

Cite this: *RSC Adv.*, 2018, 8, 29400

Recent development of boronic acid-based fluorescent sensors

Guqian Fang,^{abcd} Hao Wang,^{abcd} Zhancun Bian,^{abcd} Jie Sun,^{abcd} Aiqin Liu,^{abcd}
Hao Fang,^e Bo Liu,^{abcd} Qingqiang Yao^{abcd} and Zhongyu Wu^{*abcd}

As Lewis acids, boronic acids can bind with 1,2- or 1,3-diols in aqueous solution reversibly and covalently to form five or six cyclic esters, thus resulting in significant fluorescence changes. Based on this phenomenon, boronic acid compounds have been well developed as sensors to recognize carbohydrates or other substances. Several reviews in this area have been reported before, however, novel boronic acid-based fluorescent sensors have emerged in large numbers in recent years. This paper reviews new boron-based sensors from the last five years that can detect carbohydrates such as glucose, ribose and sialyl Lewis A/X, and other substances including catecholamines, reactive oxygen species, and ionic compounds. And emerging electrochemically related fluorescent sensors and functionalized boronic acid as new materials including nanoparticles, smart polymer gels, and quantum dots were also involved. By summarizing and discussing these newly developed sensors, we expect new inspiration in the design of boronic acid-based fluorescent sensors.

Received 26th May 2018
Accepted 8th August 2018

DOI: 10.1039/c8ra04503h

rsc.li/rsc-advances

1. Introduction

Different elements form a rich and colorful world dynamically, and they are in diverse forms of existence through a series of physical effects and biochemical reactions. To accurately understand these processes, we need to give consideration to their existence at the molecular level. The objects of scientists' research vary from single ions to complex and changeable proteins. In order to deeply understand them, scientists have devoted much time to developing effective recognizing tools, and molecular recognition sensors are utilized extensively. Normally, two conditions should be taken into consideration while fabricating an ideal sensor. First, it is necessary to have a specific recognition site that combines with objects such as the human microenvironment of ions, carbohydrates, peptides, *etc.* Second, the dynamic changes made by these combinations can be detected by monitoring environment, and some of the extensively used reporters are optical and electrical.¹ The interactions of recognition originate from noncovalent bonding, such as hydrogen bonds, van der Waal's forces, π - π interactions, electromagnetic effects and so on, extending to

covalent bonds and other sensory systems.^{2,3} In recent years, using boronic acid groups to fabricate a variety of fluorescent sensors have attracted great interest among scientists. Based on the principle that boronic acid forms a reversible five- or six-membered cyclic boronic esters with *cis*-1,2- or 1,3-diols,⁴ the fabrication of boronic acid fluorescent sensor extends from boronic acid-appended molecular sensors to apply unconventional smart new materials, including boronic acid-functionalized polymers, boronic acid-modified nanoparticles, and boronic acid-based electrochemical sensors.^{4,5} For instance, boronic acid-functionalized hydrogels are important smart materials that can be used to fabricate the self-controlled insulin releasing device in the biomedical field.⁶ Hydrogels endows special properties to boronic acid sensors due to their compatibility with organisms to a certain degree.^{7,8} Recently, numerous new types of boronic acid sensors have been fabricated to detect blood glucose concentrations,^{9–13} ionic compounds,^{14–17} traces of water in solvents,^{18,19} hydrogen peroxide (H₂O₂),^{20–22} catecholamines,²³ as well as using boronic acids as biochemical tools for various applications, including tumor cell imaging,^{24,25} enzyme inhibitors²⁶ and cell delivery systems.²⁷ Therefore, the boron-based fluorescent sensor is still hot in today's research. This review summarized the recent development of boronic acid-based fluorescent sensors for carbohydrates, catecholamines, reactive oxygen species (ROS), ionic compounds and new materials. Although numerous remarkable achievements have been mentioned in previous reviews,²⁸ some areas of research have faded and many new and exciting areas have developed. In order to update knowledge of this rapidly developing field, it is worth highlighting their

^aSchool of Medicine and Life Sciences, University of Jinan-Shandong Academy of Medical Sciences, Jinan 250200, Shandong, China. E-mail: wu_med@foxmail.com

^b*Institute of Materia Medica, Shandong Academy of Medical Sciences, Jinan 250062, Shandong, China*

^cKey Laboratory for Biotech-Drugs Ministry of Health, Jinan 250062, Shandong, China

^dKey Laboratory for Rare & Uncommon Diseases of Shandong Province, Jinan 250062, Shandong, China

^eDepartment of Medicinal Chemistry, School of Pharmaceutical Sciences, Shandong University, Jinan, Shandong 250012, China

merits and discussing the remaining shortcomings, as well as the development perspective of fabricating boronic acid sensors. It is also hoped that inspires others to exploit novel sensing strategies.

2. Carbohydrates boronic acid sensors

As the important material basis, carbohydrates widely distribute in the body and maintain the normal operation of life. They are usually divided into mono-, di-, and polysaccharides, which play numerous roles in nature. For example, glucose serves as the primary form of energy for basic life processes such as nervous system regulation, cell proliferation, *etc.* Cellulose endows nature with structural rigidity. Starch and glycogen can serve as energy reserves to sustain life. In addition, they can combine with other molecules to form glycoproteins, glycolipids and so on,²⁹ which play key roles in many biological basic activities such as cancer migration,³⁰ cell fusion,³¹ protein function regulation³² and embryo development.³³ Consequently, the recognition of carbohydrates in the medical, cell biology and other life sciences is of great significance.³⁴

2.1. Chemical basis for the combination of boronic acid and carbohydrates

The initial study of forming reversible covalent bonds between boronic acids and 1,2- or 1,3-diols can be traced back to 1959. Lorand and Edwards compared different covalent bond constants between the phenylboronic acids (PBA) and diols compounds involving saccharides *via* the observation of a pH drop.³⁵ As depicted in Fig. 1, boronic acid interacts with water, resulting in a rapid transformation of the boron atoms from the trivalent plane sp^2 (neutral) form **1** to the tetravalent tetrahedral sp^3 (anion) form **2**, and then releasing the proton. Due to the unique electron configuration of the elemental boron element 5, the electron configuration $1s^2 2s^2 2p^1$ allows the form of three covalent bonds in the sp^2 geometry. In the sp^2 hybrid conformation, boron has only 6 valence electrons and can accept an electron pair, thus it is Lewis acid. Namely, boron has an

“electron hole” that interacts with the Lewis base, thereby forming a covalent bond with the tetrahedral sp^3 geometry. It is an acid–base reaction that applies to the formation of borate ester. Davis *et al.* reported the relative rates of cyclic boronic esters, manifesting that the six-membered rings are thermodynamically more stable than the five-membered rings.⁵ Due to boronic acid and borate are likely to exist in two different hybrid forms of sp^2 or sp^3 , there are three processes in the borate–sugar interaction process, and the equilibrium constant is expressed by K_{trig} . The second equilibrium is the process of sp^3 hybridized borate anions **3** to borate ester anions **4** whose equilibrium constant is called K_{tet} . These two equilibrium constants alone can’t really reflect the true situation of boronic acid combined with carbohydrates. Thus the third general combination constant K_{eq} is often used, regardless of the specific hybrid state of boron. Later, Wang *et al.* found that K_{tet} was actually measured by the pH drop method, and K_{eq} was measured by spectroscopy.^{36,37} Therefore, when comparing the literature value, we need to pay special attention to the specific method of determining the binding constant.

2.2. D-Glucose boronic acid sensors

As a basic necessity of organisms, D-glucose plays an important role in biological processes. Humoral abnormal glucose level is a warning signal for medical conditions, and the development of selective glucose sensors for clinical and biomedical applications has become a crucial goal in the field of boronic acid-based chemical sensing. The selectivity of boronic acid for fructose has a higher abundance than glucose, thus reversing the intrinsic binding property has been the focus of early studies.⁴ The selectivity of glucose can be achieved *via* molecular design,³⁸ and this technology is maturing,¹³ and recent developments tend to produce glucose optical responses by inducing nanoscale self-assembly of boronic acid-containing amphiphiles or other materials.³⁹ This section will briefly introduce fluorescent sensors that were fabricated with anthracene, pyrene, heterocyclic ring as fluorescent units, and then the analysis of ribose,⁴⁰ sialic acids,^{25,41} glucosamine,⁴² α -hydroxy carboxylate,⁴³ ATP,^{44,45} amyloid- β plaques⁴⁶ fluorescent sensors are followed. This paper summarized the unique design ideas of these fluorescent sensors, the luminescence response mechanisms and the development perspective in the future.

2.2.1. Anthracene boronic acid sensors for D-glucose (Table 1). The first application of boronic acid compounds as fluorescent sensors dates back to 1992. Czarnik *et al.* reported the first anthracene boronic acid sensor **5**.⁴⁷ This work has a great significance in the development of boronic acid sensors. Schwarz *et al.* reported that anthracene has higher fluorescence quantum yields compared to benzene and naphthalene.⁴⁸ It is probably ascribed to the influence of the longer conjugated rigid planar structure. Anthracene has a stronger UV absorption (K band) in $\pi \rightarrow \pi^*$ transition. Therefore, Czarnik devised boronic acid sensor **5** using anthracene as a fluorescent unit, which recognizes D-fructose selectively in aqueous solution at pH 7.4. The sensor **5** belongs to excited state internal charge transfer (ICT), composed of anthracene unit and the boronic

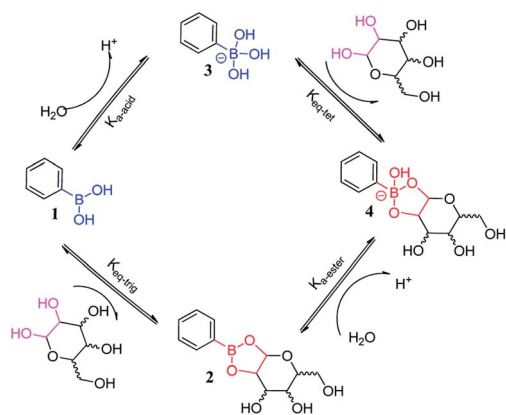


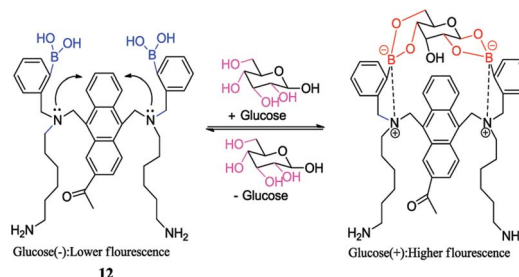
Fig. 1 Transformation of boronic acid to boronic ester.³⁷

Sensor	Structure	Spectroscopic properties (λ_{ex} ; λ_{em})	C (LOD; range)	Functions and applications
5 ⁴⁷		—; 416 nm	—; 3.7 mmol L ⁻¹	pK _a modulation, the apparent fructose dissociation constant at 7.4; providing a tight, reversible association mechanism and a signal transduction mechanism
6 ⁴⁹		348 nm; 416 nm	—; 0–50 mmol L ⁻¹	The adjacent hydrogens influence the selectivity, the binding of catechol is stronger than that of saccharide; illustrating the influence of spatial steric
7 ⁵⁰		370 nm; 420 nm	—; 0.05 mol L ⁻¹	No significant difference was found between fructose and glucose; illustrating the selectivity of monoboronic acid for fructose has a higher abundance than glucose
8 ⁵¹		370 nm; 423 nm	—; 0.3–1 mmol L ⁻¹	Diboronic acid, D-glucose (log K = 3.6); the binding of D-glucose is stronger than that of other saccharide
9 ⁵⁶		377 nm; 427 nm	—; 10 ⁻⁵ –10 ⁻¹ mol L ⁻¹	Diboronic acid, high ¹³ C chemical shifts of the binding of D-glucose; the binding of D-glucose is stronger than that of other saccharide
11 ⁵⁹		358 nm; 418 nm	0.8 μmol L ⁻¹ ; 0.003–3.0 mmol L ⁻¹	Fluorescence intensity↑, lower detection limit; successfully applied to glucose detection in human serum samples
12 ⁶²		405 nm; 488 nm	4.4 mmol L ⁻¹ ; 0–55.6 mmol L ⁻¹	Diboronic acid, good biocompatibility; applied <i>in vivo</i> and successfully tracked the fluctuation in blood glucose concentration

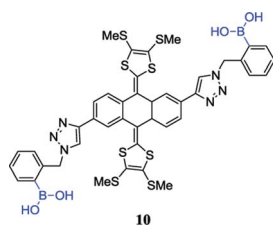
Subsequently, Shinkai *et al.* reported the anthracene mono-boronic acid sensor **7** selectively recognizing D-fructose and the anthracene diboronic acid sensor **8** which selectively recognizes D-glucose.^{50,51} The sensor **7** was combined with carbohydrates to form **7a**, and its N-B bond interaction of **7a** was enhanced,

29402 | RSC Adv., 2018, 8, 29400–29427

successfully by implanting fluorescent beads into the ear skin of mice for continuous glucose monitoring. As a result, it was found that the fluorescence intensity successfully tracked the fluctuation in blood glucose concentration from 0 mg dL⁻¹ to 1000 mg dL⁻¹.⁶¹ Subsequently, Takeuchi *et al.* went on further investigation by improving the polymerization technique.⁶² Hydrogel fibers were fabricated, which could stay in mice for up to 140 days. When implanted, they can control and quantify the amount of fluorescence. Moreover, they are easily removed from the body and have better applicability.



