Supporting Information

Photodynamic therapy by glucose transporter 1–selective light inactivation

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S1
1. Supporting Data

Table S1. Photophysical properties of compound 2-8

| Compound | $\lambda_{abs}$ (nm)[a] | $d$[b] | $\lambda_{em}$ (nm)[c] | $\Phi_f$[d] | $\Phi_\Delta$[d] |
|----------|-------------------------|-------|------------------------|------------|-------------|
| 2[e]     | 286                     | 82,000| 615                    | 6.1        | 0.57        |
|          | 451                     | 15,100|                        |            |             |
| 3[f]     | 337                     | 16,900| 551                    | <0.01      | 0.88        |
| 4        | 420                     | 2,000 | 468                    | 0.04[g]    | 0.52        |
| 5        | 510                     | 5,500 | 540                    | 0.70[b]    | 0.35        |
| 6        | 534                     | 15,800| 549                    | 0.15[i]    | 0.62        |
| 7        | 540                     | 16,900| 560                    | 0.03[i]    | 0.76        |
| 8        | 537                     | 12,300| 560                    | 0.03[i]    | 0.78        |

[a] These wavelengths were measured in the range 300 to 700 nm using a RF-6000 spectrofluorophotometer (Shimadzu corporation). [b] Absorption coefficient (L·mol⁻¹·cm⁻¹). [c] Fluorescence quantum yield ($\Phi_f$). The fluorescence quantum yield of each compound was measured with a RF-6000 spectrofluorophotometer (Shimadzu corporation). All fluorescence quantum yield were shown as relative quantum yield to the standard compound and calculated by equations (1):

$$\Phi_f = \Phi_{f,\text{std}} \cdot \left(\frac{A_{\text{std}}}{A_x}\right) \cdot \left(\frac{F_x}{F_{\text{std}}}\right) \cdot \left(\frac{n_x^2}{n_{\text{std}}^2}\right) \cdot \left(\frac{D_x}{D_{\text{std}}}\right) \cdots (1)$$

Std; standard compound, $x$; unknown sample, $A$; absorbance was obtained from absorption spectrophotometer analysis. F; area at half maximum of the corrected fluorescence spectrum peak, n; solvent refractive index, D; dilution ratio of the sample for the fluorescence spectrum measurement relative to the concentration at the time of visible spectrum measurement. [d] Singlet oxygen generation ability ($\Phi_\Delta$). Tetraphenylcyclopentadiene (TPCPD, $\lambda_{abs} = 495$ nm)[1] were used as a singlet oxygen indicator. 200 $\mu$M of the singlet oxygen indicator was mixed with each compound in CH$_2$CN, and then the solution was irradiated at the maximum absorption wavelength light in a quartz cell with an optical path length of 1 cm. The excitation light was generated with LED light (RELYON, 455 or 540 nm), and the intensity of the light source at each wavelength was measured. Finally, the absorption at 410 nm of DPBF or 495 nm of TPCPD was measured. The singlet oxygen production quantum yields ($\Phi_\Delta$) of the compounds were calculated by equation (2)[2]:

$$\Phi_\Delta = \Phi_{\Delta,\text{std}} \cdot \left(\frac{m \cdot F_{\text{std}} \cdot n_{\text{std}}}{m_{\text{std}} \cdot F \cdot n}\right) \cdots (2)$$

Std; standard compound, m; slope of the absorption decrease traces at 410 or 495 nm, F; absorption correction factors: F = 1-10$^{-A_{abs}}$ (Abs: Absorbance at the irradiation wavelength), n; relative photon numbers obtained by measurement of the light power. Benzophenone ($\Phi_{\Delta,\text{std}} = 0.3720$) was selected as the standard[3],[e] These values were previously reported[4,5],[i] The fluorescence quantum yield was previously reported[6],[g] Acriflavine ($\Phi_{f,\text{std}} = 0.81$ in H$_2$O) was selected as the standard[7]. [b] Fluorescein ($\Phi_{f,\text{std}} = 0.73$ in HEPES buffer (pH = 7.4)) was selected as the standard[8]. [i] Rhodamine 6G ($\Phi_{f,\text{std}} = 0.90$ in H$_2$O) was selected as the standard[9].
Figure S1. Absorption and fluorescence spectra of compounds 3-7.
Figure S2. Singlet oxygen generation ability ($\Phi_\Delta$) of compounds 3-7: absorbance decreases of tetraphenylcyclopentadienone (TPCPD).
Figure S3. Singlet oxygen generation assay of the compounds. The compounds (10 μM) were dissolved in EtOH/H₂O (1/1) solution containing 50 μM of 1,3-diphenylisobenzofuran (DPBF), followed by light irradiation (540 nm) for indicated times. DPBF reacts with singlet oxygen to generate its oxidizing products which lose the absorbance at 410 nm. The singlet oxygen generation can be estimated by detecting the absorbance of the unreacted DPBF at 410 nm using a microplate reader\textsuperscript{[10]}. Relative absorbance of DPBF was expressed by comparison with the absorbance obtained from one treated with the compounds without light irradiation.
Figure S4. Evaluation of anti-tumor activity of I\textsubscript{2}BODIPY FL propionic acid (27). Cells were cultured in a 96-well plate and treated with the compound 27 of indicated concentrations for 1 h. The cells were washed with PBS, followed by light irradiation at 540 nm. After 72 h incubation in DMEM, 0.5 mg/mL MTT was added and incubated for 4 h at 37°C. The medium was removed, and the MTT formazan product was dissolved in DMSO. The amount of the product was determined by measuring its absorbance at 570 nm using a microplate reader. The experiments were carried out in triplicate.

