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## **Supporting Information**

## Lysosome-specific sensing and imaging of pH variations in vitro and in vivo utilizing a near-infrared boron complex

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#### **Part I. Experimental section**

**Information of general experiments:** All chemical reagents were obtained from commercial suppliers, and used without further purification. All solvents were of analytical grade. The <sup>1</sup>H NMR spectra were obtained on a Bruker Ultra Shield Plus 400 MHz NMR instrument using deuterated solvents, while chemical shifts were referenced against external Me<sub>4</sub>Si (<sup>1</sup>H) in units of ppm. Mass spectra were recorded on a Bruker autoflex matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometer. UV-Vis absorption spectra were performed on a UV-1700 Shimadzu UV-Vis spectrophotometer. Photoluminescence (PL) spectra were carried out on an Edinburgh FL 920 spectrophotometer. The methyl thiazolyltetrazolium (MTT) assay was performed by a Power Wave XS/XS2 microplate spectrophotometer, and cells were incubated in Roswell Park Memorial Institute (RPMI 1640). Fluorescence imaging of cells were conducted by an Olympus IX81 laser scanning confocal microscope. LR-MFJ-660/500mW and LR-MFJ-532/1W lasers were used for photostability experiments. Fluorescence imaging of mice was performed via the living animal luminescence imaging system (IVIS Lumina K Series III In Vivo Imaging, PerkinElmer).

**Sources of different ions, ROS and bioactive molecules:** All chemicals were procured from commercial sources unless otherwise specified. The solution of MgSO<sub>4</sub>, CaCl<sub>2</sub>, CuCl<sub>2</sub>, BaCl<sub>2</sub>, LiCl, MnCl<sub>2</sub>, AgNO<sub>3</sub>, KCl, FeCl<sub>3</sub>, ZnCl<sub>2</sub>, NaHS. Na<sub>2</sub>S, NaClO, NaNO<sub>3</sub>, Na<sub>2</sub>SO<sub>4</sub>, H<sub>2</sub>O<sub>2</sub>, GSH, Cys, Gly, Arg, Hcy and Lys were prepared in distilled water with a concentration of 10 mM, respectively.

**Cell culture:** Hela cells cells were purchased from the Shanghai Institute of Biological Science (SIBS) CAS, and they were supplemented with 10% fetal bovine serum in a humidified incubator (5% CO<sub>2</sub>) at 37 °C. The cytotoxicity of **HCy-BIZ-BF**<sub>2</sub> toward Hela cells was investigated by MTT assay (Beyotime). Growing in log phase, cells were seeded into a 96-well cell culture plate at  $1 \times 10^4$ /well. Subsequently, **HCy-BIZ-BF**<sub>2</sub> solution was added into the treatment groups at 0, 5, 10, 20, 30, and 50 µM. When cells were incubated under 5% CO<sub>2</sub> for 24 h, MTT in PBS (5 mg mL<sup>-1</sup>) was added to each well, incubating for another 4 h. After removing the culture solution, DMSO (200 µL) was added to each well, shaking for 10 min. Finally, the absorbance of the solution at 570 nm was measured.

**Intracellular pH calibration**: Hela cells were incubated with high K<sup>+</sup> buffer (30 mM NaCl, 120 mM KCl, 1 mM CaCl<sub>2</sub>, 0.5 mM MgSO<sub>4</sub>,1 mM NaH<sub>2</sub>PO<sub>4</sub>, 5 mM glucose, 20 mM HEPES, and 20 mM NaOAc) at different pH values (4.14-8.34) with the addition of 10.0  $\mu$ M of nigericin. After 30 min, cells were treated with **HCy-BIZ-BF**<sub>2</sub> (100 nM) for 15 min at 37 °C. Then, fluorescence images were collected by confocal microscope.

**Living cells imaging:** Hela cells were incubated in culture dishes until adherence, and then washed with PBS for three times. Cells were incubated with **HCy-BIZ-BF**<sub>2</sub> in serum-free RPMI 1640 under 5% CO<sub>2</sub> at 37 °C for 15 min, and washed by PBS in the culture dishes. Finally, fluorescence imaging was performed using a laser scanning confocal microscope with an excitation wavelength at 635 nm.**Mouse imaging:** Mouse experiments were carried out in accordance with the relevant laws and the guidelines of Institutional Animal Care and Use Committee. Nude mice (8-10 weeks) were purchased from Comparative Medicine Centre of Yangzhou University.