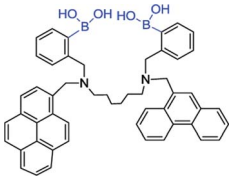
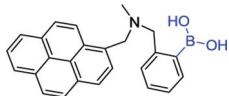
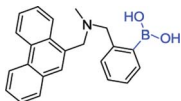
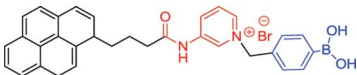
Pyrene belongs to the fused aromatic ring compounds, having highest fluorescence quantum yields among benzene, naphthalene and anthracene.⁴⁸ And it is often used in the basic theory study in the field of fluorescent sensors. A basic sensor should have three essential components: acceptor units, linker units and fluorophore units.⁶³ Based on this principle and the fluorescence resonance energy transfer (FRET) mechanism, James *et al.* fabricated a new boronic acid sensor **13**. FRET is a nonradiative energy transition phenomenon. When the fluorescent substance is excited, if the energy difference between the ground state of the donor and the vibration energy of the first excited state is equivalent to that of the acceptor or the emission spectrum of the donor is effectively overlapped with the excitation spectrum of the acceptor, the donor will effectively generate the oscillating dipole, resonate with the dipole of the proximal acceptor and transfer the energy of the donor fluorophore to the acceptor fluorophore, resulting in a change in the fluorescence intensity of the system.⁶⁴



As mentioned in the previous part, glucose selectivity can be achieved *via* exquisitely fabricating receptors with multiple boronic acid groups. Such a modular approach to saccharide recognition has been pioneered by James,⁶⁵ Wang,⁶⁶ Singaram,⁶⁷ to name but just a few. The boronic acid sensor **13** contains two PBA groups for selectivity, two different fluorophores units and a hexamethylene unit as a linker.⁶³ They found that hexamethylene was the best linker to obtain D-glucose selectivity. The emission wavelength of phenanthrene **15** (donor) was 369 nm and the excitation wavelength of pyrene **14** (acceptor) was 342 nm. They were overlapped. The conjugate of sensor **13** and the D-glucose was irradiated with the excitation wavelength of phenanthrene (299 nm), and its emission wavelength was further as the excitation wavelength of pyrene. Finally, the fluorescence intensity increased 3.9 times at 397 nm. At 299 nm and 342 nm, the fluorescence enhancement of D-fructose was 1.9 fold and 3.2 fold, respectively. D-glucose complex was a rigid

RSC Adv., 2018, 8, 29400–29427 | 29403

Sensor	Structure	Spectral properties (λ_{ex} ; λ_{em})	C (LOD; range)	Functions and applications
--------	-----------	--	------------------	----------------------------

Sensor	Structure	Spectroscopic properties (λ_{ex} ; λ_{em})	<i>C</i> (LOD; range)	Functions and applications
13 ⁶³		299, 342 nm; 417, 460 nm	—; —	Diboronic acid, the binding of D-glucose is stronger than that of other saccharide, <i>K</i> ($142 \pm 12 \text{ L mol}^{-1}$), $\uparrow 3$ -fold; serving as selective glucose sensor, offer FRET mechanism
14 ⁶³		342 nm; 397 nm	—; —	D-Glucose: <i>K</i> ($44 \pm 3 \text{ L mol}^{-1}$), $\uparrow 4.5$ -fold; poor selectivity for glucose
15 ⁶³		299 nm; 369 nm	—; —	D-Glucose: <i>K</i> ($30 \pm 7 \text{ L mol}^{-1}$), $\uparrow 1.5$ -fold; poor selectivity for glucose
16 ¹²		328 nm; 510 nm	0.1 mmol L ⁻¹ ; 0–10 mmol L ⁻¹	D-Glucose: high binding constant, <i>K</i> (1378 L mol^{-1}), $\uparrow 3.9$ -fold; knocked out the interference of D-fructose by PBA and clearly recognize D-glucose

Due to the complex process of improving glucose selectivity by synthesizing diboronic acid groups or multiple boronic acid groups, Huang *et al.* had been exploring novel sensing regimes to improve the inherent selectivity of simpler monoboronic acid sensor **16**, as depicted in Fig. 2.¹² It is generally accepted that binding affinity of the boronic acid with fructose is higher than that with glucose. The specific recognition of glucose can be explained by the stoichiometric point of glucose and fructose binding to boronic acid. In the presence of D-fructose, a boronic acid derivative was produced to form an amorphous 1 : 1 conjugates. Highly ordered 2 : 1 fluorescent conjugates were obtained in the presence of D-glucose. This sensor system utilized the selective sensing mechanism both of the interaction of boronic acid with diols and aggregation induced by pyridinium cation- π interactions. The binding constants of PBA with D-fructose and D-glucose were 4365 and 110, respectively, while the binding constant of the sensor **16** with fructose and D-glucose were 353 and 1378, respectively. Huang *et al.* used this kind of property and knocked out the interference of D-fructose

2.2.3. Heterocyclic boronic acid sensors for D-glucose (Table 3). Due to a traumatic operation of the blood will make some patients have tensional and promote blood glucose, the test results can't correctly reflect the patients' true blood glucose levels. If chemosensors can be used for continuous, non-invasive study of changes in blood glucose levels, it will greatly facilitate the clinical treatment of diabetes and related scientific research. Badugu *et al.* fabricated a water-soluble sensors **17** for non-invasive and continuous glucose detection based on the interaction between the quaternary nitrogen of the 6-methoxyquinolinium nucleus and the boronic acid group. When they are fixed on contact lenses, it is possible to use for the detection of glucose concentration in intraocular liquids.⁶⁸ Due to changes in the process of ICT, these sensors have good fluorescence intensity and suitable spectral properties, which can be excited by inexpensive lasers. In the PET mechanism, the fluorophore and the acceptor are generally joined together by

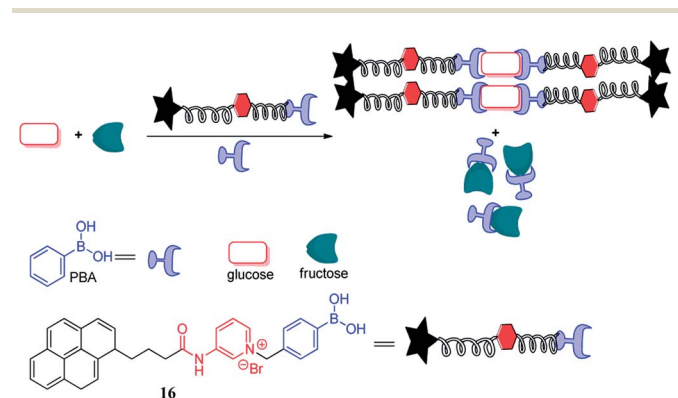
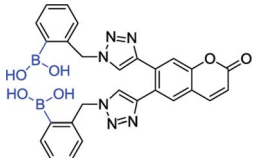
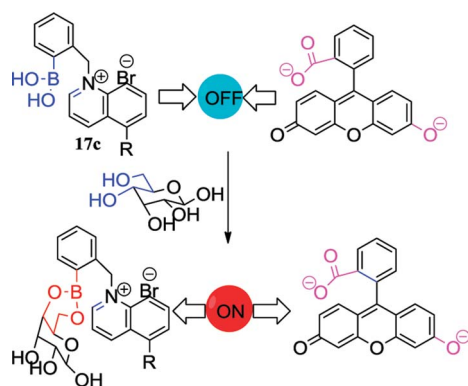


Fig. 2 Cartoon illustrating the knock-out effect of an excess of PBA.¹²

Sensor	Structure	Spectroscopic properties (λ_{ex} ; λ_{em})	<i>C</i> (LOD; range)	Functions and applications
17 ⁶⁸	 17a: R₁=CH₃ 17b: R₁=OCH₃ 17c: R₂=o-B(OH)₂ 17d: R₂=m-B(OH)₂ 17e: R₂=p-B(OH)₂	299, 342 nm; 417, 460 nm	—; 0–40 mmol L ^{−1}	D-Glucose: ↑4.5-fold; used in the contact lens and sensitive to the very low concentrations of tear glucose
21 ¹³		328 nm; 510 nm	—; 0–5 mmol L ^{−1}	D-Glucose: ↓0.79-fold; the selectivity of glucose binding is modulated by the distance, serving as an “on-off” fluorescence sensor for selective glucose detection

dipyrometheneboron difluoride (BODIPY) dye core by forming two B–O–C bonds, and the boronic acid recognition function and the fluorescence properties of BODIPY were combined into an entity.⁷⁰ The reaction of Cl-BODIPY with glucose in acetonitrile formed a 1:1 α -glucofuranose BODIPY complex **18**, a 1:2 α -glucofuranose BODIPY complex **19** and 1:2 α -glucoseptanose BODIPY complex **20**. To our knowledge, compound **20** is a novel example of unnatural septanose form of glucose. These fluorescent and hydrolytically stable conjugates open a new paradigm for carbohydrates labeling, sensing, and visualization by connecting strong fluorophores directly to carbohydrates rather than by long-range binding.

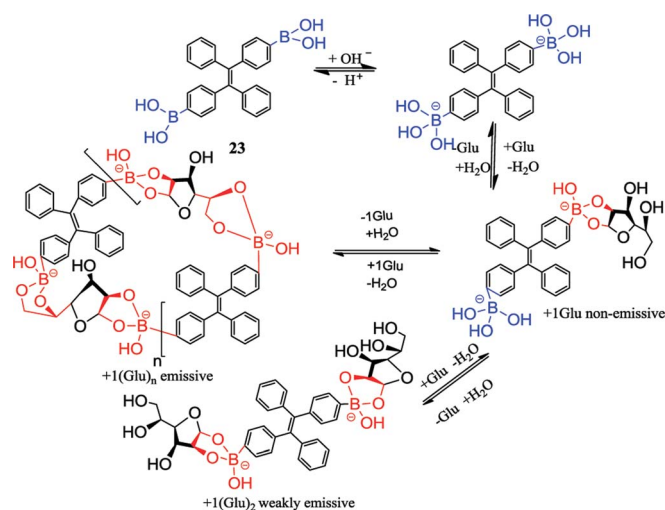


Recently, Zhai *et al.* reported the synthesis of a new bis-boronic acid sensor using copper catalysed azide-alkyne cycloaddition (CuAAC) reactions and fabricated a new glucose-selective fluorescent sensor **21**.¹³ Interestingly, isothermal titration calorimetry (ITC) experiments showed that sensor has higher binding affinity toward glucose than fructose when two linkers with BPA were in the *ortho*-position. It manifested that the selectivity of glucose binding is modulated by the distance between the two boronic acid groups. Based on this principle, they fabricated sensor **21** subsequently. Excitingly, its fluorescent intensity shows compliance with ITC experimental prediction.

In general, diol sensors are identified based on fluorophore-appended boronic acids, and their applications are often limited due to the lack of discrimination and one-dimensional response. However, Axthelm *et al.* designed a strategy that could compensate for this defect.⁷¹ The combination of fluorinated boronic acid-appended pyridinium salts **22** with ¹⁹F NMR spectroscopy enables the screening of a library of 59 biological analytes including monosaccharides. It is worth noting that these receptors are highly sensitive, selective and water-soluble. In addition, their ¹⁹F-NMR analyte fingerprint is pH-robust making them particularly suitable for medical applications. For example, in a 188 MHz NMR spectrometer, the concentration of glucose detected in synthetic urine samples was down to 1 mmol L⁻¹.