Figure S5. Cellular uptake of the compounds in HeLa, A549, and HepG2 cells. (A) The cells were incubated with 10 μM of Lg(GLUT1)-PS (8) for 1 h, followed by 0.5 μg/mL of Hoechst 33342 for 10 min. The fluorescent signals were observed with a confocal microscope using Alexa fluor 488 filter set. Scale bars; 100 μm. (B) The cells were incubated with 10 μM of talaporfin sodium for 1 h, followed by 0.5 μg/mL of Hoechst 33342 for 10 min. The fluorescent signals were observed with a confocal microscope using Cy5 filter set. Scale bars; 100 μm.
Figure S6. Evaluation of bioactivity of talaporfin sodium in cancer cells. (A) Structure of talaporfin sodium. 
(B) Evaluation of anti-tumor activity of talaporfin sodium. Cells were cultured in a 96-well plate and treated with the talaporfin sodium of indicated concentrations for 1 h. The cells were washed with phosphate-buffered saline (PBS), followed by light irradiation (660 nm). After 72 h culture in DMEM, 0.5 mg/mL thiazolyl blue tetrazolium bromide (MTT) was added and incubated for 4 h at 37°C. The medium was removed, and the MTT formazan product was dissolved by dimethyl sulfoxide (DMSO). The amount of these product was determined by measuring absorbance at 570 nm using a microplate reader. (C) Evaluation of protein light irradiation dependent knockdown ability of talaporfin sodium. Cells were treated with or without 10 μM of talaporfin sodium for 1 h and washed with PBS, followed by light irradiation (660 nm) for 15 min (Lane 2 and 4) or 30 min (Lane 6). The cells were lysed at 4°C with sonication, and then the sample was electrophoresed on SDS-polyacrylamide gel, and transferred to polyvinylidene difluoride membranes. These obtained samples were immunoblotted with anti-GLUT1, anti-α-tubulin, and anti-PCNA antibodies.
2. Synthetic protocols for ligand-conjugated photosensitizers 3–8

2.1 General Information

NMR spectra were recorded on a Bruker biospin AVANCE III (500 MHz for \(^1\)H, 125 MHz for \(^{13}\)C) instrument in the solvent indicated for each compound in the sections that follow. Chemical shifts are reported in parts per million (ppm) relative to the resonance signal (0.00 ppm) of the internal standard, tetramethylsilane. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet; br, broad; \(J\), coupling constants in Hertz. High-resolution mass spectra (HRMS) were recorded on a Bruker electrospray ionization (ESI)–time of flight (TOF)–mass spectrometer (micrOTOF II). Analytical thin-layer chromatography was performed on a glass plate of silica gel 60 GF254 (Merck). Silica gel (Fuji Silysa, CHROMATOREX PSQ 60B, 50–200 μm) was used for column chromatography. Gel permeation chromatography (GPC) experiments were conducted for sample purification purposes on a Japan Analytical Industry Model LC-9225 NEXT (recycling preparative high-performance liquid chromatography) and a Japan Analytical Industry Model UV-600 NEXT ultraviolet detector with a polystyrene gel column (JAIGEL-1H, 20 mm x 600 mm), using chloroform as solvent (flow rate: 3.5 mL/min). Preparative high-performance liquid chromatography was performed with LC-forte/R (YMC) using a C18 reverse phase column (Kanto, Mightysil RP-18 250 × 20 mm, 5 μm). All chemicals and reagents for biological experiments were obtained from commercial sources and used without further purification.

