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Synthesis and evaluation of aryl boronic acids as fluorescent artificial receptors for biological carbohydrates

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ABSTRACT

Carbohydrates in various forms play a vital role in numerous critical biological processes. The detection of such saccharides can give insight into the progression of such diseases such as cancer. Boronic acids react with 1,2 and 1,3 diols of saccharides in non-aqueous or basic aqueous media. Herein, we describe the design, synthesis and evaluation of three bisboronic acid fluorescent probes, each having about ten linear steps in its synthesis. Among these compounds that were evaluated, **9b** was shown to selectively label HepG2, liver carcinoma cell line within a concentration range of 0.5–10 μM in comparison to COS-7, a normal fibroblast cell line.

1. Introduction

Carbohydrates are essential for cell–cell recognition and various biological responses such as inflammation, lymphocyte homing, regulation of metabolic pathways, among others. In addition, the cross-talk between cell surface carbohydrates and cellular receptors has also been associated with the metastatic behavior of various cancer types. Thus far, the detection of the over-expression of such glycoproteins or lipids on membrane surfaces have been accomplished through biological receptors such as antibodies [1,2], aptamers [3,4], peptides or proteins [5], or metabolites [6,7]) linked to a fluorochrome (Fig. 1) allowing the biomarker to be detected by a light source.

Namely, due to their high affinity for their target and/or biomarker of interest, monoclonal antibodies are widely used as biological probes in fluorescence imaging. There are several monoclonal antibodies available for *in vivo* fluorescence imaging applications, anti-PSMA (prostate specific membrane antigen) [8] labels prostate tumor cells, anti-VEGF (vascular endothelial growth factor) [9] labels tumor cells associated with angiogenesis, and anti-HER-2 (human epidermal growth factor recptor-2) [10] labels breast, ovary, and other carcinomas. However, the disadvantages in using monoclonal antibody conjugates as biological imaging probes are contributed to their size. Large biomolecules tend to exhibit lower penetration in tissue of host animal and longer clearance time, allowing background fluorescence interference. Although monoclonal antibodies are engineered genetically near 100% human phenotype, there is always a possibility of eliciting an adverse immunogenic response. There is an evident need to continue the efforts in designing target-specific fluorophores to aid in the detection of tumorigenesis, presence metastasis, and in addition, provide visual guide in the removal of tumor masses.

We are interested in the design and synthesis of small organic molecules with the ability to recognize specific oligosaccharide patterns. Boronic acid moieties, since the 1940s, have been known to form rapid reversible complexes with 1,2 and 1,3 cis diols [11–13]. Much development has been geared toward sensory design [14,15,21–24,26,27,29–33] and cell labeling [34–36] for biological carbohydrates with the use of boronic acid serving as the artificial receptor, which make boronic acid an ideal biological probe for the detection of a cell surface carbohydrates over-expressed on various cancer types. Aryl boronic acid scaffolds targeting cell surface carbohydrates can be considered antibody mimics as they have high affinity and selectivity as antibodies. The advantages of having smaller molecules present creates faster clearance time, higher tissue penetration, and the structural framework can be altered to enhance the pharmacodynamics and pharmacokinetics, leading to a more lucrative imaging probe candidate for *in vivo* applications.

An ideal *in vivo* biosensor for carbohydrates consists of: (1) a recognition moiety with high affinity and specificity and (2) a spectroscopic reporter, which gives off a measurable signal upon binding. Numerous of peer-reviewed articles have provided insight in the design of biomolecular sensors that contain an 'on' and 'off' state through a fluorescence quenching mechanism [37–39]. This attribute