2.2.4. Other types of boronic acid sensors for D-glucose. Liu *et al.* fabricated a novel diboronic acid fluorescent sensor **23** based on tetraphenylethylene (TPE), which limits the intramolecular rotation of the TPE aryl rotor by forming oligomers to respond toward glucose.⁵⁷ Interestingly, the sensor **23** was mixed with D-fructose, D-galactose or D-mannose, but the light emission hardly changed. When the glucose concentration reached to 0.2 mmol L⁻¹, two glucose units bound to the TPE, resulting in a decrease in the activity of the adduct formation, thereby releasing the fluorescence. When the concentration of glucose increased to 5 mmol L⁻¹, the adduct further aggregated and the fluorescence intensity reached the maximum. Due to the oligomerization was a reversible equilibrium process, the adduct began to dissolve and the fluorescence intensity began to decrease when the concentration was further increased.



In another intriguing example, Li *et al.* recently reported a similar glucose fluorescent sensor **24** (TPEA + BAP) with the same response mechanism but a different method to induce aggregation, as depicted in Fig. 3.⁷² Negatively charge of

phenylboronic acid-containing polymer (BAP) induced positively charged tetraphenylethylene (TPEA) aggregation by electrostatic interaction, thus aryl rotor intramolecular rotation was limited, and the excited state released fluorescence through the radiation decay. Subsequently, after adding glucose and glucose oxidase, there was the formation of H₂O₂ that would react with PBA and then formed a weak acid phenol, thereby reducing the negative charge on the BAP, resulting in disaggregation of TPEA. The limited internal rotation was liberated, and radiation decay transferred to non-radiation decay, resulting in fluorescence intensity weakening. Simultaneously, the team found that sensor **24** has small fluorescence changes when added D-fructose, D-galactose, and D-mannose, and then they successfully used sensor **24** to detect glucose in human serum. This is the first fluorescent sensor based on the difference in acidity between PBA and phenol, which brings a new concept for the study of glucose fluorescent sensors.

2.3. Ribose boronic acid sensors (Table 4)

Ribose can be used for the treatment of hepatitis B virus (HBV) and other diseases, the detection of ribose concentration in the body is very important.⁷³ Zhang *et al.* synthesized a set of differently substituted diboronic acid sensor arrays (25), which achieved a discrimination of all tested five disaccharides and six monosaccharides by linear discriminant analysis (LDA).⁷⁴ Fructose and ribose are the most selective in the binding selectivity of tested monosaccharides. The occurrence of different selectivity may be ascribed to the rigid and coplanar furanose form containing a pair of adjacent hydroxyl groups, which prefer to combine with boronic acid in order to minimize the angular strain. Moreover, the spatial orientation of the diol moiety largely regulates the combined process. This is the first time the IDA protocol involving diboronic acid sensors, providing new ideas for the development of sensors.

Lopez *et al.* described a new long-wavelength fluorescent sensor **26** containing a tricarbo-cyanine and boronic acid



Fig. 3 Cartoon illustrating sensor **24** detecting glucose.⁷²



structure.⁷⁵ By adjusting the pH of the medium, this sensor can selectively recognize different kinds of carbohydrates. In one typical example, sensor **26** can selectively recognize ribose and fructose in the pH range of 7.8 to 8.3. Interestingly, this sensor has the longest fluorescent emission reported upon carbohydrates interaction. After excited at 720 nm or 637 nm, it has a maximum at 820 nm. Due to a sensitive signal in aqueous media and avoiding the use of co-solvents, sensor **26** can yield a true fluorescent response. Therefore, this sensor is well-suited for detecting glycan abundance in cells or tissues as well as other bioanalytical applications.

Cell surface glycoprotein is composed of sugar and protein, such as sialyl Lewis X, sialyl Lewis A, *etc.* closely correlated with the development of tumor cells. These cell surface carbohydrates are normally regarded as markers of tumor cells.⁷⁴ Borate compounds can bind to tumor cells and visualize them *via* fluorescence. A sensor (such as anthracene boronic acid sensors) prepared by linking two boronic acid groups with a peptide has highly selective to sialyl Lewis X and can be used to selectively label the surface of human hepatoma cells.⁷⁶ Sialyl Lewis X is a kind of carbohydrates, which is not only considered a tumor cell marker but also as an antigen associated with the malignant behavior of tumor cells.⁷⁷

In early 2002, Wang *et al.* reported the synthesis of an anthracene diboronic acid sensor **27** for sialyl Lewis X detection by an exquisite fabrication between diboronic acid groups.⁷⁸ The sensor **27** has a strong affinity with sialyl Lewis X and is capable of selectively labeling sialyl Lewis X of HepG2 cells. Encouraged by the positive result, Wang *et al.* recently fabricated a novel fluorescent sensor **28** which is capable of selectively labeling the HEPG2 and HEP3B cell lines at low concentration (1 $\mu\text{mol L}^{-1}$).⁷⁹

Chu *et al.* developed boronolectin with high affinity and selectivity to recognize sialyl Lewis X, and fabricated sensor **29** by conjugated boronolectin with known fluorescent group BODIPY. In a further study, sensor **29** was successfully applied

to fluorescence imaging of implanted tumor in mice.²⁵ This work indicates that boronolectin can be used for selective imaging tumor *in vivo*.

Wang *et al.* synthesized four anthracene-based fluorescent diboronic acid sensors (**30a–d**) and examined the selectivity of different length linkers for sialyl Lewis.⁸⁰ It was found that the fluorescence of **30a** increased after binding to sialyl Lewis Y. The result indicates that **30a** has a high sensitivity and selectivity for sialyl Lewis Y. Although all the diboronic acids **30a–d** have very similar molecular structures, the different length linkers may affect the difference in the relative positions of the boronic acid groups, thereby causing different selectivity. Subsequently, Wang and co-worker evaluated the ability of **30a** to selectively label sialyl Lewis Y-expressing cells and found that sensor **30a** selectively stained HEP3B cells. To date, there are no sensitive and selective boronic acid-based sensors for sialyl Lewis Y, therefore sensor **30a** is a very valuable research tool and potential diagnostic agent.

Chang *et al.* synthesized three potential diboronic acid fluorescent sensors **31–33** to detect sialyl Lewis X, which bind to sialyl Lewis X antigens by PET mechanism.²⁴ Wherein the sensor **33** exhibits the strongest fluorescence enhancement when combined with sialyl Lewis X. Moreover, it was confirmed non-toxic to the cells and well selective to detect sialyl Lewis X. This sensor holds great potential for the diagnosis of tumor cells.

Sialic acids are unusual carbohydrates that are widely expressed at the termini of glycan chains on the cell surface. In particular, compared to normal cells, it has a much higher expression level on the cancer cells surface.^{81,82} Zhang *et al.* reported a novel method to analyze sialic acids on cancer cells surface *via* inductively coupled plasma mass spectrometry (ICP-MS).⁴¹ Under physiological conditions (pH 7.4), biotinylated 3-aminophenylboronic acid (biotin-APBA) **34** selectively recognizes sialic acids. Based on this property, gold nanoparticles (AuNPs) can significantly enhance the biotin-APBA signal in ICP-MS when AuNP are used as labeled elements biotin-APBA, as depicted in Fig. 4. The result demonstrated that the

Table 5 Key information of sialic acid boronic acid sensors

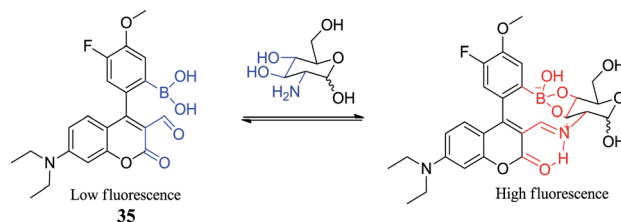
Sensor	Structure	Spectroscopic properties (λ_{ex} ; λ_{em})	<i>C</i> (LOD; range)	Functions and applications
27 ⁷⁸		370 nm; 426 nm	—; 60 $\mu\text{mol L}^{-1}$	Fluorescence intensity enhancement (nearly 40%); binding with sialyl Lewis X, labeling sialyl Lewis X of HepG2 cells
28 ⁷⁹		367 nm; 415 nm	—; 60 $\mu\text{mol L}^{-1}$	Fluorescence intensity $\uparrow$; binding with sialyl Lewis X, staining HepG2 and HEP3B liver carcinoma cells
29 ²⁵		651 nm; 660 nm	—; —	The intensity of tumor (95 ± 12); binding with sialyl Lewis X, imaging of implanted tumor in mice
30 ⁸⁰		375 nm; 424 nm	—; 60 $\mu\text{mol L}^{-1}$	Fluorescence intensity enhancement (over 70%); 30a and 30d recognize sialyl Lewis Y with selectivity over other Lewis sugars
31 ²⁴		400 nm; 617 nm	—; 0.1 to 20 $\mu\text{mol L}^{-1}$	94% yield, $> \uparrow 2$ -fold ($1 \mu\text{mol L}^{-1}$); binding with sialyl Lewis X, showed close integration with hepatocellular carcinoma cell-line HepG2 and with colon cancer cell-line Colo 205, and with Cos-7
32 ²⁴		400 nm; 614 nm	—; 0.1 to 20 $\mu\text{mol L}^{-1}$	89% yield, $> \uparrow 2$ -fold ($1 \mu\text{mol L}^{-1}$); binding with sialyl Lewis X, showed close integration with hepatoma B cell-line PLC/PRF/5, with HepG2
33 ²⁴		400 nm; 607 nm	—; 0.1 to 20 $\mu\text{mol L}^{-1}$	82% yield, $\uparrow 3$ -fold ($0.10 \mu\text{mol L}^{-1}$); binding with sialyl Lewis X, showed specific integration with PLC/PRF/5 and with HepG2

proposed method is highly selective to tumor cells. HepG2 cells and MCF-7 cells were used as two tumor models to evaluate the expression level of sialic acid on the cancer cells surface. The mean numbers of sialic acid expression on MCF-7 cells and HepG2 cells were 7.0×10^9 and 5.4×10^9 , respectively. For systematic extension of the research, the numbers of HepG2 and MCF-7 cells were 120 and 64, respectively under the limits of detection. The relative standard deviations were 9.6% and 8.9%, respectively. And the linear ranges for HepG2 cell and MCF-7 cell were 300–1000 and 170–11 000, respectively. This method can be applied to analyze sialic acid on the tumor cells surface, which is favorable to diagnose cancer according to tumor markers.⁸³

2.5. Glucosamine boronic acid sensors

Although pharmacokinetics and pharmacodynamics of glucosamine are unclear, glucosamine is one of the most popular non-prescription nutritional products on the market that is used to treat osteoarthritis. However, reports related glucosamine on the treatment of diseases are various, such as rheumatoid arthritis, gastric ulcer and hepatitis.⁸⁴ The concentration of glucosamine in normal living cells is between 1 and 2 mmol L⁻¹, but it can reach 10 mmol L⁻¹ if oral administration. High concentrations of glucosamine or its derivatives can inhibit certain tumor cells.⁸⁵ Those findings are favorable in developing new drugs for the treatment of cancer, thus the detection of glucosamine is particularly important. Tam Minh Tran *et al.* reported a novel sensor **35** for glucosamine.⁴² Based on a boronic acid-containing coumarin aldehyde, the sensor **35** has a smaller binding chamber. Due to form a boronic ester and an iminium ion, it exhibits an excellent selectivity for glucosamine. The aldehyde group of the sensor **35** can be reversibly bound to the primary amine to form an ammonium ion, and the ammonium ion enhances the ICT of the coumarin, resulting in a large red shift of the excitation spectrum. When added glucosamine at therapeutic concentration and excited at 488 nm, sensor emission increased and moved from 520 nm to 568 nm. The sensor has a higher fluorescence intensity and binding affinity towards glucosamine than other similar biomolecules. Compared to simple amino acids, the binding constant ($K_a = 4100 \text{ L mol}^{-1}$) was nearly two orders of magnitude higher. The study offered a new concept for the fabrication

of a highly selective open optical sensor that selectively detects multifunctional biomolecules.



2.6. α -hydroxy carboxylate boronic acid sensors

Lactate is a biologically important α -hydroxy carboxylate formed by the red blood cells, and its abnormally high content (>6.5 mM) is associated with sepsis, trauma and other severe diseases. Therefore, monitoring lactate content is an important significance for intensive care unit diagnosis and prevention of diseases. Hansen *et al.* reported that BODIPY-based boronic acid pinacolate derivatives sensors **36a** and **36b** act as high lactate selectivity detectors at physiological pH (7.4).⁴³ Interestingly, some biologically important monosaccharides (D-glucose, D-fructose, and D-mannose) were found to have no response to sensors **36a** and **36b**. The potentially interfering substances (L-malate, vitamin C) are often overlooked because their concentrations are constant and low in the body. Sensors **36a** and **36b** have absorption maxima at 612 nm and 613 nm respectively, and their respective absorption spectra are the same as their excitation spectra. As the DL-lactate concentration is increased, sensors **36a** and **36b** exhibit a significant increase in excitation and emission intensity. This phenomenon may be ascribed to the fact that the electrons are less likely to be accepted by the arylboronate unit, resulting in the oxidative quenching of the BODIPY core upon arylboronate formation decreasing.