2.2 Synthetic scheme of carbonic anhydrase II (CAII) ligand moiety (11)

**Scheme S1. Synthesis of carbonic anhydrase II (CAII) ligand moiety (11).**

**Synthesis of 2,5-dioxopyrrolidin-1-yl 4-sulfamoylbenzoate (9).** To a solution of 4-sulfamoylbenzoic acid (2.01 g, 10 mmol) in 15 mL of DMF at room temperature, \(N\)-hydroxysuccinimide (NHS; 1.73 g, 15 mmol) was added. The reaction mixture was stirred for 15 mins, then 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl; 2.3 g, 12 mmol) was added. The reaction mixture was further stirred for 5 h at room temperature, TLC was used to monitor the reaction process. After completion, the compound was extracted by ethyl acetate (AcOEt), washed by ice water, and sat. NaHCO\(_3\) aq. for three times. The organic layer was dried over Na\(_2\)SO\(_4\), filtered and concentrated in vacuo. The white solid crude product was used in the next reaction directly without further purification (2.1 g, 7.02 mmol, 70%). \(^1\)H-NMR (400 MHz, DMSO-\(d_6\)): δ 8.30 (2H, d, \(J = 8.7\) Hz), 8.08 (2H, d, \(J = 8.7\) Hz), 7.71 (2H, s), 2.93 (4H, s). \(^{13}\)C-NMR (125 MHz, DMSO-\(d_6\)) δ 170.58 (x2), 161.47, 150.32, 131.37 (x2), 127.68 (x2), 127.16, 26.04 (x2); HRMS (ESI, Positive): m/z calced. for C\(_{11}\)H\(_{10}\)N\(_3\)O\(_6\)S, [M+Na\(^+\)]:321.0152, found: 321.0151.

**Synthesis of N-(6-azidohexyl)-4-sulfamoylbenzamide (10).** To a solution of compound 9 (254 mg, 0.85 mmol)
in 5 mL of DMF at room temperature, 6-azidohexan-1-amine (121 mg, 0.85 mmol) and triethylamine (Et3N; 0.14 mL, 1.02 mmol) was added. The reaction mixture was stirred for 4 h, TLC was used to monitor the reaction process. After completion, the compound was extracted by AcOEt, washed by ice water, 1 M HCl aq. and sat. NaHCO₃ aq. for three times. The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography with hexane : AcOEt = 1 : 1 to afford compound 10 as white solid (179 mg, 0.52 mmol, 61%). ¹H-NMR (DMSO-d₆, 400 MHz): δ 8.64 (1H, t, J = 6.0 Hz), 7.96 (1H, d, J = 8.1 Hz), 7.88 (2H, d, J = 8.8 Hz), 7.48 (2H, s), 3.33-3.22 (4H, m), 1.54 (4H, t, J = 7.0 Hz), 1.33 (4H, t, J = 4.1 Hz); ¹³C-NMR (125 MHz, DMSO-d₆) δ 165.55, 146.58, 138.07, 128.23, 126.04, 51.08, 29.31, 28.65, 26.45 (x2), 26.35; HRMS (ESI, Positive): m/z calced. for C₁₃H₁₉N₃O₅S, [M+Na]⁺: 348.1101, found: 348.1109.

Synthesis of N-(6-aminohexyl)-4-sulfamoylbenzamide (11). To a solution of compound 10 (39 mg, 0.11 mmol) in 2 mL of MeOH at room temperature, Pd/C (1.5 mg) was added under argon condition. The reaction mixture was stirred for 10 min, then argon condition was exchanged to H₂ atmosphere. The reaction was further stirred for 2 h, TLC was used to monitor the reaction process. After completion, the reaction mixture was filtered with celite and concentrated in vacuo to afford compound 11 as white solid (63 mg, 0.2 mmol, 95%). ¹H-NMR (DMSO-d₆, 400 MHz): δ 8.63 (1H, s), 7.97 (2H, d, J = 8.4 Hz), 7.89 (2H, d, J = 8.4 Hz), 6.37 (2H, d, J = 36.9 Hz), 3.26 (2H, s), 2.93 (2H, s), 1.52 (10H, t, J = 7.2 Hz), 1.44-1.24 (10H, m). ¹³C-NMR (125 MHz, DMSO-d₆) δ 165.68, 146.59, 138.06, 128.18 (x2), 126.03 (x2), 41.83, 33.31, 29.44, 26.83 (x2), 26.57; HRMS (ESI, Positive): m/z calced. for C₁₃H₂₁N₃O₅S, [M+Na]⁺: 322.1196, found: 322.1192.

