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# Boronate affinity material-based sensors for recognition and detection of glycoproteins

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Glycoproteins are closely linked to the occurrence and development of many diseases. Therefore, it is of great importance to develop highly selective, sensitive, efficient detection methods for glycoproteins. To overcome the problems with traditional detections methods, such as mass spectrometry, chromatography-mass spectrometry, and enzyme-linked immunosorbent assay, boronate affinity material (BAM)-based sensors have developed rapidly for the specific recognition and detection of glycoproteins because of the advantages of pH-controlled binding/release, reversibility of the reaction, high specificity, and high selectivity, showing their wide application prospects. In recent years, there have been many significant leaps in the use of BAMs for sensing and detecting glycoproteins, but there are still many challenges and room for development. Therefore, this review critically investigates and summarizes recent advances with BAM-based sensors for glycoprotein detection. We focus on the common boronate affinity ligands of BAMs and their grafting methods, functional materials utilized in the synthesis of BAM-based sensors, advanced technologies, and applications. Finally, we propose the remaining challenges and future perspectives to accelerate the development of BAMs, and to utilize it for further developing versatile BAMs with a variety of promising applications.

## 1. Introduction

Glycoproteins, the family of glycosylated proteins, are a kind of *cis*-diol-containing biomolecule. Large quantities of glycoproteins are found in nature, including enzymes, antigens, antibodies, and peptide hormones.[1] As we can see, glycoproteins play a vital role in the biological activities of organisms, such as in cell recognition,[2] immunomodulation,[3] and growth regulation.[4] Meanwhile, abnormal glycosylation of proteins *in vivo* is an important feature in disease progression, being related to the occurrence and development of many diseases, such as infections, tumours, cardiovascular diseases, liver diseases, kidney diseases, diabetes, and certain genetic diseases, so the detection of glycoproteins is of great value in clinical diagnosis, biological research, disease prevention, and so on.[5,6] The traditional methods of glycoprotein detection, such as mass spectrometry,[7,8] chromatography-mass spectrometry,[9] and ELISA,[10] are time-consuming, professional, and demanding for sample purity, so some facile sensors have been developed. They do not require the glycosyl groups to be released from the glycoproteins and include optical sensors,[11–13] electrochemical sensors,[14–16] and quality sensors.[17–19] An important part of glycoprotein detection is the specific recognition of glycoprotein by the sensors. For recognition of glycoproteins, molecules such as lectins,[20] antigens/antibodies,[21] and boronic acids[22] that have specific binding functions to the glycosyl groups are usually used as recognition elements. In addition, the specific spatial recognition sites of MIP synthesized by molecular imprinting technique also play an important role in glycoprotein recognition.[23] Among them, sensors made of boronate affinity[24] materials (BAMs) have the advantage of high selectivity and show great application prospects for glycoprotein recognition and detection.

BAMs are a kind of novel adsorbent material based on the properties of specific binding between boronic acid and *cis*-diols, which actively contribute to the recognition, separation, enrichment or detection of *cis*-diols.[25,26] The central principle is that boronic acids can specifically recognize *cis*-diols and reversibly form five- or six-membered cyclic esters in certain

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environments. One of the key factors that determined whether boronic acid combines with *cis*-diols is the $pK_a$ of boronic acid.[27–29] When the surrounding environmental pH is greater than the $pK_a$ of boronic acid, cyclic esters are formed, otherwise, cyclic esters are decomposed. Thereby, since the high binding pH is not suitable for the actual physiological detection environment, it is very important to choose an appropriate boronic acid as the ligand. Besides, there are many parameters that need to be taken into comprehensive consideration, including selectivity, affinity, and binding capacity. In addition to the above-mentioned pH-controlled BAMs, temperature-controlled BAMs have also been proposed for the detection of glycoproteins.[30] As early as 1930s, the interaction between boronic acids and *cis*-diol compounds was extensively studied.[31] It was not until nearly four decades later that a sensor for the quantitative detection of glycoprotein using BAMs was proposed.[32] During that time, because of their great advantages, such as pH-controlled binding/release, reversibility of the reaction, high specificity, and high selectivity,[33,34] a large number of studies were carried out on the enrichment and purification of glycoproteins using BAMs.[35–37] In recent years, there have been many significant leaps in the use of BAMs for sensing and detecting glycoproteins, showing their application prospects and becoming a research hotspot. Various boronate ligands and functional materials were applied, combined with some advanced technologies, and more applications and potential were discovered. However, there are still many challenges and room for development.