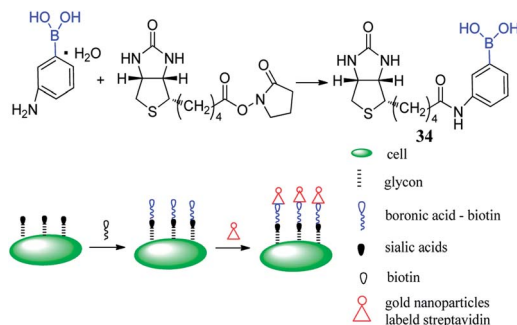
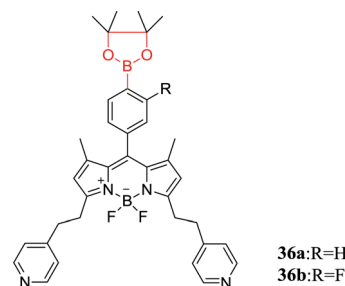
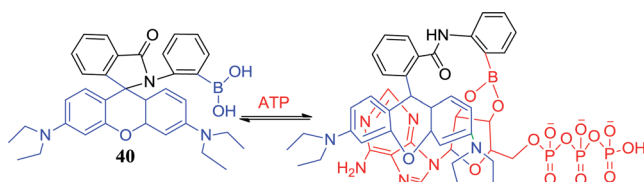


Fig. 4 Cartoon illustrating sensor 34 combining with AuNPs.⁴¹

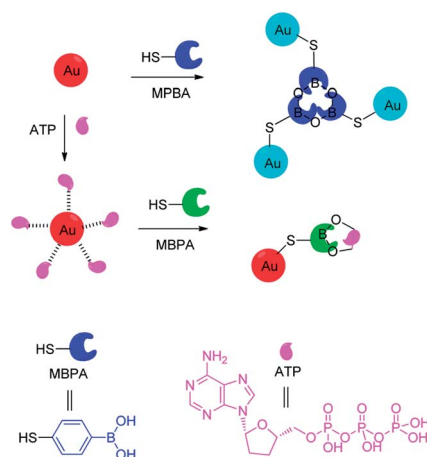
Owing to most pharmaceutical agents requires asymmetric synthesis in the progress of discovery and production, the fabrication of available analytical tools for the recognition of the enantio-composition of reaction products plays a key role. Wu *et al.* fabricated chirality sensors **37** and **38** for α -hydroxy carboxylates by linked boronic acid groups to a perylene bisimide (PBI) chromophore and induced helical aggregation of achiral PBI.⁸⁶ PBI chromophore functionalized with boronic acid moieties is shown to be efficient chirality sensors for α -hydroxy carboxylates. The aggregates displayed induced circular dichroism (CD) signals from the PBI chromophore and indicated

Adenosine triphosphate (ATP) mainly provides energy for cells and plays an important role in the activation of neuronal transmission,⁸⁸ ion channel.⁸⁹ The development of sensors that effectively detect intracellular ATP concentrations is important for the study of human metabolic activity and the monitoring of health levels.⁹⁰ Wang *et al.* reported sensor **40** that has good biocompatibility and membrane permeation can rapidly detect intracellular ATP.⁴⁴ There were three aspects facilitating the formation of ring-opening structure and produce strong fluorescence. First, the boronic acid group combined with the ribose moiety of ATP *via* the reversible covalent bond and forms boronic acid esters. Second, the π - π stack was formed by xanthane and adenine. Third, there was the electrostatic interaction between the amino group and the phosphoric acid ester group. Sensor **40** is effective in response to ATP at a concentration of $10\ \mu\text{mol L}^{-1}$, while has no significant fluorescence changes with other biomolecules such as carbohydrates, metal ions, *etc.* The team cultured cells with high levels of ATP by using camptothecin-induced apoptosis, and then sensed them with fluorescent sensor **40**. The results showed that camptothecin-treated cells were clearly stained, while the untreated control group was not stained. The sensor can effectively monitor intracellular ATP levels in real time and provides an effective strategy for the development of such sensors.



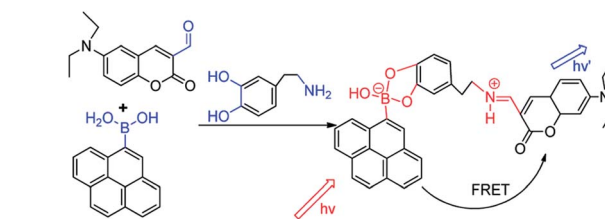
2.8. Amyloid- β plaques boronic acid sensors

Amyloid- β (A β) plaques are mainly composed of the amyloid- β peptide, which is a key pathological feature of AD.⁹¹ Thus, the detection of A β plaques can be used to monitor the potential for AD progression *in vitro* and *in vivo*.⁹² Recently, the interest in the research of the A β plaque dye has increased, such as Thioflavin T,⁹³ DAPI,⁹⁴ Congo red⁹⁵ and so on. Jung *et al.* found that boronic acid has a good selectivity to A β aggregation and fabricated a boronic acid fluorescent sensor **41c**, which significantly increased the fluorescence intensity in response to A β aggregation (64.37 fold, $F_{A\beta}/F_0$), and the wavelength had a blue shift (105 nm).⁴⁶ They found that boronic acid as a functional group improved the binding affinity with the A β aggregates (K_D value = $0.79 \pm 0.05 \mu\text{mol L}^{-1}$ for **41c**) and confirmed that **41c** selectively stained A β plaques in brain slices of APP/PS1 mice. Using mice (normal and APP/PS1) for fluorescence imaging *in vitro* also showed that **41c** is able to penetrate the blood-brain barrier (BBB) and stains the A β -plaque in the brain. From these results, it showed that **41c** will be useful as a fluorescent sensor in AD-related preclinical studies and provides valuable information for the development of A β -plaque sensors.

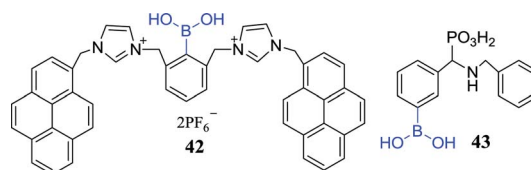


29410 | RSC Adv., 2018, 8, 29400–29427

In a further study of catecholamines, the analytical methods are increasingly diversified. It is important to choose a high selectivity and sensitivity method for catecholamines. Up until now, the main analytical methods are based on high-performance liquid chromatography (HPLC). It is less application *via* combining capillary electrophoresis with fluorescence spectrophotometry or combining electrochemical analysis with liquid chromatography as analytical methods.⁹⁸ Catecholamines are chemically characterized by a dihydroxybenzene nucleus and a side chain with amino groups. In the biological sample, the content of catecholamines is very low. Furthermore, catecholamines have extremely poor stability and are easily oxidized. In addition, it is difficult to accurately determine the concentration of catecholamines in the biological sample by adding various endogenous chemical disruptors. High selectivity and sensitivity in the determination of catecholamines in biological samples such as the precise determination of serum norepinephrine or adrenaline are currently required to achieve the clinical goal, thus the development of a simple operation,



In another intriguing example, Jun *et al.* fabricated a fluorescent sensor **42** which is used to detect catecholamines, such as dopamine, dopa, and 3,4-dihydroxyphenylacetic acid (DOPAC).¹⁰¹ They found that DOPAC shows the largest association constant with sensor **42** and displays fluorescence quenching effects, while D-fructose, D-glucose, and phenylalanine have no remarkable fluorescence change. In addition, they carefully explained the unique intermolecular excimer formation and fluorescence quenching effects with DOPAC and catechols based on the theoretical calculations. Ptak *et al.* investigated the interaction of PBA with noradrenaline, dopamine, L-DOPA, DOPA-P and catechol *via* potentiometry and NMR spectroscopy, respectively. For comparison, they fabricated sensor **43** and did the same test. They found that PBA has a high affinity to noradrenaline, while sensor **43** shows promising ability to bind dopamine.¹⁰²



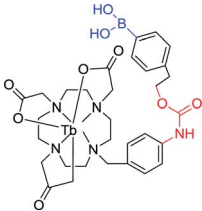
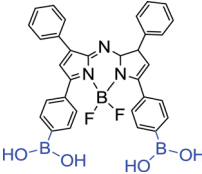
RSC Adv., 2018, 8, 29400–29427 | 29411



Sensor	Structure	Spectroscopic properties (λ_{ex} ; λ_{em})	C (LOD; range)	Functions and applications
45 ²²		332 nm; 454 nm	—; 0–100 $\mu\text{mol L}^{-1}$	$\uparrow$ 100-fold, high quantum yield and emission in the visible region; useful for the <i>in vitro</i> and <i>in vivo</i> detection of H_2O_2
46 ¹⁰⁶		400 nm; 475 nm	—; 0–250 $\mu\text{mol L}^{-1}$	$\uparrow$ 5-fold; good selectivity for H_2O_2 over other ROS
47 ¹⁰⁷		391 nm; 522 nm	$6.8 \times 10^{-8} \text{ mol L}^{-1}$; 1.0×10^{-7} to $2.5 \times 10^{-5} \text{ mol L}^{-1}$	Absorption band reached its maximum over a pH range from 9.0 to 12.0; applied to detect H_2O_2 in rain water
48 ¹⁰⁸		330 nm; 488 nm	3 mmol L^{-1} ; —	Fluorescence intensity $\uparrow$, a blue shift; demonstrating the biggest “off-on” response upon reaction with H_2O_2
49 ¹⁰⁸		350 nm; 500 nm	3 mmol L^{-1} ; —	Fluorescence intensity $\downarrow$; visualizing a bright signal against a dark background and providing easier analysis of H_2O_2 in a biological sample
50 ¹⁰⁸		350 nm; 455 nm	3 mmol L^{-1} ; 0 to 21 mmol L^{-1}	$\uparrow$ 3.6-fold; offering a new strategy to optimize the acidity of the boronic acid groups to enhance the reaction with nucleophilic ROS, whilst maximizing the amount of free sp^2 boron available for the reaction
51 ¹¹⁰		410 nm; 540 nm	—; 200 $\mu\text{mol L}^{-1}$	Emission intensities (F_{540}/F_{475}) $\downarrow$ 12-fold; visualize H_2O_2 produced in living cells by ratiometric imaging
52 ²⁰		370 nm; 450, 500 nm	—; 1 mmol L^{-1}	Emission intensities ($F_{\text{green}}/F_{\text{blue}}$) $\uparrow$ 17-fold; a marked blue-to-green emission color change in response to H_2O_2 , visualizing H_2O_2 levels in live cells
53 ¹¹¹		365 nm; 525 nm	—; 100 $\mu\text{mol L}^{-1}$	$\uparrow$ 20-fold (1 h), two photon imaging of H_2O_2 in live RAW264.7 cells; superior signal to noise and higher spatial resolution compared to other commonly used sensors for ROS, DCF and DHR
54 ¹¹²		400 nm; 650 nm	5 $\mu\text{mol L}^{-1}$; 5×10^{-3} to 100 mmol L^{-1}	16-Fold lower LOD and higher absorption, $\uparrow$ 1.6–1.8-fold (100 mmol L^{-1}); a promising tool for the detection of H_2O_2 in modern medicine and environmental monitoring
55 ¹¹⁴		280 nm	—; 200 $\mu\text{mol L}^{-1}$	$\uparrow$ 6-fold, time-gated; capable of detecting changes in H_2O_2 levels in living cells by time-gated emission spectroscopy



Table 6 (Contd.)

Sensor	Structure	Spectroscopic properties (λ_{ex} ; λ_{em})	<i>C</i> (LOD; range)	Functions and applications
56 ¹¹⁴		280 nm 545 nm	—; 200 $\mu\text{mol L}^{-1}$	$\uparrow$ 6-fold, time-gated; capable of detecting changes in H_2O_2 levels in living cells by time-gated emission spectroscopy
57 ¹¹⁵		600 nm; 682, 724 nm	—; 0.2 to 500 mmol L^{-1}	Fluorescence intensity increase (F_{730}/F_{680}), $\uparrow$ 0.47-fold; near-infrared imaging and dual-wavelength detection of intracellular H_2O_2

4.1.1.2. Hydrogen peroxide boronic acid sensors with broken linker. The researchers connected the borate with the benzyloxycarbonyl group and formed a novel fluorescent sensor. When it encounters H_2O_2 , the borate is converted to a hydroxyl group, causing the cleavage of the benzyloxycarbonyl group and releasing the fluorophore.¹⁰⁹ Based on a similar mechanism, Chang *et al.* fabricated two-photon fluorescent sensor **51**¹¹⁰ and **52**,²⁰ which have good selectivity for H_2O_2 while imaging H_2O_2 produced in living cells. Two-photon confocal microscopy showed that sensor **51** is able to detect H_2O_2 produced during the cellular immune response. Sensor **52** has good light stability and negligible toxicity, which can observe the distribution of H_2O_2 in cells and tissues.