2.3 Synthetic scheme of CAII ligand-conjugated 4-nitro biphenyl (3).

Scheme S.2. Synthesis of CAII ligand-conjugated 4-nitro biphenyl (3).

Synthesis of 4-((6-azidohexyl)oxy)-4'-nitro-1,1'-biphenyl (14). To a solution of 1,6-dibromohexane (800 mg, 3.28 mmol) in 5 mL of DMF at room temperature, NaN₃ (235 mg, 3.61 mmol) was added. The reaction was stirred for 10 min, then heated at 50°C for overnight. TLC was used to monitor the reaction process. After completion of the reaction, the reaction mixture was cooled to room temperature and concentrated in vacuo to afford compound 12 as yellow liquid. Next, to a solution of compound 12 (924 mg, 4.48 mmol) in 5 mL of DMF at room temperature, K₂CO₃ (680 mg, 4.93 mmol) and 4'-nitro-[1,1'-biphenyl]-4-ol [⁷] (compound 13;
1058 mg, 4.92 mmol) was added. The reaction mixture was stirred for 10 min, then heated at 80°C for overnight. TLC was used to monitor the reaction process. After completion, the compound was extracted by AcOEt, washed by sat. NaHCO₃ aq. The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography with hexane : AcOEt = 7 : 3 to afford compound 14 as yellow solid. (581 mg, 1.71 mmol, 52%). 1H NMR (CDCl₃, 400 MHz): δ 8.26 (2H, d, J = 9.0 Hz), 7.68 (2H, d, J = 8.0 Hz), 7.57 (2H, d, J = 8.7 Hz), 7.01 (2H, d, J = 8.9 Hz), 4.03 (2H, t, J = 6.4 Hz), 1.90-1.78 (2H, m), 1.73-1.62 (2H, m), 1.58-1.45 (4H, m).; 13C NMR (125 MHz, CDCl₃) δ 159.98, 147.23, 146.52, 130.89, 128.53 (x2), 126.99 (x2), 124.11 (x2), 115.16 (x2), 67.95, 51.39, 29.08, 28.80, 25.50, 25.69; HRMS (ESI, Positive): m/z calced. for C₁₈H₂₂N₄O₃, [M+Na]⁺: 363.1428, found: 363.1418.

**Synthesis of 6-((4'-nitro-[1,1'-biphenyl]-4-yl)oxy)hexan-1-amine (15).** To a solution of compound 14 (85.8 mg, 0.25 mmol) in 1 mL of THF at room temperature, triphenylphosphine (99.2 mg, 0.38 mmol) and HCl aq. (pH=5-6) were added. The reaction was stirred overnight. TLC was used to monitor the reaction process. After completion of the reaction, the compound was extracted by AcOEt, washed by sat. NaHCO₃ aq. and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo to give 15 as a white solid, which was used in the next reaction directly without further purification (40.4 mg, ca. 0.13 mmol). Synthesis of compound 3 from 15 is described in Method of the manuscript.

### 2.4 Synthetic scheme of CAII ligand-conjugated coumarin (4)

Ethyl 7-(diethlamino)-2-oxo-2H-chromene-3-carboxylate (16), 7-(diethlamino)-2-oxo-2H-chromene-3-carboxylic acid (17) were synthesized according to previously reported procedure[11].

![Scheme S3. Synthesis of CAII ligand-conjugated coumarin (4).](image)

**Synthesis of 7-(diethlamino)-6-iodo-2-oxo-2H-chromene-3-carboxylic acid (18).** Compound 17 (266.7 mg, 1.02 mmol) was added to 5 mL of 1 M NaOH aq., the reaction mixture was stirred for 10 min at room temperature. Next, I₂ (142.1 mg, 1.12 mmol) was added to the reaction mixture. The reaction mixture was further stirred at room temperature for 1 h and neutralized with a 6 M HCl aq. to a pH value of approximately 7. Subsequently, the compound was extracted by AcOEt, washed by Na₂S₂O₃ aq. The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel column...
chromatography with CH₂Cl₂ : MeOH = 20 : 1 to afford compound 18 as a yellow solid. (30.1 mg, 0.078 mmol, 7%).