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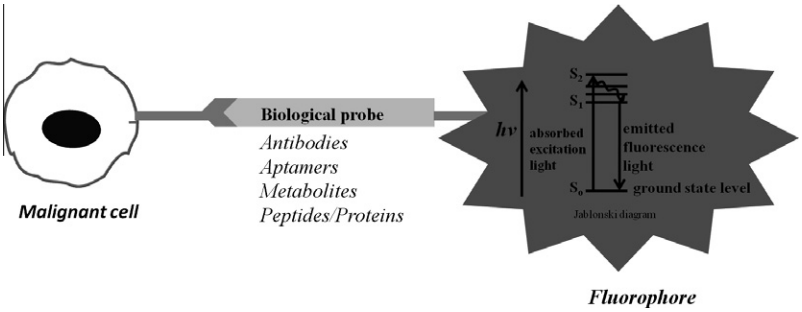


Fig. 1. The design of a site-specific fluorescence probe.

of 'turning on' only at the target site has been termed activatable or 'smart'. Several mentionable molecular quenching mechanisms that have been used in literature are; photoinduced electron transfer (PET), internal charge transfer (ICT), metal–ligand charge transfer (MLCT), and most commonly used in the development of smart probes, fluorescence resonance electron transfer (FRET). The advantages of using molecular fluorescence can be summarized, high sensitivity of detection, and a signal generated only after being bound to the specific biomarker resulting in low to no background noise.

In our initial design an anthracene–boronic acid system (Fig. 2) was chosen as the fluorescent probe. This system was first introduced in 1992 by the Czarnik group (**3**, Fig. 3) [40], and was later used by Shinkai. In Shinkai system a 1, 5 relationship between an amine and boron was incorporated to create more electron density around the boron center. In doing so, they developed monoboronic acid **1**, which is intrinsically selective for fructose and a diboronic derivative also selective for glucose [41]. In this system the amine regulates the fluorescence intensity. The anthracene moiety is quenched by an excited state photoinduced electron transfer (PET), which is considered to be the 'off' state of the sensor. Upon addition of a diol, the fluorescence intensity increases, which represent the 'on' state of the sensor **2**; therefore, creating a smart or 'activatable' probe for the detection of cell surface carbohydrates with low background fluorescence. There are two proposed mechanisms in literature that have been introduced as the mechanisms which stop the quenching process of the anthracene motif [41,42]. Shinkai and co-workers proposed that there is a B–N bond formation which stops the quenching process. Upon addition of a diol, leading to the formation of a boronic ester, the p*K*a of the boron species is decreased. This causes the amine to react with the boron, forming a B–N bond, stopping the quenching process. Later, the Wang group published a paper with detailed experiments providing additional insight as to the mechanism in which the quenching process is eliminated in aqueous medium. They proposed the mechanism is stopped through a hydrolysis mechanism. The B–N bond is labile; as a result it is hydrolyzed. The amine is then protonated, stopping the quenching process.

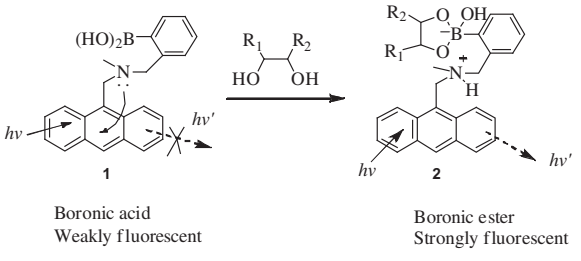


Fig. 2. Signaling unit for anthracene based photoinduced electron transfer (PET) system.

When designing a boronic acid scaffold as an artificial probe for a carbohydrate of interest, the appropriate spatial arrangement is imperative for optimal binding [41,45]. In continuing the efforts of developing fluorescent artificial receptors, we have synthesized a series of rigid dianthracene acid compounds. Our goal is to obtain the framework of previously synthesized diboronic acid [46], heteroatom(s) were added within the di-carboxylic acid linker in compound **4** in hopes of increasing the hydrophilicity. The tertiary amine attached to the carbonyl group was changed to a secondary amine to evaluate how a slight change in electronic properties and reduction of a possible steric effect may alter and/or enhance selectivity. With that in place, three di-anthracene boronic acids were synthesized. Since **4** labeled HepG2, hepatocellular liver carcinoma cells, at 1 μM, concentrations between 0.5 and 10 μM were used in fluorescent cell labeling studies. To evaluate the ability of the newly synthesized bisboronic acid derivatives selectively labeling cancer cell only, COS-7, a normal fibroblast mammalian cell line was used in parallel.

