side and Z-conformation on the other side. (b) DFT optimized structure of **4** having Z- conformation on both sides. (c) DFT-optimized structure of **4**+Zn(II) complex.



**Figure S27:** - (a) Energy gap in the HOMO and LUMO of **4** in E conformation on one side and Z-conformation on the other side. (b) Energy gap in the HOMO and LUMO of **4** with both sides having Z- conformation.





Figure S28: - Energy gap in the HOMO and LUMO of 4 and 4+Zn(II).

**Figure S29:** - Proposed binding mode between **4** and Zn(II) ion highlighting the observed CHEF mechanism through restriction of the PET processes.

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