Lindberg *et al.* reported H₂O₂ sensor 53 using a quinazolinone precipitating dye (QPD) connected to a boronic acid-based immolative linker.¹¹¹ QPD is highly photostable and capable of highly localizable fluorescent signals in cells. Synthetic B(OH)₂-QPD, in the presence of H₂O₂, yields the *para*-benzyl hydroxyl and QPD, causing a strong fluorescence precipitate. In addition, in the live cell experiments performed, bright fluorescence precipitates were observed, demonstrating a selective response to hydrogen peroxide in a cellular context and enabling the visualization of endogenous hydrogen peroxide in phagosomes.

Jia *et al.* reported a new optical sensing method for detecting H₂O₂, which introduced phenylboronic acid groups can effectively enhance the response of polydiacetylene vesicles to H₂O₂.¹¹² Sensor **54** has maximum absorption at 650 nm. It has a good linear relationship in the concentration range from 5×10^{-3} to 100 mmol L⁻¹, and R^2 reaches 0.991. The detection limit is 5 μ mol L⁻¹.

4.1.3. Other types of hydrogen peroxide boronic acid sensors. Rare earth luminescence sensors have the advantages of large stokes shift and narrow emission range, thus they can reduce the interference of background fluorescence and can be applied to the field of biological detection.¹¹³ However, the molar extinction coefficient of the rare earth compound is relatively low, and the organic ligand needs to be sensitized by energy transfer. Based on this mechanism, Chang *et al.* fabricated two lanthanide-based luminescent sensors **55** and **56**.¹¹⁴ The electron-withdrawing boronic acid group on the aromatic ring sensitized the rare earth compound by hydrolyzed to a phenolic hydroxyl group or an amino group in the presence of H_2O_2 , and then the sensors generated fluorescence.

Xu *et al.* reported that borate-functionalized azaborine-methylene dyes 57 showed changes in intracellular H_2O_2 during biological processes, as depicted in Fig. 9.¹¹⁵ This is a designed sensor for near-infrared imaging and dual-wavelength detection. Due to proper cell permeability and long excitation and emission wavelengths, it can avoid autofluorescence from natural cell interference. Moreover, the selectivity of the boronic acid group to react with hydrogen peroxide is higher than other ROS.

4.2. Peroxynitrite boronic acid sensors

Peroxynitrite (ONOO^-) is a highly active oxidant and an effective nitrating agent in physiological and pathological processes, which is formed by nitric oxide (NO) and O_2^{2-} .¹¹⁶ The use of simple and rapid methods for the effective and applicable detection of ONOO^- is increasingly significant. Han *et al.* synthesized a fluorescent borate-based sensor **58** for rapid

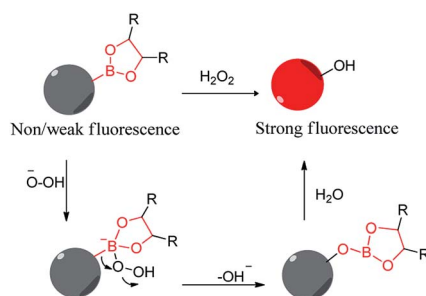


Fig. 8 H₂O₂ detection diagram.



Fig. 9 Cartoon illustration of intracellular hydrogen peroxide using sensor **56**.¹¹⁵

detection of ONOO^- by a reaction-based indicator displacement assay (RIA).¹¹⁷ The fluorescent sensor KB7 was based on the effective coupling between DCM and the boronic acid moiety. DCM dye had a long excitation and emission wavelength¹¹⁸ and the boronic acid moiety was acted as a saccharide receptor.¹¹⁹ The boronic acid moiety interacted rapidly with lactulose in an aqueous media and formed a fluorescent KB7-lactulose complex (sensor **58**) that exhibits higher sensitivity and better selectivity for ONOO^- than other tested substances. The introduction of the glycosyl group not only improved the water solubility and biocompatibility of KB7-lactulose complex, but also protected the boronic acid from oxidation by other oxidants. This might be ascribed to the mechanism that ONOO^- attacked aromatic carbon adjacent to the boron atom, resulting in partial cracking of the boronic acid. The sensor of KB7 ($20 \mu\text{mol L}^{-1}$)-lactulose (100 mmol L^{-1}) can penetrate into viable cells and show strong fluorescence throughout the cytoplasm. Sensor **58** can be used for visualization of ONOO^- . Subsequently, cytotoxicity tests conducted by the team showed non-toxic. Compared to other competitive ROS or nitrogen species (RNS), the sensor exhibits better selectivity for ONOO^- and is more useful for measuring trace amounts of ONOO^- in live cells and real water samples. This study offers insight into the development of displacement test based on fluorescent sensors with enhanced water solubility and biocompatibility.



5. Ions boronic acid sensors (Table 7)

Owing to the simplicity and the low detection limit of the fluorescence, sensors based on the ion-induced changes in fluorescence have attracted numerous researchers devoting their time and energies to the investigation. Recently, an abundance of boronic acid sensors is fabricated to detect all kinds of ionic compounds, including fluoride sensors,¹⁷ copper ions,^{120,121} mercury ion,¹²² etc.

5.1. Fluoride ion boronic acid sensors

Low concentrations of fluoride anions have been shown to be effective in preventing dental caries, and their levels in water are above 4 ppm, which can seriously affect human health, such as fluorosis. It is becoming extremely important to monitor the concentration of fluoride in real time by the simple and efficient method.¹²³ Mohammadpour *et al.* reported that carbon nano-dots (CDs) can be used as a fluorescence platform for recognition of fluoride ions by the inner filter effect (IFE) of simple aryl boronic acid, and conducted the comprehensive experiments and theoretical studies of water-soluble fluoride sensors.¹⁷ The comparison of the UV spectra of NPBA and PBA has reflected that the acidic power of the NPBA's acid surpassed that of the PBA when adding the fluoride. It indicated a significant effect on the acidic power of the aromatic acid by the resonance overlap when the electron withdrawing groups was on the *para*-position of the benzene ring. In this experimental condition, it was determined to achieve maximum fluorescence change when the NPBA concentration was adjusted to 0.5 mmol L^{-1} under buffer conditions (phosphate acetate 0.05 mol L^{-1} , pH 4) and after incubated for 5 minutes. The signal of the CDs/NPBA solution was gradually increasing and then suppressed when the concentration of fluoride ions was continuously increased. Furthermore, fluorescence signal changed with fluoride concentration manifesting a linear range of 0 to 15 mmol L^{-1} , and the LOD value of $1.46 \times 10^{-4} \text{ (L)}$ was still meeting EPA's safety requirements for water. Selective experiments indicated that the boron center of NPBA is highly selective for fluoride and has no significant affinity for chlorides, bromides, acetates, phosphates, and nitrates. Subsequently, DFT calculations indicated that the introduction of electron-withdrawing groups on the benzene ring of NPBA may increase the Lewis acids properties and facilitates to fabricate a more sensitive fluoride sensor.

Sensor **16** was reported by Huang *et al.* for recognizing D-glucose. Interestingly, it can detect fluoride ions in another sensing system. Wu *et al.* reported a sensing system based on sensor **16** capable of directly detecting fluoride ions.¹²⁴ This is a combination of fluoride ions that triggers the aggregation of sensor **16** with catechol in an acidic aqueous solution, resulting in intense fluorescence changes. The fluoride binding constant is higher than 10^3 L mol^{-1} . This may be ascribed to the presence of the catechol increasing the Lewis acidity, thereby enhancing the fluoride affinity of the boronic acid. In addition, the boronate fluoride complex is mixed with bulk water to enhance the apparent fluoride affinity.



Table 7 Key information of ionic compounds boronic acid sensors

Sensor	Structure	Spectroscopic properties (λ_{ex} ; λ_{em})	C (LOD; range)	Functions and applications
59 ¹²⁰		450 nm; 525 nm	—; 0–10 $\mu\text{mol L}^{-1}$	Red-shift, fluorescence intensity $\downarrow$ 75%; displaying high selectivity for Cu^{2+} in living cells, 59 - Cu^{2+} displayed fluorescence enhancement with fructose, and the system could be described as a fluorescence INHIBIT logic gate
59a ¹²⁰		450 nm; 525 nm	—; —	No fluorescence intensity changes; suggesting the importance of the boronic acid moiety in 59 for the binding of Cu^{2+}
59b ¹²⁰		450 nm; 525 nm	—; —	No fluorescence intensity changes; suggesting the imine group plays a role in the coordination of Cu^{2+}
60 ¹²¹		270 nm; 435 nm	—; $5 \times 10^{-3} \text{ mol L}^{-1}$	Huge chemical shift, colourimetric and “turn on” fluorescence sensor of F^- ; distinct visual color changes (colorless to yellow), a colorimetric sensor for Cu^{2+} in aqueous medium; acting as colorimetric sensor for Cu^{2+} and colorimetric as well as fluorimetric sensor for F^- among the studied ions
61 ¹²²		510 nm; 580 nm	—; 3×10^{-3} to 1.5 mol L^{-1}	The colorimetric change, fluorescence intensity $\uparrow$; “Off-On”-type fluorescent and colorimetric changes for Hg^{2+}
62 ¹²²		510 nm; 580 nm	—; 3×10^{-3} to 0.6 mol L^{-1}	The colorimetric change, $\uparrow$ 9-fold; “Off-On”-type fluorescent and colorimetric changes for Hg^{2+}
63 ¹²⁶	—	<400 nm; 520, 690 nm	8 nmol L^{-1} ; 0.01 to $5 \mu\text{mol L}^{-1}$	Fluorescence intensity $\downarrow$, colorimetric sensor, changed from blue to red; meeting the requirement of the WHO standard for the detection of the maximum allowable level of Hg^{2+} in drinking water
64 ¹²⁹		319 nm; 540 nm	645 ppm; $500 \mu\text{mol L}^{-1}$	Blue shift, color change from yellow to colorless, fluorescence quenching; selective fluorescent sensor toward CN^- in the presence of most competing anions
65 ¹³²	—	490 nm; 540 nm	$0.28 \mu\text{mol L}^{-1}$; 1.39 to $260 \mu\text{mol L}^{-1}$	Fluorescence intensity $\downarrow$; detecting $\text{Cr}(\text{VI})$

Copper ions (Cu^{2+}) play a key role in the catalysis of cytochrome C oxidase, tyrosinase, *etc.* And excessive copper ions are highly toxic to organisms and can induce neurodegenerative diseases.¹²⁵ Based on these biological implications, fluorescent

sensors for Cu^{2+} have been extensively explored. Li *et al.* reported three fluorescent sensors (**59**, **59a** and **59b**). Wherein borate fluorescent sensor **59** showing high selectivity for Cu^{2+} in living cells, which uses naphthamide as a mother nucleus and boronic acid group as a binding site.¹²⁰ This is few examples of boronic acid-based fluorescent chemosensors for Cu^{2+} . The



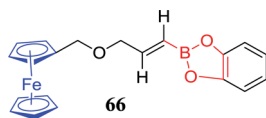
5.3. Mercury ion boronic acid sensors

Zhou *et al.* have designed a simple and rapid colorimetric sensor **63** for detecting Hg^{2+} that induced AuNP aggregation by MPBA in an aqueous medium.¹²⁶ Hg^{2+} inhibited this aggregation, resulting in a visible color change of the AuNP solution from red to blue, while no significant color change was observed

Owing to mining, electroplating, dyes and other industries discharge a large amount of waste water containing Cr, it brings great harm to the environment. The development of sensors capable of efficiently monitoring Cr in real time can undoubtedly control the random discharge of Cr and reduce the pollution of heavy metals to the environment.¹³¹ Tian *et al.* used 3-aminophenylboronic acid as a starting material to prepare nitrogen and boron co-doped carbon dots sensor **65** that has a high quantum yield.¹³² It has a good linear relationship in the concentration range from 1.39 to 260 $\mu\text{mol L}^{-1}$, and R^2 reaches 0.997. The detection limit is 0.28 $\mu\text{mol L}^{-1}$. The synthesized N/B-CD exhibited strong green fluorescence, which is applied to real sample detection. The moreover, the sensor was utilized for the analysis of dopamine in biological samples.

