Development of a switching-type fluorescence sensor for the detection of boronic acid-containing agents

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Abstract
Since the therapeutic effect of boron neutron capture therapy is influenced by the intracellular distribution profile of boronoagents containing $^{10}\text{B}$ atoms, it is necessary to establish a method that can determine the intracellular distribution profile of boronoagents. We aimed to develop a small molecule-based fluorescence sensor that changes its fluorescence properties upon complexation with the boronic acid moiety of a boronoagent. Thus, we designed a 2-(2-pyridyl)phenol derivative PPN-1 by introducing a N,O ligand substructure into a zinc sensor probe with excellent fluorescence properties. To investigate the effectiveness of PPN-1, we synthesized PPN-1 and evaluated its fluorescence properties compared to DAHMI, a current available boronic acid sensor. Consequently, PPN-1 showed favorable off/on fluorescence switching ability with a large Stokes shift after the addition of $p$-boronophenylalanine (BPA). Notably, after adding BPA, PPN-1 exhibited a rapid increase and reached a fluorescence plateau within 5 min, which is much shorter than the 2 h needed for DAHMI. Further, PPN-1 has excellent selectivity and detection and quantification limits similar to those of ICP-OES. These results demonstrated that PPN-1 is a practical scaffold for the detection and quantification of boronic acids and will provide essential insights for the development of boronic acid-targeted fluorescent sensors in the future.

Keywords Fluorescence sensor · Boronic acid · Boron neutron capture therapy · Switching

Introduction
Boron neutron capture therapy (BNCT) is a cancer treatment method that uses high linear energy transfer (LET) radiation, i.e., alpha rays and Li nuclei, generated by the nuclear reaction between externally irradiated thermal neutrons and boron ($^{10}\text{B}$) atoms. Since these high LET radiations have a range shorter than 10 $\mu$m, which is less than the diameter of a cell [1, 2], BNCT can efficiently kill tumor cells when $^{10}\text{B}$ atoms are selectively accumulated in the tumor cells prior to neutron irradiation. Therefore, $^{10}\text{B}$-containing agents that are effectively delivered through the bloodstream to the intracellular space of tumor cells after intravenous administration are prerequisites for BNCT. In Japan, $p$-boronophenylalanine (BPA) which is taken up by tumor cells via L-type amino acid transporter 1 (LAT1) has been developed and is currently being marketed under the name Borofalan (Stebofalon®) (May 2020) for locally advanced or locally recurrent unresectable head and neck cancer [3, 4]. However, BPA does not apply to tumors with a low or negligible expression of LAT1 [5] and shows low water solubility, leading to a high dose of additive sugar solubilizer. Therefore, there is a need to develop novel boronoagents [6], and various boronic acid compounds are currently being developed [7–9].

Since the interaction of $^{10}\text{B}$-derived high LET radiation with cell organelles is a fundamental part of BNCT, the intracellular distribution profile of such boronoagents may significantly impact the therapeutic effect. Thus, it is necessary to establish a method that can determine the intracellular distribution profile of boronoagents containing $^{10}\text{B}$ atoms. While inductively coupled plasma optical emission spectrometry (ICP-OES) and inductively coupled plasma mass spectrometry (ICP-MS) are widely used for the quantification of atoms of interest [10], it does not fit
this purpose because it requires ashing of the samples. An autoradiographic method using neutron irradiation enables the visualization of $^{10}$B atom distribution in thin sections of tissues of interest [11]. However, it is not convenient because it requires a specialized facility for neutron irradiation [12, 13] and does not apply to living cells because it needs a fixation prior to neutron irradiation. Therefore, establishing a simple detection and quantification method applicable to living cells can contribute to the development of boronoagents for BNCT.