2. Materials and methods

2.1. Biology

2.1.1. Cell culture

Cell lines were purchased from ATCC. HEPG2 and COS7 cells were maintained in RPMI with 10% FBS (fetal bovine serum), 1% L-glutamine, and 0.5% gentamicin sulfate (50 mg/ml) (MediaTech). All cells were maintained at 37 °C in a 5% CO_2 incubator. Remaining materials were purchased from Media-Tech unless otherwise noted.

2.1.2. Fluorescent labeling studies

HEPG2 and COS7 cells were harvest in six well plates in growth medium until ca. 50% confluency. Cells were then washed with PBS following fixation with 4% paraformaldehyde at 4 °C for 25 min or in 1:1 solution of MeOH/PBS for 25 min. After fixation the cells were washed with PBS twice. Next, 1 ml of 1:1 MeOH/PBS was placed in each well, followed by the desired concentration of anthracene boronic acid derivative (0.5–10 μM). The six well plates were placed at 4 °C for 45 min. The cells were viewed with a blue emission filter.

2.1.3. Imaging

Phase contrast and fluorescence overlay images were taken with Carl Zeiss Axiovert 200 M by the process imaging software Axiovision with the use of a blue long pass filter (emission wavelength: 397 nm).

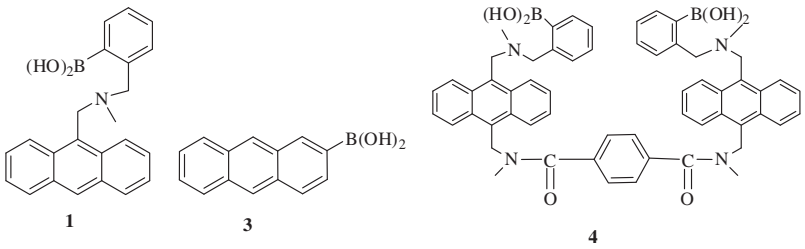


Fig. 3. Anthracene-based fluorescent chemosensors for saccharides.

2.2. Chemistry

2.2.1. General

All ^{1}H and ^{13}C NMR were recorded at 400 MHz and 100 MHz, respectively, with tetramethylsilane as the internal reference. Elemental and mass spectral analyses were performed at Georgia State University Analytical Facilities. All commercial reagents were used without further purification unless otherwise noted. Acetonitrile (CH_3CN) and dichloromethane (CH_2Cl_2) were distilled from CaH_2. Tetrahyrofuran (THF) was distilled from Na and benzophenone.