Electrochemical sensors detect compounds by converting biological events to an electronic signal through the special combination or catalytic reaction on the electrode surface.^{133,134} The electrochemical biosensor is typically fabricated by modifying the surface of the metal and carbon electrode with special materials, such as polymers, self-assembled monolayers, organic oils, biomaterials (enzymes, antibodies), and so on.¹³⁵

Thakur *et al.* fabricated a new ferrocene-modified boronic acid sensor **66** and found the electrochemical and spectral properties in acetonitrile.¹³⁹ The sensor exhibits large cathodic displacements of the redox potential of Fe (II/III) pairs when combined with fluoride ions ($K = 10^6 \text{ L mol}^{-1}$), whereas it displays a negligible affinity towards other effective competitors, such as Cl^- , Br^- , I^- , AcO^- . It indicated that the sensor has good selectivity for fluoride ion in organic solvents. Consequently, it can induce a strong color change from yellow to deep green associated with aerobic oxidation of the Fc moiety, and the fluorescence emission is quenched drastically. Due to the transformation of boronic esters to anionic borates, there is a strong effect on the redox potential and color adjacent to ferrocene. Therefore, it holds the potential to “naked eye” detection of fluoride ions.



The scheme illustrates the synthesis of the ERGO-GC conjugate. It begins with Graphene Oxide (GO) reacting with 4-aminophenylboronic acid to form the ERGO-GC conjugate. The ERGO-GC conjugate is then reacted with a sugar derivative (a cyclic sugar with a carboxylic acid group and a hydroxyl group) to form the final conjugate structure.

Zhou *et al.* reported that the CdS QDs were immobilized in a microgel containing boronic acid groups and have a good

Table 8 Key information of smart polymeric materials boronic acid sensors

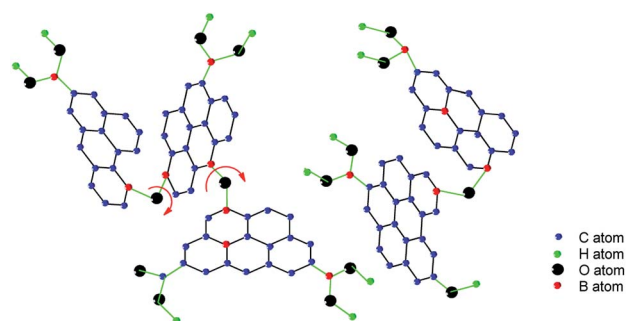
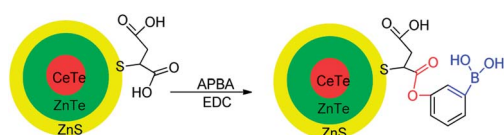
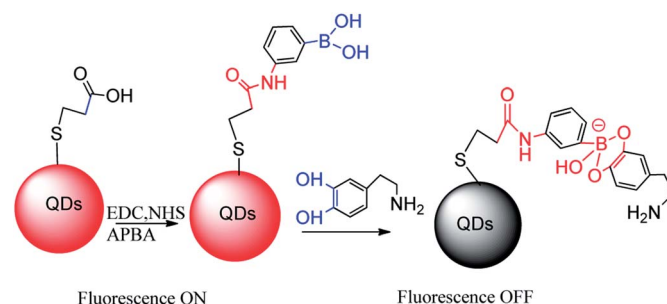
Sensor	Structure	Spectroscopic properties (λ_{ex} ; λ_{em})	C (LOD; range)	Functions and applications
67 ¹⁵⁰	—	620 nm; 736 nm	0.2 $\mu\text{mol L}^{-1}$; 0–400 $\mu\text{mol L}^{-1}$	Fluorescence intensity↓; applied to the detection of dopamine in human serum sample
68 ¹⁵¹	—	—; 653 nm	23.1, 118.7 $\mu\text{mol L}^{-1}$; 0–30 mmol L^{-1}	Fluorescence intensity↑; serving as “turn-on” detection of glucose in blood serum
70 ¹⁶⁰	—	360 nm; 500 nm	2 mg mL^{-1} ; 2 to 75 mg mL^{-1}	Fluorescence intensity↑; easily synthesized and can be stored for a period of long time for the detection based application
72 ¹⁶¹	—	260 nm; 340 nm	0.12 $\mu\text{mol L}^{-1}$; 1–100 mmol L^{-1}	Fluorescence intensity↑; fast and ultrasensitive determination of carbohydrates in biofluids and semi-solid biotissues carbohydrate
73 ¹⁷⁰	—	302 nm; 388 nm	—; 0–200 mmol L^{-1}	Fluorescence intensity↓, higher binding constant of sialic acid compared to other carbohydrates ($K_{\text{pH}7.4} = 12.3$, $K_{\text{pH}6.5} = 12.7$); offering a highly translational approach for clinical diagnosis and therapy of solid tumors
74 ¹⁷¹	—	281 nm; 418 nm	0.167 nmol L^{-1} ; 0–100 nmol L^{-1}	Fluorescence intensity↑; determining the 5hmC content of genomic DNA in tissue samples, serving as a useful diagnostic and prognostic tool for disease

selectivity to glucose.¹⁴⁴ For the expanded research, they modified CdTe/ZnTe/ZnS core-shell (CS) QDs with PBA, and incorporated them into mouse melanoma cells, as depicted in Fig. 11. As a result, they could successfully image mouse melanoma cells.¹¹

Zhang *et al.* reported firstly the method of boron-doped graphene quantum dots (BGQD), which selectively recognize glucose on the surface of BGQD,¹⁴⁹ as depicted in Fig. 12. This may be ascribed to the reaction of two *cis*-diols units in glucose with two boronic acid groups on the surface of BGQD. They produced a structurally rigid BGQD-glucose aggregation that limited intramolecular rotation, blocked nonradiative relaxation channels, and filled the radiation attenuation, resulting in a substantial increase in the strength of PL. Due to the absence of two *cis*-diols units, fructose, galactose or mannose were simply combined with BGQDs containing exposed boronic acid groups, but couldn't be further combined to form an aggregation. They found that the signal intensity increases with increasing glucose concentration in the range of 0.1 to 10 mmol L^{-1} , the detection limit is about 0.06 mmol L^{-1} . This study brought a new scientific understanding of glucose detection.

Due to boronic acids formed stable boronate complexes with vicinal diols, Liu *et al.* functionalized water-soluble sensor 67 (CuInS₂ QDs) with 3-aminophenyl boronic acid by the one-step hydrothermal method.¹⁵⁰ The CuInS₂ QDs were covalently bound to the 3-aminophenyl boronic acid and formed 3-aminophenyl boronic acid functionalized CuInS₂

quantum dots (F-CuInS₂-QDs). This sensor contained boronic acid groups, which were capable of reacting with *ortho*-diols to form a five- or six-membered cyclic ester in an aqueous alkaline solution. This combination caused F-CuInS₂-QDs fluorescence quenching. Consequently, the sensor could be applied to detect dopamine based on this property, as depicted in Fig. 13. Under the optimum conditions, the linear range of dopamine detection is 0.5 to 40 mol L^{-1} , and the detection limit is 0.2 mol L^{-1} .

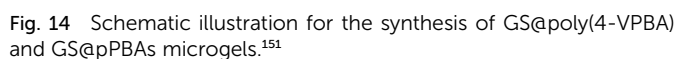
Fig. 12 Schematic illustration of the BGQD.¹⁴⁹Fig. 11 Schematic illustration of modification progress of CdTe/ZnTe/ZnS core-shell (CS) QDs with PBA.¹¹Fig. 13 Boronic acid QDs synthesis and dopamine detection diagram.¹⁵⁰

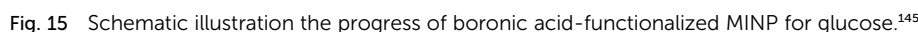
The hydrogel is a polymer network that can swell and retain aqueous solutions, meeting the need of functional and tunable biomaterials.¹⁵² Cai *et al.* synthesized a glucose-reactive hydrogel **69** that 3-acrylamidophenyl boronic acid copolymerized with ethylaminoethyl methacrylic (p(APBA-b-LAMA)).²⁷ When glucose was added, the insulin release was significantly increased, indicating that glucose was triggered by the molecular exchange process. Subsequently, cytotoxicity analysis *in vitro* showed that the presence of carbohydrates polymers did not adversely affect cell proliferation. Due to the introduction of the carbohydrates moiety, cell compatibility of the carbohydrates-polymer hydrogel with PBA is significantly improved, which makes it potentially useful in the biomedical field. Consequently, the development of intelligent glucose response insulin delivery system in the treatment of diabetes has an important practical application.



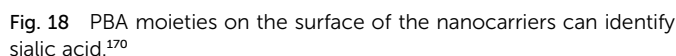
The molecularly imprinted polymer (MIP) is selectively detected the target compound by binding the binding cavity. Target compound polymerizes with the crosslinking agent and functional acceptor, and then binding cavity forms by removing the target compound under appropriate conditions, which is similar to target compound on size, shape and surface chemical properties. Owing to the prepared binding cavity is suitable for the target compound, selective recognition can be performed.¹⁵³ Zhao *et al.* developed the biologically significant sensor for glucose, mannose, and galactose through the borate affinity MIP method,¹⁴⁵ as depicted in Fig. 15. They converted glucose into diborate and then implanted it into the micelle by copolymerization with the methacrylate group in the micellar nucleus, followed by washing with different polar solutions to remove the glucose and obtained a binding cavity. The K_a value between MINP (glucose) and glucose is $1.18 \times 10^3 \text{ L mol}^{-1}$, and the K_a value of the other monosaccharides is negligible, which is in good agreement with the expected selective binding of the target compound. Molecular imprinting creates complementary objects that are increasingly popular,¹⁵⁴ and the number of binding sites of per nanoparticle can be controlled by the ratio of surfactant to the target compound. It is completely water-soluble and can be used to precisely position and orient the binding groups on a cross-linked micelle, which distinguishes different carbohydrates.

For small molecule sensors, there are some constraints to improving the selectivity by changing their structure, such as increasing the amount of boronic acid groups as recognition sites. Owing to the comfortable spatial position between boronic acids also plays an important role in the selectivity of the sensor, increasing the molecular structure undoubtedly increases the difficulty of synthesis. Thus, designing higher selective sensors requires the assistance of other fields of technology. Nanosensors have the high surface area, strong adsorption capacity and good electrical conductivity, which endows special properties to some small molecule sensors. Nanomaterials are very sensitive to changes in the external environment, such as temperature, light, humidity, *etc.*, which can cause rapid changes in surface or interface ion valence and electron output.¹⁵⁵ Therefore, the small molecule sensors connected to the nanomaterial interact with detection object causing a small change, which is amplified by the nanomaterial, making easily captured by the detector, thereby improving the selectivity and sensitivity of the sensor to a certain extent. Carbon nanometer is an ideal building material. For instance,



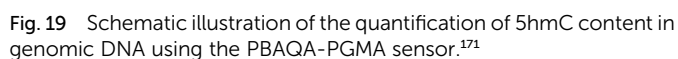


Ouyang *et al.* reported an ultra-sensitive solid phase micro-extraction (SPME) sensor 72. It was fabricated by PBA functionalizing CNTs and successfully applied to direct recognition of carbohydrates in biological fluids and semi-solid biological tissue *in vitro* or *in vivo*.¹⁶¹ First, PBA functionalized CNTs acted as carbohydrates nanoreceptors. Nano-receptors hybridized with acid resisting polyacrylonitrile (PAN) groups in an appropriate ratio and then linked to a pretreated quartz fiber *via* the dip-coating method. In this progress, 3D interconnected architecture was formed, which facilitated the sensor binding to carbohydrates, and its enrichment factor was up to 151. The proposed sensor is able to couple with GC-MS after changing the pH, which is remarkably increasing the sensitivity of carbohydrates recognition, as depicted in Fig. 16. The sensor offered a specific scaffold of the diols unit, in particular, *cis*-diols. Thus carbohydrates that have various 1,3 or 1,2 *cis*-diols units can be easily captured by the scaffolds. Up until now, the



8. Conclusions and perspective

In recent years, the design of boronic acid sensors has become more sophisticated, and the more fields involved. As mentioned in the review above, the selectivity can be increased by adding a boronic acid groups to the molecular structure and maintaining a comfortable spatial position, or by connecting a new material such as a quantum dots to increase the fluorescence intensity. Some new material fields endow unique properties to boronic acid sensors. For example, a smart gel that forms a multifunctional hybrid nanogel with boronic acids can respond to the release of insulin regulation by a glucose sensor detecting the blood glucose concentration. Owing to smart gels can remain in patients for long periods of time, hydrogels with highly selective glucose sensors have enormous potential for clinical treatment of diabetes.¹⁷⁵ Simultaneously, some research