#### Synthesis work

All chemical reagents were procured from commercial sources, and used without further purification. All solvents used were of analytical grade, or further purified according to standard procedures.



Scheme S1. Synthetic routes of HCy-BIZ and HCy-BIZ-BF2.

**Synthesis of compound C1.** 2,3,3-Trimethylindolenine (478 mg, 3 mmol), iodoethane (515 mg, 3.3 mmol) and anhydrous acetonitrile (10 mL) were added into a flask (50 mL). Then the mixture was refluxed at 70 °C under nitrogen atmosphere for 15 h. The reaction was cooled

down to room temperature, and petroleum ether (20 mL) was added into the mixture, resulting in precipitation of pink solids. Finally, the pure Compound C1 (570 mg) was obtained after filtration as a pink solid. Yield: 60%. <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  (ppm): 8.00–7.91 (m, 1H), 7.89–7.77 (m, 1H), 7.66–7.56 (m, 2H), 4.47 (q, *J* = 7.3 Hz, 2H), 2.81 (s, 3H), 1.51 (s, 6H), 1.42 (t, *J* = 7.4 Hz, 3H).

Synthesis of compound C2 and C3. N,N-Dimethylformamide (DMF, 1.14 g, 13.1 mmol) and methylene chloride (3 mL) were added into a flask (100 mL), stirring at ice bath under nitrogen atmosphere for 10 min. Then hosphorus oxychloride (2 g 13.1 mmol) and methylene chloride (3 mL) was added dropwise via a syringe into the mixture. After 10 min, cyclohexanone (430 mg, 4.38 mmol) and methylene chloride (3 mL) was added into the system. After being refluxed at 50 °C for 3 h, the mixture was cooled to room temperature and poured slowly into water (pre-cooled to 0 °C), and placed overnight to obtain a yellow sediment. Finally, the product filtered as a yellow solid (615 mg). Yield: 80%. Compound C1 (315 mg, 1 mmol), Compound C2 (87.3 mg, 0.5 mmol) and potassium acetate (45 mg) were placed in a flask containing anhydrous acetic anhydride (15 mL), stirring at 100 °C under nitrogen atmosphere. After 2 h, the mixture was cooled to room temperature with green sediment. The green solid with metallic luster was filtered from the solution and compound C3 (288 mg) was obtained. Yield: 90%. <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  (ppm): 8.25 (d, *J* = 14.0 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.47–7.39 (m, 4H), 7.32–7.22 (m, 2H), 6.30 (d, *J* = 14.0 Hz, 2H), 4.23 (q, *J* = 7.2 Hz, 4H), 2.69 (t, *J* = 6 Hz, 4H), 1.88–1.79 (m, 2H), 1.68 (s, 12H), 1.29 (t, *J* = 7.2 Hz, 3H).

**Synthesis** of compound C4. 1,2-diaminobenzene (216)mg, 2.0mmol), 2,4-dihydroxybenzaldehyde (276 mg, 2.2 mmol) and sodium pyrosulfite (190 mg, 2.0 mmol) were added into a flask (50 mL) with 15 mL DMF. After stirring at 160 °C for 4 h, the mixture was cooled down to room temperature. Then, deionized water (50 mL) was added into the system, generating a yellow crude product. These crude products were then purified by silica gel flash chromatography using ethyl acetate/dichloromethane (2:1) as eluent to give the pure compound C5 as a yellow solid (295 mg). Yield: 65%. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  (ppm): 9.97 (s, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 6.4 Hz, 1H), 7.51 (d, J = 6.0 Hz, 1H), 7.21 (m, 2H), 6.42 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.38 (d, *J* = 2.4 Hz, 1H).

**Synthesis of compound HCy-BIZ.** Compound C5 (160 mg, 0.7 mmol) and triethylamine (70.7 mg, 0.7 mmol) were added into a flask with further addition of 5 mL DMF, stirring at room temperature under nitrogen atmosphere. After 10 min, compound C3 (150 mg, 0.23 mmol) in DMF (5 mL) was injected to the reaction via a syringe, and the mixture was stirring at 50 °C for 4 h. Cooled to room temperature, the mixture was poured into a separatory funnel with addition of dichloromethane (30 mL), and washed with deionized water (20 mL) for three times. After being dried with anhydrous sodium sulfate, the solid was obtained by removing the solvent under reduced pressure. The crude products were further purified by silica gel flash chromatography using dichloromethane/methyl alcohol (10: 1) as eluent to give compound **HCy-BIZ** as a dark blue solid (62 mg). Yield: 42%. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ (ppm): 8.43 (d, *J* = 14.4 Hz, 1H), 8.23 (s, 1H), 7.74–7.60 (m, 3H), 7.56–7.42 (m, 3H), 7.34–7.20 m, 3H), 6.64 (s, 1H), 6.34 (d, *J* = 14.4 Hz, 1H), 4.4–4.2 (m, 3H), 2.72 (s, 2H), 2.65 (s, 2H), 1.81 (t, *J* = 4.4 Hz, 2H), 1.69 (s, 6H), 1.31 (t, *J* = 6.8 Hz, 3H). MS (MALDI-TOF-MS) [m/z]: C<sub>34</sub>H<sub>32</sub>N<sub>3</sub>O<sub>2</sub><sup>+</sup> [M<sup>+</sup>]: 514.64. Found: 514.376.