With this as our basis, we aimed to develop a small molecule-based fluorescence sensor that changes its fluorescence properties upon complexation with the boronic acid moiety of a boronoagent, focusing on the convenience, quantification, and applicability to living organisms of the fluorescence analyses [14, 15]. Thus, we designed a 2-(2-pyridyl) phenol derivative PPN-1 (Fig. 1) by introducing a N,O ligand substructure into a zinc sensor probe based on a 2,2'-bipyridine scaffold with excellent fluorescence properties such as off/on reactivity, high quantum yield, and large Stokes shift [16]. The N,O ligand is commonly used as a substructure of compounds sensing the boronic acid moiety [17, 18]. While a boronic acid sensor with the same substructure, DAHMI, has been developed [19], it still exhibits deficiencies such as a low quantum yield and a slow reaction rate with a boronic acid moiety [20], which necessitates the improved fluorescence properties of sensors. In this study, we designed and synthesized PPN-1 (Scheme 1), evaluated its fluorescence properties compared to DAHMI, and determined the effectiveness of PPN-1 as a novel fluorescence sensor for the detection of boronoagents.

**Methods**

**Reagents and instruments**

All reagents and solvents were purchased from Wako Pure Chemical Industry (Osaka, Japan), Nacalai Tesque (Kyoto, Japan), or Tokyo Chemical Industry (Tokyo, Japan) and used without further purification. $^1$H NMR spectra were measured using a Varian NMR system (400 MHz, Agilent...
Technologies, CA, USA). Chemical shifts are indicated as δ (ppm) values using tetramethylsilane as an internal standard. Mass spectra (MS) and high-resolution mass spectra (HRMS) were collected with a JMS-700(2) mass spectrometer (JEOL Ltd., Tokyo, Japan). UV/vis spectra were obtained on a UV-2450 spectrometer (SHIMADZU Corporation, Kyoto, Japan). Fluorescence spectra and intensity were obtained on a FP-8600 spectrometer (JASCO Corporation, Tokyo, Japan) and EnSpire Multilabel Reader 2300 (PerkinElmer Japan, Kanagawa, Japan).

**Synthesis**

1-(2-(Methoxymethoxy)phenyl)ethan-1-one (2)

2-Hydroxyacetophenone (1) (3.0 mL, 24.9 mmol) and sodium hydride (1.34 g, 55.9 mmol) were mixed in 45 mL of anhydrous tetrahydrofuran (THF) and stirred at 0 °C for 30 min. After the dropwise addition of chloromethyl methyl ether (3.78 mL, 49.8 mmol), the mixture was stirred overnight at room temperature. To the solution, a saturated sodium bicarbonate solution was added and extracted with ethyl acetate. The organic layer was washed with brine and dried with anhydrous magnesium sulfate. After evaporation under reduced pressure, the residue was purified by column chromatography to obtain 2 as a colorless oil.

2.37 g (Yield 64%). 1H-NMR (CDCl3): 2.65 (s, 3H, SCH3), 3.52 (s, 3H, CH3), 5.29 (s, 2H, CH2), 7.03–7.07 (t, 1H, 16 Hz), 7.18–7.20 (d, 1H, 8 Hz), 7.42–7.46 (m, 1H, 1H), 7.70–7.73 (dd, 1H, 12 Hz).

EI-MS: m/z: 180 Measured: 180.

1-(2-(Methoxymethoxy)phenyl)-3,3-bis(methylsulfanyl) prop-2-en-1-one (3)

Under an argon atmosphere, 2 (2.37 g, 13.1 mmol) was slowly added to 31 mL of anhydrous THF containing potassium tert-butoxide (3.04 g, 13.1 mmol). After the dropwise addition of carbon disulfide (3.04 g, 27.1 mmol) and iodomethane (2.53 mL, 40.7 mmol) at 0 °C, the solution was stirred overnight at room temperature. To the solution, 60 mL of water was added and extracted with dichloromethane, washed with water, and dried over anhydrous magnesium sulfate. After evaporation, 60 mL of 28% ammonia solution was added to the brown residue and refluxed for 2 h. After adding 100 mL of water and neutralized with 10% HCl, the solution was extracted with dichloromethane, washed with water, and dried over anhydrous magnesium sulfate. After evaporation, 60 mL of 28% ammonia solution was added to the brown residue and refluxed for 2 h. After evaporation, the residue was purified by column chromatography to obtain 4 as a yellow solid.