- 32 A. Aroca, J. M. Benito, C. Gotor and L. C. Romero, *J. Exp. Bot.*, 2017, **68**, 4915–4927.
- 33 R. Emmerstorfer, K. Radefeld, V. Havlicek, U. Besenfelder, H. Yu, C. Mayrhofer, C. Vogl, G. Brem and S. Papp, *Reprod., Fertil. Dev.*, 2017, **30**, 205–206.
- 34 N. K. Broeker, D. Andres, Y. Kang, U. Gohlke, A. Schmidt, S. Kunstmann, M. Santer and S. Barbirz, *Perspect. Sci.*, 2017, **11**, 45–52.
- 35 J. P. Lorand and J. O. Edwards, *J. Org. Chem.*, 1959, **24**, 769–774.
- 36 G. Springsteen and B. Wang, *Chem. Commun.*, 2001, 1608–1609.
- 37 G. Springsteen and B. Wang, *Tetrahedron*, 2002, **58**, 5291–5300.
- 38 T. D. James, K. R. A. S. Sandanayake and S. Shinkai, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2207–2209.
- 39 X. Wu, Z. Li, X. X. Chen, J. S. Fossey, T. D. James and Y. B. Jiang, *Chem. Soc. Rev.*, 2013, **42**, 8032–8048.
- 40 S. Jiang, J. O. Escobedo, K. K. Kim, O. Alptürk, G. K. Samoei, S. O. Fakayode, I. M. Warner, O. Rusin and R. M. Strongin, *J. Am. Chem. Soc.*, 2006, **128**, 12221–12228.
- 41 X. Zhang, B. Chen, M. He, Y. Zhang, L. Peng and B. Hu, *Analyst*, 2016, **141**, 1286–1293.
- 42 T. M. Tran, Y. Alan and T. E. Glass, *Chem. Commun.*, 2015, **51**, 7915–7918.
- 43 J. S. Hansen, T. Hoeg-Jensen and J. B. Christensen, *Tetrahedron*, 2017, **73**, 3010–3013.
- 44 L. Wang, L. Yuan, X. Zeng, J. Peng, Y. Ni, J. C. Er, W. Xu, B. K. Agrawalla, D. Su and B. Kim, *Angew. Chem.*, 2016, **55**, 1773–1776.
- 45 G. Jiang, W. Zhu, X. Shen, L. Xu, X. Li, R. Wang, C. Liu and X. Zhou, *Microchim. Acta*, 2017, 1–8.
- 46 S. J. Jung, J. Y. Lee, T. H. Kim, D. E. Lee, J. Jeon, S. D. Yang, G. H. Min, J. J. Min and D. P. Yong, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 1784–1788.
- 47 J. Yoon and A. W. Czarnik, *J. Am. Chem. Soc.*, 1992, **114**, 276–277.
- 48 F. P. Schwarz and S. P. Wasik, *Anal. Chem.*, 1976, **48**, 524–528.
- 49 J. Yoon and A. W. Czarnik, *Bioorg. Med. Chem.*, 1993, **1**, 267–271.
- 50 T. D. James, K. R. A. S. Sandanayake and S. Shinkai, *J. Chem. Soc., Chem. Commun.*, 1994, **47**, 477–478.
- 51 T. D. James, R. Iguchi and S. Shinkai, *J. Am. Chem. Soc.*, 1995, **117**, 8982–8987.
- 52 M. A. Fox, *Photochem. Photobiol.*, 1990, **52**, 617–627.
- 53 J.-r. Wei, Y.-l. Ni, W. Zhang, Z.-q. Zhang and J. Zhang, *Anal. Chim. Acta*, 2017, **960**, 110–116.
- 54 S. Cecioni and D. J. Voadlo, *J. Am. Chem. Soc.*, 2017, **139**, 8392–8395.
- 55 X. Sun, T. D. James and E. V. Anslyn, *J. Am. Chem. Soc.*, 2018, **140**, 2348–2354.
- 56 H. Eggert, J. Frederiksen, C. Morin and J. C. Norrild, *ChemInform*, 1999, **64**, 3846–3852.
- 57 Y. Liu, C. Deng, L. Tang, A. Qin, R. Hu, J. Z. Sun and B. Z. Tang, *J. Am. Chem. Soc.*, 2011, **133**, 660–663.
- 58 M. Shao and Y. Zhao, *Tetrahedron Lett.*, 2010, **51**, 2508–2511.
- 59 C. Wang, Y. Li and Y. Wei, *Sens. Actuators, B*, 2017, **247**, 595–601.
- 60 T. Kawanishi, M. A. Romey, P. C. Zhu, M. Z. Holody and S. Shinkai, *J. Fluoresc.*, 2004, **14**, 499–512.
- 61 H. Shibata, Y. J. Heo, T. Okitsu, Y. Matsunaga, T. Kawanishi and S. Takeuchi, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 17894–17898.
- 62 Y. J. Heo, H. Shibata, T. Okitsu, T. Kawanishi and S. Takeuchi, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 13399–13403.
- 63 S. Arimori, M. L. Bell, C. S. Oh and T. D. James, *Org. Lett.*, 2002, **4**, 4249–4251.
- 64 R. M. Clegg, *Curr. Opin. Biotechnol.*, 1995, **6**, 103–110.
- 65 Y. J. Huang, Y. B. Jiang, S. D. Bull, J. S. Fossey and T. D. James, *Chem. Commun.*, 2016, **52**, 3456–3469.
- 66 S. Jin, Y. Cheng, S. Reid, M. Li and B. Wang, *Med. Res. Rev.*, 2010, **30**, 171–257.
- 67 Z. Sharrett, S. Gamsey, L. Hirayama, B. Vilozy, J. T. Suri, R. A. Wessling and B. Singaram, *Org. Biomol. Chem.*, 2009, **7**, 1461–1470.
- 68 R. Badugu and C. D. Lakowicz JR Geddes, *Bioorg. Med. Chem.*, 2005, **13**, 113–119.
- 69 D. Bruen, C. Delaney, L. Florea and D. Diamond, *Sensors*, 2017, **17**, 1866.
- 70 B. Liu, N. Novikova, M. C. Simpson, M. S. Timmer, B. L. Stocker, T. Söhnle, D. C. Ware and P. J. Brothers, *Org. Biomol. Chem.*, 2016, **14**, 5205–5209.
- 71 J. Axthelm, A. Shc, M. Elstner, U. R. Gandra, H. Görls, P. Bellstedt and A. Schiller, *J. Am. Chem. Soc.*, 2017, **139**, 6165–6170.
- 72 H. Li, L. Zhu, X. Zhu and H. Zhang, *Sens. Actuators, B*, 2017, **246**, 819–825.
- 73 N. Dey and S. Bhattacharya, *Chem.–Eur. J.*, 2017, **23**, 16547–16554.
- 74 X. T. Zhang, S. Wang and G. W. Xing, *Chem.–Asian J.*, 2015, **10**, 2594–2598.
- 75 L. C. Samaniego, M. A. Lago Huvelle, M. L. Uhrig, L. F. Coluccio and C. C. Spagnuolo, *Chem. Commun.*, 2015, **51**, 4895–4898.
- 76 X. D. Xu, H. Cheng, W. H. Chen, S. X. Cheng, R. X. Zhuo and X. Z. Zhang, *Sci. Rep.*, 2013, **3**, 2679.
- 77 T. M. Kolben, F. Kraft, T. Kolben, C. Goess, A. Semmlinger, C. Dannecker, E. Schmoedel, D. Mayr, N. N. Sommer, S. Mahner and U. Jeschke, *Future Oncol.*, 2017, **13**, 145–157.
- 78 W. Yang, S. Gao, X. Gao, V. V. Karnati, W. Ni, B. Wang, W. B. Hooks, J. Carson and B. Weston, *ChemInform*, 2002, **12**, 2175–2177.
- 79 Y. E. Wang, R. X. Rong, H. Chen, M. Y. Zhu, B. H. Wang and X. L. Li, *Chin. Chem. Lett.*, 2017, **28**, 1262–1267.
- 80 Y. Wang, R. Rong, H. Chen, M. Zhu, B. Wang and X. Li, *Bioorg. Med. Chem. Lett.*, 2017, **27**, 1983–1988.
- 81 D. Wang, E. Ozhegov, L. Wang, A. Zhou, H. Nie, Y. Li and X. L. Sun, *Glycoconjugate J.*, 2016, **33**, 725–733.
- 82 A. Varki and P. Gagneux, *Ann. N. Y. Acad. Sci.*, 2012, **1253**, 16–36.