Synthesis of compound HCy-BIZ-BF<sub>2</sub>. HCy-BIZ (100 mg, 0.16 mmol) was placed in a flask containing anhydrous tetrahydrofuran (5.0 mL). Boron fluoride ethyl ether (0.1 mL) and triethylamine (32.4 mg) were added into the flask. After stirring at 50 °C under nitrogen for 15 h, the solution was concentrated under reduced pressure. The resulting crude product was purified by silica gel flash chromatography using dichloromethane/methyl alcohol (10: 1) as eluent to give compound HCy-BTZ-BF<sub>2</sub> as a dark blue solid (55 mg). Yield: 52%. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 8.40 (s, 1H), 8.22 (d, *J* = 13.2 Hz, 1H), 7.77 (s, 1H), 7.62 (s, 2H), 7.52 (d, *J* = 6.4 Hz, 1H), 7.40–7.03 (m, 5H), 6.55 (s, 1H), 5.99 (d, *J* = 13.6 Hz, 1H), 4.03 (m, 2H), 3.58 (s, 2H), 2.75–2.50 (m, 4H), 1.85–1.70 (m, 3H), 1.67 (s, 6H). <sup>19</sup>F NMR (376.5 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): -(137.63–137.70) (m). MS (MALDI-TOF-MS) [m/z]: C<sub>34</sub>H<sub>31</sub>BF<sub>2</sub>N<sub>3</sub>O<sub>2</sub><sup>+</sup> [M<sup>+</sup>]: 562.44. Found: 562.346.

## Part II. Supplementary figures



**Fig. S1** (a) Absorption spectra of **HCy-BIZ-BF**<sub>2</sub>(10  $\mu$ M) in PBS with different pH values (1% DMSO). (b) Pictures of **HCy-BIZ-BF**<sub>2</sub> PBS with different pH values.



Fig. S2 Calculated molecular orbitals (a) and theoretical absorption spectra (b) of HCy-BIZ-BF<sub>2</sub>-H and HCy-BIZ-BF<sub>2</sub>.



Fig. S3 Fluorescent intensity of HCy-BIZ-BF<sub>2</sub> (10  $\mu$ M) with different ions, ROS and bioactive molecules.  $\lambda_{ex} = 635$  nm,  $\lambda_{em} = 740$  nm.



Fig. S4 Plot of pH versus  $\log[(F_{max}-F)/(F-F_{min})]$ , where F is the observed fluorescence intensity of HCy-BIZ-BF<sub>2</sub> at 740 nm excited by 635 nm. The y-intercept is the pKa value (5.03) of HCy-BIZ-BF<sub>2</sub>.



Fig. S5 MTT assay for HeLa cells treated with various concentrations of  $HCy-BIZ-BF_2$  from 0 to 50  $\mu$ M for 24 h.



**Fig. S6** Colocalization images of Hela cells incubated with **HCy-BIZ-BF**<sub>2</sub> (50 nM,  $\lambda_{ex} = 635$  nm,  $\lambda_{em} = 650-750$  nm) and commercial tracker of endoplasmic reticulum (100 nM,  $\lambda_{ex} = 488$  nm,  $\lambda_{em} = 500-550$  nm) and Golgi apparatus (5  $\mu$ M,  $\lambda_{ex} = 488$  nm,  $\lambda_{em} = 510-550$  nm). Scale bar: 20  $\mu$ m.



**Fig. S7** Representative confocal images for Hela cells incubated with **HCy-BIZ-BF**<sub>2</sub> (100 nM,  $\lambda_{ex} = 635$  nm,  $\lambda_{em} = 650-750$  nm) in Hep-G2 cells, MCF-7 cells and A549 cells, respectively. Scale bar = 20  $\mu$ m.