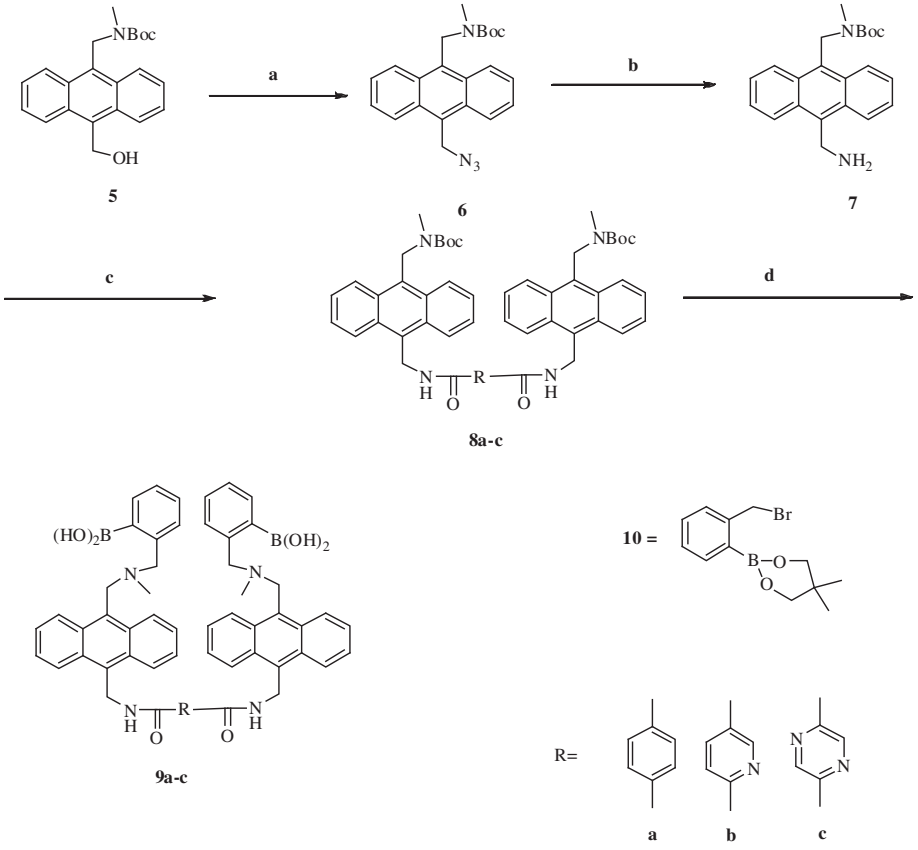
2.2.2. Fluorescent binding studies

A constant concentration of (sensor) bisboronic acid (2×10^{-6} M in MeOH) was mixed with various sugars solution in 0.1 M phosphate buffer (pH 7.4) with increasing concentrations at equal volumes. The mixture was allowed to mix for 20 min and fluorescence intensity was recorded with a Shimadzu RF-5301PC fluorometer. The fluorescent intensity readings were normalized with the sensor solution only and fitted to non-linear regression (sigmoidal–dose response) curve an overlaid with one-site binding curve (fructose) and two-site binding curve (sorbitol) by the software GraphPrism 4.0. Triplicate measurements were taken and correlation coefficients were $\geqslant 0.95$ for each fit.

2.3. Synthesis and structural analysis

2.3.1. Preparation of (10-azidomethyl-anthracen-9-ylmethyl)-methyl carbamic acid tert-butyl ester (**6**)

Triphenylphosphine (717 mg, 2.74 mmol), carbon tetrachloride (1 ml), and 2 ml of dry DMF were added to a round bottom flask followed by alcohol derivative **5** (300 mg, 0.856 mmol), in 3 ml of dry DMF. After disappearance of **5** as monitored by TLC, sodium azide (208 mg, 3.16 mmol) was added. The reaction was allowed to stir at room temperature until completion as indicated by TLC and GC–MS analysis. Ice water (10 ml) was added to reaction and the reaction mixture was stirred for 5 min. Then the reaction solution was diluted with ether (50 ml). The organic layer was washed (2×10 ml) with water and brine, dried over anhydrous magne-



Scheme 1. Synthesis of bis-anthracene boronic acid derivatives. (a) DMF, PPh_3, CCl_4, NaN_3, RT; 90%; (b) (aq.) THF, PPh_3, RT; 85%; (c) CH_2Cl_2, DMF, EDCI, HOBt, TEA, HOOCRCOOH, 0 °C → RT; 50–80%; (d) i. TFA, CH_2Cl_2, ii. K_2CO_3, cat. KI, CH_3CN, 10, iii. 10%$NaHCO_3$, CH_2Cl_2, H_2O, RT; 15–30%.

sium sulfate, and concentrated. The residue was purified by flash chromatography with ethyl acetate/hexanes (15:85) to produce a yellow oil, (277 mg, 90% yield).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.52–8.36 (m, 4H), 7.64–7.59 (m, 4H), 5.57 (s, 2H), 5.37 (s, 2H), 2.51 (s, 3H), 1.59 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 155.8, 131.0, 130.4, 127.1, 126.5, 126.1, 126.0, 125.1, 124.3, 79.9, 46.5, 42.7, 31.8, 28.5; ESI MS: [M+(Na)] calculated 400.2, found 400.1.