- 83 H. Wang, M. He, B. Chen and B. Hu, *J. Anal. At. Spectrom.*, 2017, **32**, 1650–1659.
- 84 J. Runhaar, R. Rozendaal, M. v. Middelkoop, J. Bijlsma, M. Doherty, K. Dziedzic, L. Lohmander, T. McAlindon, W. Zhang and S. Bierma-Zeinstra, *Ann. Rheum. Dis.*, 2017, **76**, 973–974.
- 85 Z. Xu, S. Wu, G. Huang, H. Ding, R. Gui and B. Zhu, *Mater. Lett.*, 2017, **195**, 131–135.
- 86 X. Wu, X. X. Chen, B. N. Song, Y. J. Huang, Z. Li, Z. Chen, T. D. James and Y. B. Jiang, *Chemistry*, 2014, **20**, 11793–11799.
- 87 X. X. Chen, X. Wu, P. Zhang, M. Zhang, B. N. Song, Y. J. Huang, Z. Li and Y. B. Jiang, *Chem. Commun.*, 2015, **51**, 13630–13633.
- 88 C. Sobieski, M. J. Fitzpatrick and S. J. Mennerick, *J. Neurosci.*, 2017, **37**, 1888–1899.
- 89 Z. Zhang, F. Liu and J. Chen, *Cell*, 2017, **170**, 483–491.
- 90 M. Maffei, E. Longa, A. Sabatini, A. Vacca and S. Iotti, *Eur. Biophys. J.*, 2017, **46**, 195–202.
- 91 R. H. Takahashi, T. Nagao and G. K. Gouras, *Pathol. Int.*, 2017, **67**, 185–193.
- 92 C. Zhang, A. Griciuc, E. Hudry, Y. Wan, L. Quinti, J. Ward, A. M. Forte, X. Shen, C. Ran, D. R. Elmaleh and R. E. Tanzi, *Sci. Rep.*, 2018, **8**, 1144.
- 93 E. Cabrera, P. Mathews, E. Mezhericher, T. G. Beach, J. Deng, T. A. Neubert, A. Rostagno and J. Ghiso, *Biochim. Biophys. Acta, Mol. Basis Dis.*, 2018, **1864**, 208–225.
- 94 K. H. Han, B. M. Arlian, M. S. Macauley, J. C. Paulson and R. A. Lerner, *Proc. Natl. Acad. Sci. U. S. A.*, 2018, **115**, E372–E381.
- 95 B. Baumann, A. Woehrer, G. Ricken, M. Augustin, C. Mitter, M. Pircher, G. G. Kovacs and C. K. Hitzemberger, *Sci. Rep.*, 2017, **7**, 43477.
- 96 J. Sedó, J. Saiz-Poseu, F. Busqué and D. Ruiz-Molina, *Adv. Mater.*, 2013, **25**, 653–701.
- 97 L. Eichhorn, F. Erdfelder, F. Kessler, R. C. Dolscheidpommerich, B. Zur, U. Hoffmann, R. K. Ellerkmann and R. Meyer, *Int. J. Sports Med.*, 2016, **38**, 85–91.
- 98 A. D. Andersen, M. Blaabjerg, M. Binzer, A. Kamal, H. Thagesen, T. W. Kjaer, E. Stenager and J. B. P. Gramsbergen, *J. Neurochem.*, 2017, **141**, 614–625.
- 99 D. Seto, T. Maki, N. Soh, K. Nakano, R. Ishimatsu and T. Imato, *Talanta*, 2012, **94**, 36–43.
- 100 Z. Wu, M. Li, H. Fang and B. Wang, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 7179–7182.
- 101 E. J. Jun, H. Liu, Y. C. Ji, Y. L. Jin and J. Yoon, *Sens. Actuators, B*, 2013, **176**, 611–617.
- 102 T. Ptak, P. Młynarz, A. Dobosz, A. Rydzewska and M. Prokopowicz, *J. Mol. Struct.*, 2013, **1040**, 59–64.
- 103 J. S. A. Devi, B. Aswathy, S. Asha and S. George, *J. Anal. Chem.*, 2017, **72**, 445–459.
- 104 R. J. Aitken, *Mol. Reprod. Dev.*, 2017, **84**, 1039–1052.
- 105 B. Xiao, J. Y. Goh, L. Xiao, H. Xian, K. L. Lim and Y. C. Liou, *J. Biol. Chem.*, 2017, **292**, 16697–16708.
- 106 L. Du, N. Ni, M. Li and B. Wang, *Tetrahedron Lett.*, 2010, **51**, 1152–1154.
- 107 X. Q. Zhao, B. Y. Su, H. Zheng and J. H. Yan, *Anal. Chim. Acta*, 2010, **658**, 175–179.
- 108 E. V. Lampard, A. C. Sedgwick, X. Sun, K. L. Filer, S. C. Hewins, G. Kim, J. Yoon, S. D. Bull and T. D. James, *ChemistryOpen*, 2018, **7**, 262–265.
- 109 Y. Liu, J. Niu, J. Nie, F. Meng and W. Lin, *New J. Chem.*, 2017, **41**, 3320–3325.
- 110 D. Srikun, E. W. Miller, D. W. Domaille and C. J. Chang, *J. Am. Chem. Soc.*, 2008, **130**, 4596–4597.
- 111 E. Lindberg and N. Winssinger, *ChemBioChem*, 2016, **17**, 1612–1615.
- 112 C. Jia, J. Tang, S. Lu, Y. Han and H. Huang, *J. Fluoresc.*, 2016, **26**, 121–127.
- 113 P. Mahata, S. K. Mondal, D. K. Singha and P. Majee, *Dalton Trans.*, 2016, **46**, 301–328.
- 114 A. R. Lippert, T. Gschneidner and C. J. Chang, *Chem. Commun.*, 2010, **46**, 7510–7512.
- 115 J. Xu, J. Zhai, Y. Xu, J. Zhu, Y. Qin and D. Jiang, *Analyst*, 2016, **141**, 2380–2383.
- 116 R. Radi, *J. Biol. Chem.*, 2013, **288**, 26464–26472.
- 117 K. B. Li, L. Dong, S. Zhang, W. Shi, W. P. Jia and D. M. Han, *Talanta*, 2017, **165**, 593–597.
- 118 X. Wu, X. Sun, Z. Guo, J. Tang, Y. Shen, T. D. James, H. Tian and W. Zhu, *J. Am. Chem. Soc.*, 2014, **136**, 3579–3588.
- 119 W. Zhai, X. Sun, T. D. James and J. S. Fossey, *Chem.-Asian J.*, 2015, **10**, 1836–1848.
- 120 M. Li, H. Ge, R. L. Arrowsmith, V. Mirabello, S. W. Botchway, W. Zhu, S. I. Pascu and T. D. James, *Chem. Commun.*, 2014, **50**, 11806–11809.
- 121 D. Maity, N. Hari and S. Mohanta, *ChemistrySelect*, 2017, **2**, 9037–9045.
- 122 S. K. Kim, K. M. K. Swamy, S. Y. Chung, H. N. Kim, J. K. Min, Y. Jeong and J. Yoon, *Tetrahedron Lett.*, 2010, **51**, 3286–3289.
- 123 M. Li, Z. Liu, H. C. Wang, A. C. Sedgwick, J. E. Gardiner, S. D. Bull, H. N. Xiao and T. D. James, *Dyes Pigm.*, 2017, **149**, 669–675.
- 124 X. Wu, X. X. Chen, B. N. Song, Y. J. Huang, W. J. Ouyang, Z. Li, T. D. James and Y. B. Jiang, *Chem. Commun.*, 2014, **50**, 13987–13989.
- 125 C. Paolucci, I. Khurana, A. A. Parekh, S. Li, A. J. Shih, H. Li, I. J. Di, J. D. Albarracincaballero, A. Yezerets and J. T. Miller, *Science*, 2017, **357**, 898–903.
- 126 Y. Zhou, H. Dong, L. Liu, M. Li, K. Xiao and M. Xu, *Sens. Actuators, B*, 2014, **196**, 106–111.
- 127 Y. Kong, J. Shen and A. Fan, *Anal. Sci.*, 2017, **33**, 925–930.
- 128 E. P. Randviir and C. E. Banks, *TrAC, Trends Anal. Chem.*, 2015, **64**, 75–85.
- 129 S. T. Wang, Y. W. Sie, C. F. Wan and A. T. Wu, *J. Lumin.*, 2016, **173**, 25–29.
- 130 A. a. O. El-Ballouli, Y. Zhang, S. Barlow, S. R. Marder, M. H. Al-Sayah and B. R. Kaafarani, *Tetrahedron Lett.*, 2012, **53**, 661–665.
- 131 X. Liu, T. Li, Q. Wu, X. Yan, C. Wu, X. Chen and G. Zhang, *Talanta*, 2017, **165**, 216.
- 132 T. Tian, Y. He, Y. Ge and G. Song, *Sens. Actuators, B*, 2017, **240**, 1265–1271.

- 133 T. N. Narayanan, S. Alwarappan and M. O. Valappil, *Curr. Org. Chem.*, 2015, **19**, 1163–1175.
- 134 X. R. Cheng, B. Y. Hau, T. Endo and K. Kerman, *Biosens. Bioelectron.*, 2014, **53**, 513–518.
- 135 L. Liu, N. Xia, Y. Xing and D. H. Deng, *Int. J. Electrochem. Sci.*, 2013, **8**, 11161–11174.
- 136 M. Li, S. Y. Xu, A. J. Gross, J. L. Hammond, P. Estrela, J. Weber, K. Lacina, T. D. James and F. Marken, *ChemElectroChem*, 2015, **2**, 867–871.
- 137 B. Wang, S. Takahashi, X. Du and J. Anzai, *Biosensors*, 2014, **4**, 243–256.
- 138 N. Xia, X. Wang, D. Deng, G. Wang, H. Zhai and S. J. Li, *Int. J. Electrochem. Sci.*, 2013, **8**, 9714–9722.
- 139 A. Thakur, D. Mandal, S. Sao and S. Ghosh, *J. Organomet. Chem.*, 2012, **715**, 129–135.
- 140 M. Li, W. Zhu, F. Marken and T. D. James, *Chem. Commun.*, 2015, **51**, 14562–14573.
- 141 Y. Zhou, H. Dong, L. Liu, J. Liu and M. Xu, *Biosens. Bioelectron.*, 2014, **60**, 231–236.
- 142 G. Wulff, *Pure Appl. Chem.*, 1982, **54**, 2093–2102.
- 143 M. M. Muscatello, L. E. Stunja and S. A. Asher, *Anal. Chem.*, 2009, **81**, 4978–4986.
- 144 W. Wu, T. Zhou, J. Shen and S. Zhou, *Chem. Commun.*, 2009, 4390–4392.
- 145 J. K. Awino, R. W. Gunasekara and Z. Yan, *J. Am. Chem. Soc.*, 2016, **138**, 9759–9762.
- 146 A. L. Bulin, M. Kucinska, M. Broekgaarden, E. Briars, I. Rizvi and T. Hasan, *Photodiagn. Photodyn. Ther.*, 2017, **17**, A67–A68.
- 147 M. Liu, O. Voznyy, R. Sabatini, F. P. García de Arquer, R. Munir, A. H. Balawi, X. Lan, F. Fan, G. Walters, A. R. Kirmani, S. Hoogland, F. Laquai, A. Amassian and E. H. Sargent, *Nat. Mater.*, 2016, **16**, 258–263.
- 148 C. Hunsur Ravikumar, J. Schiffman and B. Geetha, *Quantum Dots as Fluorescent Probes: Synthesis, Surface Chemistry, Energy Transfer Mechanisms, and Applications*, 2018.
- 149 L. Zhang, Z. Y. Zhang, R. P. Liang, Y. H. Li and J. D. Qiu, *Anal. Chem.*, 2014, **86**, 4423–4430.
- 150 S. Liu, F. Shi, X. Zhao, L. Chen and X. Su, *Biosens. Bioelectron.*, 2013, **47**, 379–384.
- 151 M. Zhou, J. Xie, S. Yan, X. Jiang, T. Ye and W. Wu, *Macromolecules*, 2014, **47**, 6055–6066.
- 152 T. E. Brown and K. S. Anseth, *Chem. Soc. Rev.*, 2017, **46**, 6532–6552.
- 153 J. Wackerlig and R. Schirhagl, *Anal. Chem.*, 2016, **88**, 250–261.
- 154 L. Li, Y. Lu, Z. Bie, H. Y. Chen and Z. Liu, *Angew. Chem.*, 2013, **52**, 7451–7454.
- 155 M. Ghaani, N. Nasirizadeh, S. A. Y. Ardakani, F. Z. Mehrjardi, M. Scampicchio and S. Farris, *Anal. Methods*, 2016, **8**, 1103–1110.
- 156 K. Yum, T. P. McNicholas, B. Mu and M. S. Strano, *J. Diabetes Sci. Technol.*, 2013, **7**, 72–87.
- 157 M. B. Lerner, N. Kybert, R. Mendoza and R. VILLECHENON, *Appl. Phys. Lett.*, 2013, **102**, 183113–183114.
- 158 Q. Wang, I. Kaminska, J. Niedziolkajonsson, M. Opallo, M. Li, R. Boukherroub and S. Szunerits, *Biosens. Bioelectron.*, 2013, **50**, 331–337.
- 159 T. V. Shishkanova, P. Fitl, V. Král and J. Barek, *J. Electroanal. Chem.*, 2016, **761**, 106–111.
- 160 S. K. Basiruddin and S. K. Swain, *Mater. Sci. Eng., C*, 2016, **58**, 103–109.
- 161 G. Ouyang, G. Chen, J. Qiu, J. Xu, X. A. Fang, Y. Liu, S. Liu, R. Jiang, T. Luan and F. Zeng, *Chem. Sci.*, 2016, **7**, 1487–1495.
- 162 G. Ouyang, K. D. Oakes, L. Bragg, S. Wang, H. Liu, S. Cui, M. R. Servos, D. G. Dixon and J. Pawliszyn, *Environ. Sci. Technol.*, 2011, **45**, 7792–7798.
- 163 O. P. Togunde, K. D. Oakes, M. R. Servos and J. Pawliszyn, *Environ. Sci. Technol.*, 2012, **46**, 5302–5309.
- 164 F. S. Mirnaghi and J. Pawliszyn, *Anal. Chem.*, 2012, **84**, 8301–8309.
- 165 W. J. Ramsay and H. Bayley, *Angew. Chem., Int. Ed. Engl.*, 2018, **57**, 2841–2845.
- 166 T. Nishino, H. Shiigi, M. Kiguchi and T. Nagaoka, *Chem. Commun.*, 2017, **53**, 5212–5215.
- 167 W. Zhang, W. Liu, P. Li, H. Xiao, H. Wang and B. Tang, *Angew. Chem.*, 2014, **126**, 12697–12701.
- 168 M.-H. Park, E. Reátegui, W. Li, S. N. Tessier, K. H. K. Wong, A. E. Jensen, V. Thapar, D. Ting, M. Toner, S. L. Stott and P. T. Hammond, *J. Am. Chem. Soc.*, 2017, **139**, 2741–2749.
- 169 A. Matsumoto, H. Cabral, N. Sato, K. Kataoka and Y. Miyahara, *Angew. Chem., Int. Ed.*, 2010, **49**, 5494–5497.
- 170 S. Deshayes, H. Cabral, T. Ishii, Y. Miura, S. Kobayashi, T. Yamashita, A. Matsumoto, Y. Miyahara, N. Nishiyama and K. Kataoka, *J. Am. Chem. Soc.*, 2013, **135**, 15501–15507.
- 171 H. Y. Chen, J. R. Wei, J. X. Pan, W. Zhang, F. Q. Dang, Z. Q. Zhang and J. Zhang, *Biosens. Bioelectron.*, 2017, **91**, 328–333.
- 172 A. Szwagierczak, S. Bultmann, C. S. Schmidt, F. Spada and H. Leonhardt, *Nucleic Acids Res.*, 2010, **38**, e181.
- 173 A. Matsumoto, K. Kataoka and Y. Miyahara, *Polym. J.*, 2015, **46**, 483–491.
- 174 P. M. Cal, R. F. Frade, C. Cordeiro and P. M. Gois, *Chemistry*, 2015, **21**, 8182–8187.
- 175 Z. Li, Q. Huang, Y. Liu, Q. Wang, L. Wang, S. Xiao, F. Bi and J. Ding, *Materials*, 2017, **10**, 170.