At present, there are many comprehensive reviews on BAMs, including discussions about the key properties of BAMs,[38,39] boronate affinity chromatographic columns,[40] the effects and application of BAMs on carbohydrates,[41,42] and the application of BAMs in sample preparation[43] and biomedicine.[44,45] BAM applications involving glycoproteins have also been reviewed,[46] mainly focussing on the separation and enrichment of glycoproteins by BAMs. In addition, some reviews about sensing analysis have been presented, including on green biosensors,[47] sensing analysis for $HbA_{1c}$,[48] and optical chemical sensing analysis of heavy metals.[49] BAMs-based sensors for carbohydrate analysis have been proposed,[50–53] with the reviews mainly discussing and commenting on the basic mechanisms, different types of sensors, and further applications, and providing valuable references for the development of BAM-based sensors for carbohydrate analysis. These mentioned reviews all played a vital role in the development of BAMs-based sensors and absolutely inspired the research in this field. However, there is a lack of critical reviews focussing on the analysis of glycoproteins using BAM-based sensors. In this work, we focus on the recent advances in the specific detection of glycoproteins by BAM-based sensors. Common boronate affinity ligands of BAMs and their grafting methods, functional materials utilized in the synthesis of BAM-based sensors, advanced technologies, and their applications are systematically discussed. Additionally, special emphasis will be placed on which merits can be provided by different BAMs to overcome challenges in advanced detection.

## 2. Common boronate affinity ligands of BAMs and their grafting methods

The basic consideration for designing a type of BAM is the selection of the boronate affinity ligand, which directly determines the efficiency of recognition and detection. So, we summarize the common boronate affinity ligands and their basic properties. Furthermore, the main grafting methods are discussed.

### 2.1 Common boronate affinity ligands

According to the complexity of the structure of boronate affinity ligands, they are currently divided into single boronic acid ligands, teamed boronate affinity ligands, and dendrimeric boronic acids ligands.[38]

**2.1.1 Single boronic acid ligands.** As shown in Table 1, several kinds of single ligands are often used in the fabrication of BAMs for glycoprotein detection.

The choice of boronate affinity ligand is decided by the binding pH, capacity, and affinity of BAMs; generally speaking, we prefer BAMs with lower binding pHs, higher binding capacity, and higher binding affinity, which basically rely on

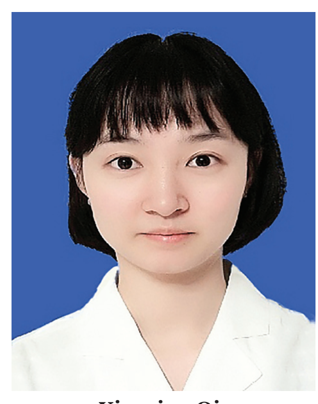
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**Table 1** Information about commonly used boronate affinity ligands

| Full name | Abbreviation | Structure | $pK_a$ [a] | Ref. |
|---|---|---|---|---|
| 4-Amino phenylboronic acid | 4-APBA | | 9.2 | 102 |
| 3-Amino phenylboronic acid | APBA | | 8.8 | 56–59 and 71 |
| 4-(Aminomethyl) phenylboronic acid | AMPBA | | 8.4 | 78 |
| 3-Acrylamino phenylboronic acid | AAPBA | | 8.2 | 67 |
| 4-Vinylphenylboronic acid | VPBA | | 8.2 | 30, 70, 75 and 80 |
| 4-Formyl phenylboronic acid | FPBA | | 7.3 | 64, 68 and 83 |
| 4-Mercapto phenylboronic acid | MPBA | | 6.2 | 6,56,72–77,79,83 |
| 4-Carboxy phenylboronic acid | CPBA | | 4.1 | 69 |
| 2–4-Dihydroxyborane phenyl-4-carboxyquinoline | QPBA | | — | 60 |
| (3-((11-Mercaptoun-decanamido)methyl)phenyl) boronic acid | MDM-PBA | | — | 118 |

[a] The data source for the $pK_a$ values is http://www.chemicalbook.com.

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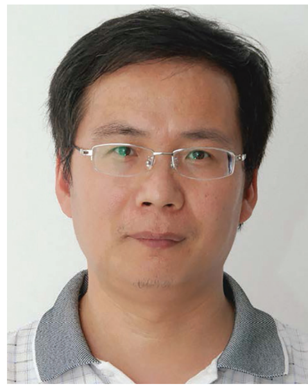
the p$K_a$. When the environmental pH is greater than p$K_a$, the glycoprotein will bind to the boronic acid group, otherwise, the reaction will reverse and the compound will dissociate. Thus, the lower p$K_a$ allows the higher binding affinity. Most of the single boronic acid ligands have lower p$K_a$ values, some of which are higher than pH 8 (Table 1). A higher p$K_a$ value means a higher binding pH value. However, the pH of real samples, such as blood and urine, is mostly below pH 8. If the pH value of real biological samples is adjusted higher for analysis and detection, not only could the biological molecules be destroyed, but the experimental results may also be inaccurate.