*2.3.2. Preparation of (10-Aminomethyl-anthracen-9-ylmethyl)-methyl-carbamic acid tert-butyl ester (**7**)*

Compound **6** (154 mg, 0.410 mmol) and triphenylphosphine (268 mg, 1.02 mmol) in aqueous THF (1:100) was stirred at RT for 16 h. The solution was then concentrated and purified by means of flash chromatography with CH_2Cl_2/MeOH (90:10) to give 122 mg of a yellow solid, 85% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.45–8.38 (m, 4H), 7.57–7.52 (m, 4H), 5.50 (s, 2H), 4.83 (s, 2H), 2.47 (s, 3H), 1.55 (s, 9H); ^{13}C NMR ($CDCl_3$): 155.8, 135.8, 131.2, 129.0, 128.5 125.8, 125.7, 125.1, 124.5, 79.7, 42.5, 38.4, 31.7, 28.5; MS(EI) calculated 350, found 350.

*2.3.3. General procedure for preparation of Boc-protected diamides (**8**)*

The di-acid (0.543 mmol, 1 equivalent), *N*-hydroxybenzotriazole (HOBt, 1.9 mmol, 1.47 mg), 1-(2-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI, 1.07 mmol, 213 mg), and then compound **7** (1.14 mmol, 400 mg) was added to round bottom flask, followed by the addition of 30 ml of dry CH_2Cl_2. The solution was allowed to mix for 30 min at 0 °C, then triethylamine (TEA) was added to obtain a slight basic solution. Then the reaction temperature was slowly raised to room temperature and allowed to stir for 18 h. The reaction mixture was washed with 5% sodium bicarbonate (10 ml), 5% citric acid (10 ml), and brine (10 ml). The organic layer was dried over anhydrous magnesium sulfate, gravity filtered, and concentrated. The crude product was purified by flash chromatography with CH_2Cl_2/MeOH or precipitation from CH_2Cl_2/hexanes.

[10-({[4-({10-[(tert-Butoxycarbonyl-methyl-amino)-methyl]-anthracen-9-ylmethyl}-methyl-carbamoyl)-benzoyl]-aminomethyl)-anthracen-9-ylmethyl]-methyl-carbamic acid tert-butyl ester (**8a**). 80% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.49–8.39 (m, 8H), 7.70–7.59 (m, 8H), 7.70–7.69 (s, 12H), 5.64 (s, 4H), 5.54 (s, 4H), 2.49 (s, 6H), 1.57 (s, 18H).

[10-({[4-({10-[(tert-Butoxycarbonyl-methyl-amino)-methyl]-anthracen-9-ylmethyl}-methyl-carbamoyl)-pyridine-2-carbonyl]-anthracen-9-ylmethyl]-methyl-carbamic acid tert-butyl ester (**8b**). 60% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.68 (s, 1H), 8.42–8.40 (m, 2H), 8.35–8.31 (m,6H), 8.12 (s, 1H), 8.05 (s, 1H), 7.53–7.44 (m, 8H), 5.58 (d, J = 4.4 Hz, 2H), 5.45 (s, 4H), 5.31 (s, 2H), 2.42 (s, 3H), 2.36 (s, 6H), 1.51 (s, 18H).

[10-({[4-({10-[(tert-Butoxycarbonyl-methyl-amino)-methyl]-anthracen-9-ylmethyl}-methyl-carbamoyl)-pyrazine-2-carbonyl]-aminomethyl)-anthracen-9-ylmethyl]-methyl-carbamic acid tert-butyl ester (**8c**). 50% yield ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.22–9.20 (m, 1H), 8.51–8.40 (m, 8H), 8.05–8.04 (m, 1H), 7.2–7.56 (m, 8H), 5.67 (s, 4H), 5.54 (s, 4H), 2.52 (s, 6H), 1.66 (s, 18H).