0.225 g (Yield 18%). mp: 137–142 °C. 1H-NMR (CDCl3): 2.38 (s, 3H, SCH3), 3.49 (s, 3H, CH3), 4.29 (br s,2H, NH2), 5.23 (s, 2H, CH2), 7.12–7.16 (m, 2H), 7.22–7.24 (d, 1H, 8 Hz), 7.33–7.38 (m, 1H), 7.44–7.47 (m, 1H), 7.73–7.76 (m, 2H), 8.64 (m, 1H), 8.68–8.70 (dd, 1H, 8 Hz). FAB-MS: m/z: 353 Measured: 354 [M + H+].

6-[2-(Methoxymethoxy)phenyl]-4-(methylsulfanyl)-[3,3′-bi pyridin]-2-amine (4)

To 20 mL of dimethylsulfoxide (DMSO) containing 3 (1.0 g, 3.48 mmol) and 3-pyridineacetonitrile (0.38 mL, 3.48 mmol), sodium hydroxide (0.28 g, 6.96 mmol) was added and stirred at room temperature for 2 h. After adding 100 mL of water and neutralized with 10% HCl, the solution was extracted with dichloromethane, washed with water, and dried over anhydrous magnesium sulfate. After evaporation, 60 mL of 28% ammonia solution was added to the brown residue and refluxed for 2 h. After evaporation, the residue was purified by column chromatography to obtain 4 as a yellow solid.

0.098 g (Yield 67%). mp: 232–234 °C. 1H-NMR (DMSO-d6): 2.51 (s, 3H, SCH3), 6.04 (brs, 2H, NH2), 6.86–6.90 (m, 2H), 7.16 (s, 1H), 7.25–7.29 (m, 1H), 7.50–7.53 (m, 1H), 7.69–7.71 (m, 1H), 8.00–8.02 (d, 1H, 8 Hz), 8.42–8.43 (d, 1H, 4 Hz), 8.61–8.63 (dd, 1H, 8 Hz), 14.2 (s, 1H, OH). FAB-MS: m/z: 309 Measured: 310 [M + H+].

Fluorescence property

PPN-1 (1.0 mM at final concentration) was mixed with BPA (1.0 mM at final concentration) in 50% DMSO/phosphate buffered saline (PBS) solution. At 5 min, the excitation and emission spectra were measured using a spectrometer (photomultiplier voltage: 700 V) to evaluate the maximum excitation (λex) and emission (λem) wavelengths (Supplementary Fig. 1). DAHMI was similarly evaluated except that the incubation time was 120 min. All experiments were carried out three times.

The absolute quantum yield was measured (λex: 386 nm) by a spectrometer C9920-02G (Hamamatsu Photonics,
Hamamatsu, Japan) at 5 min after mixing the PPN-1 DMSO solution (0.2 mM at final concentration) and BPA PBS solution (0.2 mM at final concentration) in a 1:1 (v/v) ratio \((n = 3)\). The same method was used for DAHMI (\(\lambda_{ex}: 408\) nm), except that the final concentration was set at 50 \(\mu\)M each and the incubation time was 120 min.

PPN-1 (1.0 mM at final concentration) was then mixed with various concentrations of BPA (0–1.0 mM at final concentration) in 50% DMSO/PBS solution \((n = 3)\). At 5 min, the fluorescence spectra were measured (\(\lambda_{ex}: 387\) nm; photomultiplier voltage: 700 V) to evaluate the relationship between the fluorescence intensity and BPA concentration (Fig. 2).

PPN-1 (1.0 mM at final concentration) was mixed with BPA (0, 5, 10, 20, 40 \(\mu\)M at final concentration) in 50% DMSO/PBS at 1:1 (v/v) ratio \((n = 5–6)\). At 5 min, the fluorescence intensity (\(\lambda_{ex}/\lambda_{em}: 387/442\) nm; photomultiplier voltage: 1130 V) was measured. A linear regression analysis was performed to fit the data (Fig. 3) to calculate a detection limit and a quantification limit from the following equations: detection limit = \(3\sigma/slope\), quantification limit = \(10\sigma/slope\), where the \(\sigma\) is a standard deviation of the fluorescence intensities of samples at 0 \(\mu\)M, and the slope from the regression line.