For this reason, it is necessary to reduce the binding pH of BAMs. Molecular imprinting technology can be applied to reduce the binding pH. Utilizing molecular imprinting technology, a specific spatial recognition site for the target can be synthesized on the substrate, and a material with high selectivity can be obtained.[54] To reduce the binding pH, the imprinted layer of the target glycoprotein can be synthesized on the surface of the BAM,[55] in addition to switching to a boronate affinity ligand with a lower p$K_a$ value. After the removal of the glycoprotein template, 3D holes can not only specifically bind glycoprotein, but also improve the binding affinity. This has been well confirmed in actual research. For example, a kind of proposed electrochemical sensor showed its action on the detection of glycoprotein.[56] It used APBA, with a higher p$K_a$ value (8.8), as the boronate affinity ligand to create recognition sites on the electrode. At the same time, the imprinted layer was formed on its surface by electrochemical polymerization. The high selectivity of 3D holes made up for the problem of the higher p$K_a$ value. Most BAMs utilizing boronate affinity ligands in the process of preparation have synthesized imprinted layers on their surfaces and showed a good binding affinity.[57–60]

Moreover, a long chain phenylboronic acid can offer more binding space and sites for glycoprotein to improve the binding affinity and capacity.[61]

**2.1.2 Teamed boronate affinity ligands.** In contrast to single boronate affinity ligands, a teamed boronate affinity ligand is a teamed molecule or a complex. It usually consists of a boronic acid and an amine, connected by a B–N coordination bond. The B–N coordination bond makes teamed boronate affinity ligands function as Wulff-type boronic acids and reduces the p$K_a$ of the ligands.[62] Liang and Liu[63] constructed a magnetic nanoparticle using a teamed boronate affinity ligand (synthesized by self-assembly of thiophene-3-boronic acid and 2-mercaptoethylamine), which could specifically recognize and purify RNase B from a mixture. Moreover, this study proved that, compared with thiophene-3-boronic acid, the teamed boronate affinity ligand improved the selectivity of the target. However, there is still a lack of research on the preparation of BAM-based sensors using teamed boronate affinity ligands for the recognition and quantitative detection of glycoprotein.

**2.1.3 Dendrimeric boronic acids ligands.** 3D dendrimers with multivalent binding sites, a sort of macromolecule with high branching and monodispersity, can provide a large binding surface and interface. The use of dendrimeric boronic acids ligands could solve the problem of low binding strength between single boronic acid ligands and glycoproteins. An electrochemical biosensor[64] was designed using dendrimeric boronate acids ligands to increase the number of boronic acid groups as an interface material. The PAMAM G4 dendrimer with a great many amine groups provided binding sites for FPBA and enhanced the affinity for FPBA. A magnetic nanoparticle with dendrimeric boronic acids ligands was proposed by Wang and co-workers[65] and showed good ability to extract trace glycoproteins as low as $2 \times 10^{-14}$ M. A novel dendrimer-conjugated benzoboroxole was proposed and bound to magnetic beads to improve glycoprotein enrichment and it provided a new idea for protein sensing analysis.[66] In addition, the high branched PAMAM has obvious disadvantages of high rigidity and high cost, and more suitable interface materials



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have appeared. Therefore, there are more research directions and more development space for related research.

### 2.2 Grafting of boronate affinity ligands

Boronate affinity ligands are often grafted on the substrate or functional material by chemical reaction, thiophile affinity of Au and Ag, or electrostatic interaction. There is no bias in the choice of these three interaction forces, and the grafting methods depend on the groups and properties of the grafted ligands. The glycans of glycoproteins contain the *cis*-diol structure so boronic acids can also bind to glycoproteins specifically, as shown in Fig. 1.