*2.3.4. General procedure for preparation of diboronic acids (**9**)*

Deprotection of the amine moiety of diamide **8** was accomplished by dissolving it in dry CH_2Cl_2 (15 ml) followed by trifluoroacetic acid addition and stirring at room temperature 15 min. After removal of Boc-protected group, the residue was concentrated and dried in vacuo for 3 h. The reaction mixture was then subsequently placed in a round bottom flask. Then dry acetonitrile (35 ml), potassium carbonate (2.2 mmol, 305 mg), catalytic amount of potassium iodide, and compound **10** (0.88 mmol, 251 mg) were added to the same flask. The reaction mixture was allowed to stir for 18 h. The insoluble materials were filtered, and the filtrate was evaporated *in vacuo*. The resulting residue was dissolved in CH_2Cl_2, 20 ml of 10% sodium bicarbonate, and 8 ml of water for the removal of protecting group of the boronate motif. The mixture was stirred for 4 h. The organic phase was washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. The crude material was precipitated from THF/hexanes.

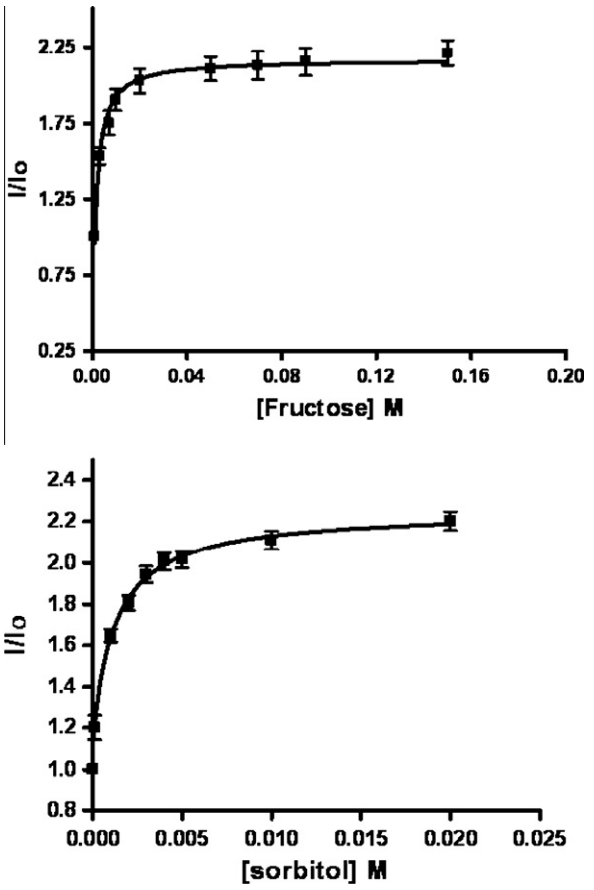


Fig. 4. (a) Fluorescence intensity changes (I/I_0) of **9c** as a function of sugar concentration at room temperature: 1.0×10^{-6} M in 50% MeOH/0.1 M aqueous phosphate buffer at pH 7.4: λ_{ex} = 370 nm, λ_{em} = 423 nm.

*Diboronic acid (**9a**).* 28% yield. ^{1}H NMR ($CD_3OD + CDCl_3$, 400 MHz) δ: 8.56–8.54 (m, 4H), 8.37 (m, 4H), 7.62–7.56 (m, 12H), 7.38–7.31 (m, 8H), 5.38 (s, 4H), 5.03 (s, 4H), 4.37 (s, 4H), 2.42 (s, 6H); HRMS(+H/D)[$-H_2O$] calculated 882.4124, found 882.4105.

*Diboronic acid (**9b**).* 25% yield. ^{1}H NMR (CD_3OD, 400 MHz) δ: 8.71–8.70 (m, 1H), 8.51–8.49 (m, 4H), 8.46–8.44 (m, 4H), 8.24–8.19 (m, 1H), 7.69–7.66 (m, 2H), 7.57–7.51 (m, 9H), 7.37–7.32 (m, 4H), 7.29–7.26 (m, 2H), 5.59 (s, 1H), 5.54 (s, 1H), 5.49 (s, 2H), 5.00 (s, 4H), 4.31 (s, 4H), 2.38 (s, 6H). HRMS(+H)[$-H_2O$] calculated 882.3997, found 882.4001.