**Job’s plot**

PPN-1 and BPA were mixed in a 1:9–9:1 ratio in 50% DMSO/PBS with a fixed total concentration of 1.0 mM \((n = 3)\). Fluorescence intensity (\(\lambda_{ex}/\lambda_{em}: 387/442\) nm; photomultiplier voltage: 1130 V) was measured at 5 min and plotted with respect to molar ratio. A linear regression analysis was performed for both half sides of the molar ratio to determine the intersection of the two regression lines (Fig. 4).

**Effects of metal cations**

PPN-1 (0.1 mM at final concentration) and metal cation (NaCl, KCl, MgCl\(_2\)-6H\(_2\)O, CaCl\(_2\), FeCl\(_2\)-4H\(_2\)O, FeCl\(_3\)-6H\(_2\)O, CoCl\(_2\)-6H\(_2\)O, ZnCl\(_2\), CdCl\(_2\)-2.5H\(_2\)O, NiCl\(_2\)-6H\(_2\)O, CuCl\(_2\), MnCl\(_2\)-4H\(_2\)O, or AlCl\(_3\)-6H\(_2\)O) (1.0 mM at final concentration) were mixed in 50% DMSO/Tris HCl buffer (100 mM, pH = 7.4) in triplicate \((n = 3)\). Fluorescence intensities of samples were measured at 5 min after being mixed by a plate reader (\(\lambda_{ex}/\lambda_{em}: 387/442\) nm). These fluorescence intensities were expressed as a relative value compared to the PPN-1 solution without adding metal cations (Supplementary Fig. 2).

PPN-1 (0.1 mM at final concentration), BPA (1.0 mM at final concentration), and each metal cation above (1.0 mM data from Fig. 2), B: 0–0.04 mM) for the assessment of linearity and range and the calculation of the detection and quantification limits, respectively. Data are shown as means ± standard deviations.
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at final concentration) were mixed in 50% DMSO/Tris HCl buffer in triplicate (n = 3), followed by the measurement of fluorescence intensities at 5 min like above. These fluorescence intensities were expressed as a relative value compared to the PPN-1-BPA solution without adding metal cations (Fig. 5). The same experiments were also applied to DAHMI (λex/λem: 411/431 nm), except that the incubation time was 120 min (Supplementary Fig. 3).

Temporal change in the fluorescence intensity

To 50%DMSO/PBS containing PPN-1 (1.0 mM at final concentration) or DAHMI (1.0 mM at final concentration), the same volume of 50%DMSO/PBS containing BPA (1.0 mM at final concentration) (n = 3) was added to each.

The fluorescence intensity (λex/λem: 387/442 nm for PPN-1, 411/431 nm for DAHMI; photomultiplier voltage: 700 V) was intermittently measured at 0, 1, 3, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120 min after mixing.

Results

Fluorescent property

After protecting the hydroxyl group of a starting compound, 2-hydroxyacetophenone, bis(methylsulfanyl)vinyl group was introduced, followed by the reaction with 3-pyridineacetonitrile to construct the bipyridine structure (Scheme 1). PPN-1 was synthesized in a total yield of 4.2%. Since PPN-1 showed fluorescence after the addition of BPA as expected (Supplementary Fig. 1), the fluorescence properties of PPN-1 compared to DAHMI were evaluated after BPA addition (Table 1). PPN-1 showed at 387 nm and 442 nm for the maximum excitation and emission wavelengths, respectively, while DAHMI showed at 411 nm and 431 nm. Thus, this leads to a broader Stokes shift of PPN-1 than that of DAHMI (55 nm vs. 20 nm). The quantum yields of PPN-1 and DAHMI after BPA addition were comparable.