¹H NMR (CDCl₃, 400 MHz): δ 12.15 (1H, s), 8.73 (1H, s), 8.17 (1H, s), 6.95 (1H, s), 3.33 (4H, q, J = 7.0 Hz), 1.16 (6H, t, J = 7.1 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 165.51, 164.41, 158.05, 153.79, 150.23, 131.93, 110.93, 108.57, 105.63, 96.86, 45.33 (x2), 12.38 (x2); HRMS (ESI, Positive): m/z calced. for C₁₄H₁₄INO₄, [M+Na⁺]: 409.9860, found: 409.9854.

Synthesis of CAII ligand-conjugated coumarin (4). Synthesis of compound 4 from 1 is described in Method of the manuscript.

2.5 Synthetic scheme of CAII ligand-conjugated BODIPY (5)

Methyl(triphenylphosphoranylidene)acetate (19), (E)-Methyl 3-(1H-pyrrol-2-yl)acrylate (20), and methyl 3-(1H-pyrrol-2-yl)propanoate (21) were synthesized according to previously reported procedure.

Scheme S4. Synthesis of CAII ligand-conjugated BODIPY (5).

Synthesis of (methyl 3-[(2-[(3,5-dimethyl-1H-pyrrol-2-yl-N)methylidene]-2H-pyrrol-5-yl-κN)propanoatato](difluoro)boron (22). Compound 21 (607 mg, 3.96 mmol) was dissolved in 30 mL of CH₂Cl₂ under argon condition, and then 3,5-dimethyl-1H-pyrrole-2-carbaldehyde was added to the ice-cooled solution. Next, POCl₃ (368 μL, 3.96 mmol) was dissolved in 5 mL of CH₂Cl₂ and added to the reaction mixture drop by drop. The reaction mixture was warmed from on-ice condition to room temperature and stirred for 5 h. TLC was used to monitor the reaction process. After completion of the reaction, BF₃·OEt₂ (2.02 mL, 15.84 mmol) and DIEA (6.4 g, 49.5 mmol) was added to the reaction mixture and stirred for overnight. After completion of the reaction, the reaction mixture was poured into CH₂Cl₂, and the organic layer was washed with ice water, 1 M HCl aq., and brine. The obtained organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography with hexane : AcOEt = 4 : 1 to afford compound 22 as brown solid with green fluorescence (614 mg, 2.01 mmol, 51%). ¹H-NMR (400 MHz,
CDCl₃ δ 7.05 (s, 1H), 6.84 (d, 1H, J=3.9 Hz), 6.23 (d, 1H, J=3.9 Hz), 6.07 (s, 1H), 3.68 (s, 3H), 3.28 (t, 2H, J=7.6 Hz), 2.75 (t, 2H, J=15.3 Hz), 2.54 (s, 3H), 2.20 (s, 3H); ¹³C-NMR (125 MHz, CDCl₃) δ 172.92, 156.91, 143.91, 135.25, 133.36, 128.08, 123.82, 120.43, 116.63, 116.51, 51.62, 33.25, 23.92, 14.81, 11.24. HRMS (ESI, Positive): m/z calcd. for C₁₅H₁₇BF₂N₂O₂. [M+Na]+: 329.1243, found: 329.1246.

Synthesis of BODIPY FL propionic acid (23). To a solution of compound 21 (310 mg, 1.01 mmol) in 45 mL THF at 0°C, 52 mL of 6 N HCl aq. was added drop by drop. Then, the reaction mixture was warmed up to room temperature and stirred for 24 h. TLC was used to monitor the reaction process. After completion of the reaction, the reaction mixture was poured into CH₂Cl₂, and the organic layer was washed with water and sat. NaHCO₃ aq. for three times. The obtained organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography with CH₂Cl₂:MeOH = 100:1 to afford compound 23 as brown solid (78.9 mg, 0.27 mmol, 26%). ¹H-NMR (MeOD, 400 MHz): δ 7.42 (1H, s), 7.02 (1H, d, J = 4.4 Hz), 7.02 (1H, d, J = 4.3 Hz), 6.35 (1H, d, J = 3.9 Hz), 6.22 (1H, s), 5.49 (7H, s), 3.23 (2H, t, J = 8.0 Hz), 2.74 (2H, t, J = 7.6 Hz), 2.53 (3H, t), 2.30 (3H, s); ¹³C-NMR (125 MHz, DMSO-d₆) δ 173.85, 159.94, 157.42, 144.77, 135.05, 133.48, 129.26, 125.88, 120.85, 117.00, 32.84, 24.01, 14.97, 11.44. HRMS (ESI, Positive): m/z calcd. for C₁₄H₁₅BF₂N₂O₂. [M+Na]+: 315.1089, found: 315.1098.