Table 1
Binding constants for the complex of sensor and saccharide.

Sensors	K_a (M^{-1}) fructose	K_a (M^{-1}) glucose	K_a (M^{-1}) sorbitol
9a	212	28	—[a]
9b	266	1	—[a]
9c	504	2	1051

K_a values were obtained using a non-linear regression curve fitting with the software GraphPad Prism 4.0.

[a] Binding constant not determined.

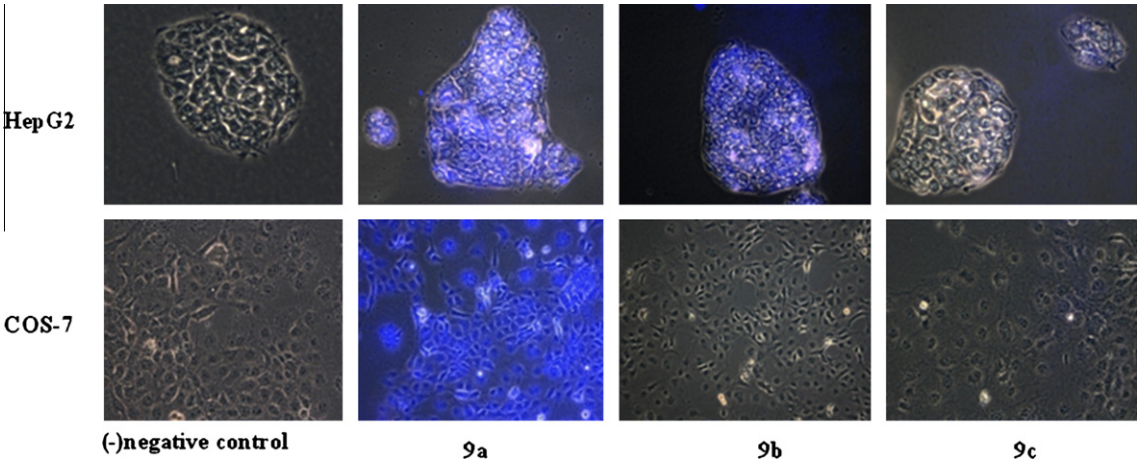


Fig. 5. Fluorescent labeling studies of a liver carcinoma cell line HepG2 and a normal fibroblast mammalian cell line COS-7 with compounds **9a–c**. The negative control contains buffer only.

*Diboronic acid (**9c**).* 20% yield. ^{1}H NMR (CD_3OD, 400 MHz) δ: 9.09 (s, 2H), 8.53–8.51 (m, 4H), 8.25–8.23 (m, 4H), 7.71–7.69 (m, 2H), 7.60–7.52 (m, 8H), 7.37–7.33 (m, 4H), 7.30–7.28 (m, 2H), 5.60 (s, 4H), 5.49 (s, 4H), 4.29 (s, 4H), 2.37 (s, 6H). HRMS(+H)[$-H_2O$] calculated 883.3951, found 883.3978.

3. Results and discussion

3.1. Synthesis of artificial receptors

The preparation of a dianthracene boronic acid for the development of a fluorescent probe for biological saccharides begin with **5**, which was prepared from a previous published paper [44]. The hydroxyl moiety of **5** was converted to an azide to give **6** in 90% yield using a mild Mitsunobu type reaction [47]. The reduction of the azide was achieved by the addition of triphenylphosphine in aqueous THF to generate amine **7** in 81% yield. The amidation reaction of **7** with various di-acids was performed by treatment with 1-(2-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) along with *N*-hydroxybenzotriazole (HOBt) to afford compounds **8a–c** in 50–60% yield. After deprotection of derivatives **7** with trifluoroacetic acid (TFA), the unprotected free amines were then reacted with aryl boronic ester **10** [41] in the presence of potassium carbonate with a catalytic amount of potassium iodide. Then deprotection of the boronate produced compounds (**9a–c**, Scheme 1) in yields of 15–30%.