Table 1 Fluorescence properties of PPN-1 and DAHMI after BPA addition

|          | λex   | λem   | Stokes shift | φ     |
|----------|-------|-------|--------------|-------|
| PPN-1    | 387 nm| 442 nm| 55 nm        | 0.009 |
| DAHMI    | 411 nm| 431 nm| 20 nm        | 0.008 |

Fluorescence Intensity (a.u)

Fig. 4 Job’s plot of PPN-1 and BPA. The total concentration of PPN-1 and BPA is fixed to 1.0 mM in 50% DMSO/PBS (λex = 387 nm, λem = 442 nm). Data are shown as means ± standard deviations.

Fluorescence intensity (%)

Fig. 5 The effects of the coexistence of metal cations in the PPN-1-BPA fluorescence (λex = 387 nm, λem = 442 nm) in 50% DMSO/Tris HCl buffer (100 mM, pH=7.4). The concentrations of PPN-1, BPA, and metal cations are 0.1 mM, 1.0 mM, and 1.0 mM, respectively. Data are shown as means ± standard deviations.
The fluorescence spectra of PPN-1 after adding BPA prepared in several different concentrations are shown in Fig. 2. This indicated a positive correlation between the fluorescence intensity and BPA concentration added to the solution. Linear regression analysis revealed linearity within 0–1.0 mM BPA concentration when using PPN-1 in 1.0 mM (Fig. 3A). Further, the analysis determined that 1.80 µM and 6.01 µM were the detection and quantification limits, respectively (Fig. 3B).

**Job’s plot**

The fluorescence intensities of PPN-1 after BPA addition were measured in a varied molar ratio with a constant total concentration (Job’s plot, Fig. 4). The two regression lines intersect around 0.5 of the molar ratio, indicating that the complex formation between PPN-1 and BPA has 1:1 stoichiometry.

**Effects of metal cations**

The changes in the PPN-1 fluorescence (0.1 mM) after the addition of various metal cations in 10 times higher concentrations (1.0 mM) were measured (Supplementary Fig. 2A). It showed no increase in fluorescence intensity with metal cations, similar to the case of DAHMI (Supplementary Fig. 2B).

Next, the effects of the coexistence of high concentrations of metal cations (1.0 mM) in the fluorescence intensity of the solution containing PPN-1 (0.1 mM) and BPA (1.0 mM) were evaluated (Fig. 5). The results showed lower fluorescence when Fe²⁺, Fe³⁺, Co²⁺, Ni²⁺, and Cu²⁺ coexisted in the PPN-1-BPA solution compared to the control. DAHMI also showed similar results (Supplementary Fig. 3).

**Temporal change in the fluorescence intensity**

Temporal changes in the fluorescence intensity of PPN-1 and DAHMI after BPA addition are shown in Fig. 6. PPN-1 showed a rapid increase in the fluorescence after BPA addition and reached a plateau within 5 min. In contrast, DAHMI showed a slow fluorescence increase after BPA addition, which required more than 120 min to reach a plateau.

**Discussion**

Although BNCT is a powerful cancer treatment even in patients with progressed or recurrent tumors [21, 22], it should be noted that only two boronoagents, BPA and BSH [23], both of which were developed more than 50 years ago, are still used in treatment. Therefore, it is imperative to develop novel boronoagents that have different tumor-targeting properties from the existing two agents, but there have been difficulties and failure to reach the same standards [24] to the best of our knowledge. This study aimed to develop a novel boronic acid-targeted fluorescence sensor that can support the development of novel boronoagents by enabling in vitro cellular evaluation. The physical nature behind the BNCT therapy comes from collisions between the short-range high energy particles, He- and Li nuclei, and cell organelles, so the intracellular distribution profile of boronoagents should be evaluated in the process of drug development because the sensitivity for such radiation differs among organelles [25]. For this purpose, fluorescence sensors should provide an optimal method to demonstrate the intracellular distribution profile of boronoagents using microscopic observation.