Synthesis of CAII ligand-conjugated BODIPY (5). Synthesis of compound 5 from 23 is described in Method of the manuscript.

2.6 Synthetic scheme of CAII ligand-conjugated di-brominated BODIPY (6)

Scheme S5. Synthesis of CAII ligand-conjugated di-brominated BODIPY (6).

Synthesis of (methyl 3-bromo-5-{2-[(4-bromo-3,5-dimethyl-1H-pyrrol-2-yl-κN)methylidene]-2H-pyrrol-5-yl-κN}propanoato)(difluoro)boron (24). To a solution of compound 22 (343 mg, 1.12 mmol) in 20 mL of CH₂Cl₂, N-bromosuccinimide (NBS; 598 mg, 3.36 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 24 h, TLC was used to monitor the reaction process. After
completion of the reaction, the reaction mixture was washed with water, sat. NaHCO₃ aq., and brine. The obtained organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography with hexane:AcOEt = 4 : 1 to afford compound 24 as brown solid (462.3 mg, 0.95 mmol, 85%).¹H-NMR (CDCl₃, 400 MHz): δ 7.07 (1H, s), 6.96 (1H, s), 3.72 (3H, s), 3.26 (2H, t, J = 8.4 Hz), 2.73 (2H, t, J = 8.3 Hz), 1.54 (6H, s).¹³C-NMR (DMSO-d₆) δ 172.04, 158.51, 153.19, 143.23, 133.72, 132.44, 129.68, 126.88, 111.03, 106.10, 52.15, 32.61, 22.94, 14.05, 11.36. HRMS (ESI, Positive): m/z calced. for C₁₅H₁₅BF₂Br₂N₂O₂. [M+Na]+: 486.9436, found: 486.9449.

Synthesis of (methyl 3-bromo-5-[(2-[(4-bromo-3,5-dimethyl-1H-pyrrol-2-yl-κN)methylidene]-2H-pyrrol-5-yl-κN)](difluoro)boron propanoic acid (25). To a solution of compound 24 (57 mg, 0.12 mmol) in 6 mL of THF at 0°C, 7 mL of 6 N HCl aq. was added to the solution drop by drop. The reaction mixture was warmed up to room temperature and stirred for 24 h. TLC was used to monitor the reaction process. After completion of the reaction, the reaction mixture was poured into CH₂Cl₂, and the organic layer was washed with water, sat. NaHCO₃ aq., and brine. The obtained organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The crude was purified by silica gel column chromatography with hexane:AcOEt = 7 : 3 to afford compound 25 as red solid (43.1 mg, 0.09 mmol, 78%).¹H-NMR (MeOD, 500 MHz): δ 7.59 (1H, s), 7.18 (1H, s), 4.60 (1H, s), 3.20 (2H, t, J = 8.5 Hz), 2.65 (2H, t, J = 8.7 Hz), 2.59 (3H, s), 2.29 (3H, s);¹³C-NMR (DMSO-d₆) δ 179.73, 160.31, 152.82, 144.453, 134.39, 130.59, 124.02, 119.35, 112.17, 108.77, 32.719, 23.65, 14.28, 11.55; HRMS (ESI, Positive): m/z calced. for C₁₄H₁₃BF₂Br₂N₂O₂. [M+Na]+: 473.9405, found: 473.9411.

Synthesis of CAII ligand-conjugated di-brominated BODIPY (6). Synthesis of compound 6 from 25 is described in Method of the manuscript.

2.7 Synthetic scheme of CAII ligand-conjugated di-iodinated BODIPY (7)

Scheme S6. Synthesis of CAII ligand-conjugated di-iodinated BODIPY (7).
Synthesis of (methyl 3-iodo-5-[(4-iodo-3,5-dimethyl-1H-pyrrolo-2-yl-κN)methylidene]-2H-pyrrolo-5-yl-κN]propanamidato)(difluoroboron) (26). To a solution of compound 22 (500 mg, 1.63 mmol) in 30 mL of CH2Cl2, N-iodosuccinimide (NIS; 1.47 g, 6.53 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 24 h, TLC was used to monitor the reaction process. After completion of the reaction, the reaction mixture was washed with water, sat. NaHCO3 aq., and brine. The obtained organic layer was dried over Na2SO4, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography with hexane : AcOEt = 4 : 1 to afford compound 26 as dark red solid (554 mg, 0.99 mmol, 61%). 1H-NMR (400 MHz, CDCl3) δ 7.04 (s, 2H), 3.72 (s, 3H), 3.26 (t, 2H, J=8.30 Hz), 2.65 (s, 3H), 2.18(s, 3H); 13C-NMR (125 MHz, CDCl3) δ 172.30, 161.62, 157.01, 147.17 134.72, 134.61, 134.17, 123.03, 84.12, 74.63, 51.84, 32.87, 24.58, 16.04, 13.82. HRMS (ESI, Positive): m/z calced. for C13H15BF3I2N2O2 [M+Na]+ : 580.9176, found: 580.9179.