### Part III. Characterization







## MALDI-TOF mass spectra



#### Part IV. Comparation of HCy-BIZ-BF2 with reported lysosomal probes

#### Summarizing about reported NIR lysosomal probes:

Fluorescent probes in near-infrared (NIR) region have been widely applied in bioimaging and biosensing owing to reduced photo-damages towards biological samples, minimum background interferences from autofluorescence and increased depth of tissue penetration. Recent efforts have been focused on lysosomal pH sensing with NIR probes mainly based on platforms of hemicyanine (probe 1-3),<sup>1-3</sup> BODIPY (probe 4 and 5)<sup>4,5</sup> and rhodamine (probe 6-10).<sup>6-10</sup> We have summarized their properties and biological applications in Table S1.

Some of these NIR lysosomal probes were designed using intensity-based strategies with over tenfold increase in fluorescence intensity towards the changed pH values, such as probe **1**, **5**, **6** and **7**. Importantly, probe **5** was a novel BF<sub>2</sub>-chelated NIR probe possessing a lysosomal-induced off-to-on fluorescence response. On the basis of this optical property and beneficial form utilization of an epi-fluorescence live-cell microscope, probe **5** was successfully utilised in 3D and 4D real-time tracking of individual lysosome trafficking and efflux during a 35-minute period.



Fig. S8 The chemical structures of reported probe 1–10.<sup>1–10</sup>

Probe	λ <sub>em</sub> (nm)	λ <sub>abs</sub> (nm)	Sensitivity	pH range of linearity	p <i>K</i> a	Application
<b>1</b> <sup>1</sup>	655	420 (pH 7.1) 546 (pH 2.3)	40-fold increase of emission from pH 7.1 to 2.3	4.0–4.9	4.4	Concentration dependent fluorescence imaging in cells
<b>2</b> <sup>2</sup>	708 (pH 7.4) 670 (pH 4.0)	680 (pH 7.4) 650 (pH 4.0)	~20-fold increase of <i>F</i> <sub>708</sub> / <i>F</i> <sub>670</sub> from pH 4.0 to 7.4	4.0–6.0	5.0	Imaging lysosomal pH fluctuatiions under heat shock
<b>3</b> <sup>3</sup>	748 (pH 8.0) 672 (pH 4.0)	718 (pH 8.0) 608 (pH 4.0)	~16-fold increase of <i>F</i> <sub>748</sub> / <i>F</i> <sub>672</sub> from pH 3.0 to 9.0	6.5–7.8	7.2	Imaging lysosomal pH fluctuatiions under under oxidative stress and visualizing pH changes in an abdominal inflammation model
<b>4</b> <sup>4</sup>	665 (pH 6.83) 569 (pH 0.82)	605 (pH 6.83) 558 (pH 0.82)	100-fold increase of <i>F</i> <sub>515</sub> / <i>F</i> <sub>665</sub> from pH 6.83 to 0.82	-	2.0	Imaging abnormal acidic environment
5 <sup>5</sup>	707	685	off–on fluorescence from pH 7.0 to 5.0	-	4.0	3D and 4D real-time tracking of individual lysosome trafficking and efflux; in vivo tumor imaging in living mice
<b>6</b> <sup>6</sup>	743	720	71-fold increase of mission from pH 7.4 to 4.1	4.9–6.6	1.8	Labeling lysosomes
<b>7</b> <sup>7</sup>	740	390 (pH 8.0) 710 (pH 3.5)	80-fold increase of mission from pH 8.0 to 3.5	4.5-5.0	4.51	Imaging exogenous pH variations in cells incubated under different pH
<b>8</b> <sup>8</sup>	737 (pH 3.0) 510 (pH 7.4)	420 (pH 3.0) 510 (pH 7.4)	238-fold increase of <i>F</i> <sub>737</sub> / <i>F</i> <sub>510</sub> from pH 7.4 to3.0	-	4.9	Imaging exogenous pH variations in cells incubated under different pH
9 <sup>9</sup>	755 (pH 2.0) 528 (pH 7.0)	723 (pH 2.0) 380 (pH 7.0)	~10-fold increase of <i>F</i> <sub>737</sub> / <i>F</i> <sub>510</sub> from pH 7.4 to 2.0	-	4.2	Imaging exogenous pH variations in cells incubated under different pH
<b>10</b> <sup>10</sup>	483 (pH 3.19) 641 (pH 7.58)	325 (pH 3.19) 455,608 (pH 7.58)	131-fold increase of <i>F</i> <sub>641</sub> / <i>F</i> <sub>483</sub> from pH 7.58 to 3.19	-	4.8	Distinguishing different lysosomal pH values stimulated with various concentrations of chloroquine
HCy-BIZ-BF <sub>2</sub>	740 (pH 3.29) 743 (pH 9.07)	607 (pH 3.29) 668 (pH 9.07)	~4-fold increase of emission from pH 3.29 to 9.07	3.29-6.24	5.03	Imaging endogenous lysosomal pH variations sitmulated with chloroquine and perofrmance investiaging in living mice

Table S1 Comparison of reported probes listed in Fig. S8 with HCy-BIZ-BF2.