We designed PPN-1 by introducing an N,O ligand scaffold into the structure of a reported small-molecule fluorescence sensor that fluoresces after reacting with intracellular labile Zn. Namely, in the design process of PPN-1, a pyridine ring of the zinc sensor was first converted to phenol to construct the N,O ligand substructure to recognize a boronic acid moiety instead of Zn. Furthermore, the benzene ring of the zinc sensor was replaced with a pyridine ring so that the expected hydrophilicity of PPN-1 (ClogP = 3.0) is comparable to that of DAHMI (ClogP = 3.3). PPN-1 showed a favorable off/on fluorescence switching ability with a large Stokes shift similar to the original compound in a solution after BPA addition. The extended Stokes shift compared to DAHMI should enable efficient excitation using a bandpass filter during observation with a fluorescence microscope. The excitation wavelength would also attract attention...
Considering bio applications of sensors. Since the maximal excitation wavelength of PPN-1 was slightly longer than the upper limit of the UV range (200–380 nm), it would help promote bio applications of PPN-1, unlike a previously reported compound [20]. PPN-1 showed a rapid increase to reach a plateau in fluorescence after BPA addition, unlike DAHMI, which requires more than 2 h before its plateau is achieved. This indicates the superior quantification of PPN-1 compared to DAHMI in a fluorescence analysis. The high reactivity of PPN-1 may be due to the restricted molecular motion of a 2-(2-pyridyl)phenol core structure compared to DAHMI leading to rapid complexation with a boronic acid moiety of BPA. Furthermore, the detection and quantification limits calculated by linear regression were similar to those of ICP-OES [26], which suggests the high potential of PPN-1 as a quantitative indicator of boron in fluorescence analysis. While ICP-OES has been used to quantify boron concentrations in patient’s blood during intravenous BPA infusion for a clinical BNCT treatment [27], fluorescence analysis using PPN-1 might be able to replace it in the future, focusing on the convenience that does not require an ashing process.

To assess the selectivity of PPN-1, we evaluated fluorescence changes after adding a variety of cations, but no metal cations increased PPN-1 fluorescence. However, the addition of Fe²⁺, Fe³⁺, Co²⁺, Ni²⁺, and Cu²⁺ in high concentrations suppressed the PPN-1-BPA fluorescence to approximately 40% at most, while Na⁺, K⁺, and Mg²⁺ present in millimolar concentrations in normal living tissues [28] did not change the fluorescence intensity. These results tend to coincide with that of DAHMI (Supplementary Fig. 3), suggesting the validity of PPN-1 as a boronic acid sensor, in part. Notably, iron and copper, known as essential trace elements for humans, function with corresponding proteins in living tissues, so the intracellular concentrations of free metals are kept below nanomolar levels against the Fenton reaction to produce reactive oxygen species. Therefore, considering that BNCT requires intracellular boron concentration at exceptionally high levels [29], suppression by trace metals should not be an issue.

As for the limitations of this study, the application of PPN-1 to a wide range of boronic-acid compounds is a remaining issue that must be addressed. We tested the basic properties of PPN-1 with BPA, a clinically used boronic acid compound, and phenylboronic acid as the simplest compound with similar results (data not shown). Second, we could not improve the quantum yield with a slight increase compared to DAHMI. Replacing the pyridine ring attached to the core structure with a benzene ring or a substituent introduction to the core structure might increase the quantum yield [30] to be worth working on in the future. Third, because of its low quantum yield, we could not obtain a clear fluorescence image to depict the boron distribution in living cells administrated with BPA under microscopic observation. The fluorescence intensity of cells was raised by the addition of BPA (data not shown) as expected from the data above in the solution, so the improved quantum yield will enable the microscopic observation of intracellular boron localization.

In conclusion, we developed PPN-1 as a novel boronic acid-targeted fluorescence sensor. This study indicates that PPN-1 has excellent selectivity and quantitative properties for BPA and showed an extended Stokes shift and a rapid reaction with BPA compared to DAHMI. These results demonstrate that the PPN-1 is a practical scaffold for detecting and quantifying boronic acids and will provide essential insights for the development of boronic acid-targeted fluorescent sensors in the future.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s44211-022-00158-8.

Data availability All data generated or analyzed during this study are included in this article and its supplementary information file.

Declarations

Conflict of interest All authors declare no conflict of interest.

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