Synthesis of (methyl 3-iodo-5-[(2-[(4-iodo-3,5-dimethyl-1H-pyrrolo-2-yl-κN)methylidene]-2H-pyrrolo-5-yl-κN])propanoic acid (27). To a solution of compound 26 (364 mg, 0.358 mmol) in 15 mL of THF at 0°C, 12 mL of 6 N HCl aq. was added to the solution drop by drop. The reaction mixture was warmed up to room temperature and stirred for 24 h. TLC was used to monitor the reaction process. After completion of the reaction, the reaction mixture was poured into CH2Cl2, and the organic layer was washed with water, sat. NaHCO3 aq., and brine. The obtained organic layer was dried over Na2SO4, filtered and concentrated in vacuo. The crude was purified by silica gel column chromatography with hexane : AcOEt = 7 : 3 to afford compound 27 as dark red solid (144 mg, 0.26 mmol, 74%). 1H-NMR (400 MHz, MeOD) δ 7.11 (s, 1H), 3.72 (t, 3H, J=6.63 Hz), 3.59 (t, 3Hm J=6.55 Hz), 2.65 (s, 1H), 2.28 (s, 1H), 1.71 (m, 2H, J=8.30 Hz), 1.90 (m, 2H, J=8.05 Hz); 13C-NMR (125 MHz, MeOD) δ 173.20, 160.89, 156.72, 148.01, 135.75, 134.63, 134.58, 125.54, 85.52, 76.35, 33.11, 24.72, 16.23, 14.06. HRMS (ESI, Positive): m/z calced. for C14H14BF3I2N2O2 [M+Na]+ : 566.9020, found: 566.9022.

Synthesis of CAII ligand-conjugated di-iodinated BODIPY (7). Synthesis of compound 7 from 27 is described in Method of the manuscript.

2.8 Synthetic scheme of glucose-conjugated di-iodinated BODIPY (8)

Scheme S7. Synthesis of glucose-conjugated di-iodinated BODIPY (8).

Synthesis of (propargyl 3-iodo-5-[(4-iodo-3,5-dimethyl-1H-pyrrolo-2-yl-κN)methylidene]-2H-pyrrolo-5-yl-κN]propanamidato)(difluoroboron) (28). To a solution of compound 27 (241 mg, 0.43 mmol) in 5 mL of DMF, EDCI-HCl (88.6 mg, 0.52 mmol) and HOBT·H2O (118.5 mg, 0.77 mmol) was added to the solution.
After stirring at room temperature for 10 min, propargyl amine (28 mg, 0.52 mmol) was added to the reaction mixture. The reaction mixture was further stirred for 24 h. TLC was used to monitor the reaction progress. After completion of the reaction, the reaction mixture was poured into AcOEt. The organic layer was washed with ice water, sat. NH₄Cl aq., sat. NaHCO₃ aq., and brine. The obtained organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography with hexane : AcOEt = 1 : 1 to afford compound 28 as dark red solid (107 mg, 0.18 mmol, 43%). ¹H-NMR (DMSO-d₆, 400 MHz): δ 8.40 (1H, t, J = 5.4 Hz), 7.82 (1H, s), 7.41 (1H, s), 3.88 (2H, q, J = 2.7 Hz), 3.09 (1H, t, J = 2.4 Hz), 3.01 (2H, t, J = 8.8 Hz), 2.39 (2H, t, J = 8.5 Hz), 2.22 (3H, s); ¹³C-NMR (125 MHz, DMSO-d₆) δ 170.34, 163.04, 160.79, 157.65, 148.05, 135.95, 134.60, 125.62, 85.37, 81.62, 73.41, 55.38, 33.90, 28.41, 24.72, 16.15, 14.00. HRMS (ESI, Positive): m/z calced. for C₁₇H₁₆BF₂I₂N₃O. [M+Na]⁺: 603.9337, found: 603.9339.