3.2. Determination of binding constants

To validate the complexation of the synthesized boronic acids and diol, various biological sugars were used to obtain the apparent binding constant. Briefly, 2 ml of sensor solution in MeOH was mixed with 2 ml of aqueous phosphate buffer solution containing saccharide of interest with increasing concentration. Next, the fluorescent intensity was obtained, and normalized by sensor solution only. As shown in Fig. 4, there is a fluorescent intensity increase with increasing concentration of carbohydrate. The apparent binding constants are displayed in Table 1, as shown there is a low binding affinity for glucose with each di-boronic acid. However there is a higher binding affinity for sugars that bind to boronic acids in a trivalent fashion, such as fructose and sorbitol [48]. The binding constants for fructose are **9c** (504 M^{-1}) > **9b** (266 M^{-1}) > **9a** (212 M^{-1}) respectively. Compound **9c** showed the highest binding affinity for fructose; therefore sorbitol was tested with this compound only, showing a binding affinity of 1051 M^{-1}. Such results show a pattern for the binding of monoboronic acids [10], one could possibly state that **9c** displays a two-binding site model between the interactions of hydroxyl groups of the saccharide (substrate) and the bisboronic acid units (receptor).

3.3. Evaluation of fluorescent labeling studies

To explore the capability of the bisboronic acids labelling carcinoma cell lines, we studied their ability to stain HepG2, liver carcinoma cells as oppose to a normal fibroblast cell line, COS-7 [44]. Briefly, cells were cultured in six-well plates with 1×10^6 M per well and incubated at 37 °C in 5% CO_2 for 48 h. The media was then removed and cells were washed with PBS. The cells were fixed with methanol/PBS. After fixation, cells were washed twice with PBS. The bis-anthracene boronic acids at 0.5–10 μM were added to each well that contained 1 ml of 1:1 MeOH/PBS, and incubated for 45 min at 4 °C. The staining of the fluorescent probes was observed using a fluorescent microscope with a blue optical filter. Images were shown as overlay images of phase contrast and fluorescent microscopy. In this way, the non-labeled cells appear as a gray scale image and labeled cells are blue[1] in color. The staining results are shown in Fig. 5.

Bisboronic acids **9a** and **9b** stained the HEPG2 cell line at similar concentration, 1 μM. However, **9a** as well stained COS-7 cell line, diminishing the selectivity of the lead compound **4** toward hepatocellular carcinoma line versus normal fibroblast cells. The pyrazine compound **9c** at concentrations between 0.5 and 10 μM showed weak or no binding affinity for either cell line.

4. Conclusion

Three dianthracene diboronic acids were synthesized and evaluated for the labeling of liver carcinoma cell line, HepG2 as oppose to a normal mammalian fibroblast cell line, COS-7. Compound **9b** showed similar staining concentration compared to model compound **4**. However **9a**, the removal of the methyl group from the amino group attached to the linker, seemed to diminish the selectivity. Compound **9c** showed weak or no selectivity for either cell line. One could speculate that there are physiochemical parameters governing non-labeling for either cell line of compound **9c**. However it is beyond the scope of this article, additional studies are underway.

[1] For interpretation of color in Fig. 5, the reader is referred to the web version of this article.

Aforementioned, there is an increasing need to design recognition moieties to be used as diagnostic tools to monitor the presence of certain oligosaccharides as they are associated with the progression and the metastatic behavior of certain cancer and tumor cell types. With the appropriate fluorescent boronic acid scaffold to detect these oligosaccharides one could begin to design boronic acid moieties as antibody mimics to serve as tumor-specific fluorphores to pursue the effector mechanisms that govern the pathogenesis of cancer and as well provide image-guided tumor resection. The design of such small organic probes could aid in the longevity of cancer patients and decrease the morbidity that is associated with later stage of cancer through early detection. With that said, additional exploratory computational and/or molecular modeling design could aid in the discovery of boronic acids with the appropriate scaffold to serve as antibody mimics.

Acknowledgments

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bioorg.2011.11.003.

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