Compared with intensity-based method, ratiometric probe was expected to be more reliable because of its self-calibration with two emission bands, for example, probe 2–4 and 8–10. Most of these probes owned high ratiometric response to pH fluctuations and appropriate  $pK_a$  value to lysosomal pH detection. Specifically, probe 2 with a good linear ratiometric response in the pH range of 4–6, was successfully applied for investigating lysosomal pH in cells under heat shock, which revealed an irreversible rising process of pH in Hela cells (from 4.58 to 4.89) and MCF-7 cells (from 4.55 to 4.91) at varied temperature from 37 to 45 °C.

# Describing advantages and disadvantages of HCy-BIZ-BF<sub>2</sub> compared with the above probes:

Compared with these reported probes, our NIR probe  $HCy-BIZ-BF_2$  was designed based on  $BF_2$ -chelated hemicyanine derivatives. And a novel boron complex was synthesized with improved photostability since a rigid hexatomic ring could restrict the intramolecular rotations and vibrations. We also introduced the benzimidazole moiety into the hemicyanine skeleton to

enhance the  $\pi$ -conjugate system, which contributed to a longer emission wavelength (740 nm) than its original structure (720 nm).

In terms of the response sensitivity towards pH variations, though **HCy-BIZ-BF**<sub>2</sub> was a kind of intensity-based probe, it showed a good linear relationship of the fluorescence intensity versus pH values (3.29–6.24), which was wider than most reported probes. It also owned an appropriate  $pK_a$  (5.03), indicating that **HCy-BIZ-BF**<sub>2</sub> was capable of responding to slight pH changes in the region of 4.0–6.5, which offered guarantees for monitoring lysosomal pH under both normal and abnormal conditions.

When applied in living cells, not only could **HCy-BIZ-BF**<sub>2</sub> quickly enter and sufficiently permeate cells in a low concentration (100 nM), but it also tended to locate in lysosome. It shared a high Pearson's Correlation Coefficient (0.92) with a commercial lysosome tracker (DND-99), which indicated its lysosome-targeting ability as excellent as most reported probes. We predicted that the lysosome-targeting mechanism was owing to its unique electronic property. Before it was protonated with H<sup>+</sup>, the whole molecule of **HCy-BIZ-PF**<sub>2</sub> maintains electrical neutrality, and could easily move into lysosome with a lipophilic amine. Once it entered into lysosome, the amine moiety would be quickly protonated and the probe turned to be positively charged, and then trapped in lysosome.

Furthermore, the applications of **HCy-BIZ-PF**<sub>2</sub> in living cells were not limited in monitoring exogenous pH fluctuations. We obtained a pH standard curve through collecting the increased fluorescent intensities of **HCy-BIZ-PF**<sub>2</sub> in Hela cells incubated with nigericin at various pH values. Importantly, according to the pH standard curve, when **HCy-BIZ-PF**<sub>2</sub> was used for investigating endogenous pH variations, we found that there was an increased trend of lysosomal pH from 4.67 to 6.58 during a 30-minute incubation with chloroquine. Meanwhile, the similar phenomena were also observed in HepG-2 cells, MCF-7 cells and A549 cells stimulated by chloroquine. However, we could not achieve further experiments like probe **5** due to limits in experimental facilities. Besides, the performance of **HCy-BIZ-PF**<sub>2</sub> was also investigated in living mouse model. Its fluorescence response to various pH could be collected through the epidermis on the backs of mouse, which demonstrated the advantages of its emission in NIR region.

Overall, **HCy-BIZ-PF**<sub>2</sub> was a NIR probe with improved photostability, linear pH sensitivity as well as high lysosomal targetability, and could be successfully applied to real-time monitor pH variations in vitro and in vivo. Meanwhile, we also hope to improve its performance and solve some technical problems to realize biological applications related to some pathological processes (e.g., inflammation and cancer) within deeper biological tissues in the future.

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