Synthesis of glucose-conjugated di-iodinated BODIPY (8). Synthesis of compound 8 from 28 is described in Method of the manuscript.
3. $^1$H and $^{13}$C NMR spectra of the compounds

$^1$H NMR (400 MHz, DMSO)

$^{13}$C NMR (125 MHz, DMSO)

Figure S7. $^1$H and $^{13}$C NMR spectra of the compound 9.
Figure S8. $^1$H and $^{13}$C NMR spectra of the compound 10.
Figure S9. $^1$H and $^{13}$C NMR spectra of the compound 11.
Figure S10. $^1$H and $^{13}$C NMR spectra of the compound 14.
Figure S11. $^1$H and $^{13}$C NMR spectra of the compound 3.
Figure S12. $^1$H and $^{13}$C NMR spectra of the compound 18.
Figure S13. $^1$H and $^{13}$C NMR spectra of the compound 4.
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)

Figure S14. $^1$H and $^{13}$C NMR spectra of the compound 22.
$^{1} \text{H NMR (400 MHz, MeOD)}$

$^{13} \text{C NMR (125 MHz, DMSO)}$

Figure S15. $^{1} \text{H}$ and $^{13} \text{C}$ NMR spectra of the compound 23.
$\textbf{1}^H$ NMR (400 MHz, DMSO)

$\textbf{1}^C$ NMR (125 MHz, DMSO)

Figure S16. $\textbf{1}^H$ and $\textbf{1}^C$ NMR spectra of the compound 5.
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, DMSO)

Figure S17. $^1$H and $^{13}$C NMR spectra of the compound 24.
Figure S18. $^1$H and $^{13}$C NMR spectra of the compound 25.
$^1$H NMR (400 MHz, DMSO)

$^{13}$C NMR (125 MHz, DMSO)

Figure S19. $^1$H and $^{13}$C NMR spectra of the compound 6.
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)

Figure S20. $^1$H and $^{13}$C NMR spectra of the compound 26.
$^1$H NMR (400 MHz, MeOD)

![$^1$H NMR spectrum of compound 27]

$^{13}$C NMR (125 MHz, MeOD)

![$^{13}$C NMR spectrum of compound 27]

Figure S21. $^1$H and $^{13}$C NMR spectra of the compound 27.
Figure S22. $^1$H and $^{13}$C NMR spectra of the compound 7.
**Figure S23.** $^1$H and $^{13}$C NMR spectra of the compound 28.
Figure S24. $^1$H and $^{13}$C NMR spectra of the compound 8.
4. Compound purity data

CAII ligand-conjugated 4-nitrobiphenyl (3)

| Peak          | Height | Area | Purity     |
|---------------|--------|------|------------|
| 1 (Unknown)   | 0.98%  | 0.35%| 0.35%      |
| 2 (Compound)  | 99.02% | 99.65%| 99.65%     |

![Figure S25. HPLC analysis of the compound 8.](image1)

CAII ligand-conjugated coumarin (4)

| Peak          | Height | Area | Purity     |
|---------------|--------|------|------------|
| 1 (Unknown)   | 0.54%  | 0.51%| 0.51%      |
| 2 (Compound)  | 99.45% | 99.49%| 99.49%     |

![Figure S26. HPLC analysis of the compound 4.](image2)
CAII ligand-conjugated BODIPY (5)

| Peak       | Height | Area | Purity |
|------------|--------|------|--------|
| 1 (Unknown)| 3.610% | 2.60%| 2.60%  |
| 2 (Compound)| 96.40% | 97.40%| 97.40% |

Figure S27. HPLC analysis of the compound 5.

CAII ligand-conjugated di-brominated BODIPY (6)

| Peak       | Height | Area | Purity |
|------------|--------|------|--------|
| 1 (Unknown)| 11.44% | 5.67%| 5.67%  |
| 2 (Compound)| 88.56% | 94.33%| 94.33% |

Figure S28. HPLC analysis of the compound 6.
CAII ligand-conjugated di-iodinated BODIPY (7)

| Peak     | Height | Area  | Purity  |
|----------|--------|-------|---------|
| 1 (Unknown) | 0.80%  | 0.66% | 0.66%   |
| 2 (Unknown) | 0.94%  | 0.63% | 0.63%   |
| 3 (Compound) | 98.30% | 98.70%| 98.70%  |

Figure S29. HPLC analysis of the compound 7.

Glucose-conjugated di-iodinated BODIPY (8)

| Peak     | Height | Area  | Purity  |
|----------|--------|-------|---------|
| 1 (Compound) | 97.99% | 97.14%| 97.99%  |
| 2 (Unknown) | 2.02%  | 2.86% | 2.02%   |

Figure S30. HPLC analysis of the compound 8.
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