**2.2.1 Chemical reaction.** The methods of grafting boronate affinity ligands by chemical reaction mainly include addition polymerization,[30,56,57,67] amide reaction,[58–60,68] simple EDC/NHS coupling method,[69] reaction between an amino group and an isothiocyanate group,[59] and "thiol–ene" click reaction[70] (as shown in Fig. 2). Addition polymerization is the most commonly used method of chemical reaction for grafting boronate affinity ligands. Addition polymerization usually involves the opening of unsaturated bonds to connect small molecules together to form macromolecules. Three such boronate affinity ligands, namely AAPBA, APBA, and VPBA, are often used in addition polymerization. AAPBA and VPBA both have an unsaturated double bond while APBA does not. Thus, AAPBA and VPBA undergo the most common process of double bond-opening polymerization into macromolecular polymers while APBA is grafted by electropolymerization[56] or oxidative polymerization.[57] Through the polymerization reaction, the active boronic acid group is installed on the substrate. The second major reaction is between an amino group and an acyl group, which is called an amide reaction. Generally, a boronate affinity ligand with an acyl group, such as QPBA or FPBA, is grafted on a substrate with an amino group or a boronate affinity ligand with an amino group, such as APBA, is grafted on a substrate with an acyl group. Another reaction[64] to form an amide bond occurs between dendrimeric boronic acids ligands with many amino groups and an active ester group. Other chemical reactions are described as follows. 4-APBA was fixed to an amino-modified substrate of bis-(succimidyl)suberate containing *N*-hydroxysuccinimide, which can react with amino groups.[102] CPBA was modified on g-$C_3N_4$ by a simple EDC/NHS coupling method, and the B–N coordination bond is formed between boron of CPBA and amino groups on the g-$C_3N_4$.[69] A boronate affinity fluorescent probe was synthesized through the reaction of the amino group of APBA and the isothiocyanate group of FITC.[59] VPBA, a boronate affinity ligand with an olefinic bond, was introduced into a substrate using a mild "thiol–ene" click reaction.[70]

In the above reactions, most of the boronate affinity ligands are connected to the substrate or functional material by a chemical bond and the binding product is relatively stable. Nevertheless, the chemical reactions occurring in the process of boronate affinity ligand grafting have certain restrictions, for example, addition polymerization is more suitable for ligands with unsaturated bond, the amide reaction requires an amino group an and acyl group, and the reaction between an amino group and an isothiocyanate group only takes place between them. The reaction is mainly related to the selection of the boronate affinity ligand so this factor should be considered in the preparation process of BAMs.

**2.2.2 Thiophile affinity of Au and Ag.** The thiophile affinity of Au and Ag is a main way of grafting MPBA. As shown in Table 1, MPBA contains a sulfhydryl group. Sulfur can easily form obvious covalent bonds or metal bonds with thiophilic elements like Au and Ag. Therefore, it is often used to modify the surface of Au NPs and Ag NPs as boronate affinity ligands.[6,56,72–77]

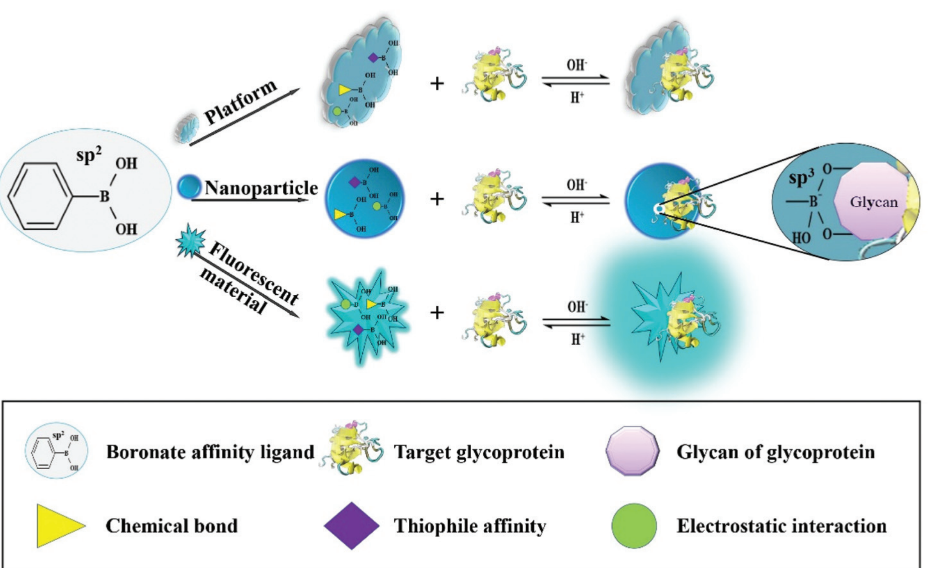


Fig. 1 Schematic diagram of the interaction between BAMs and glycoproteins.

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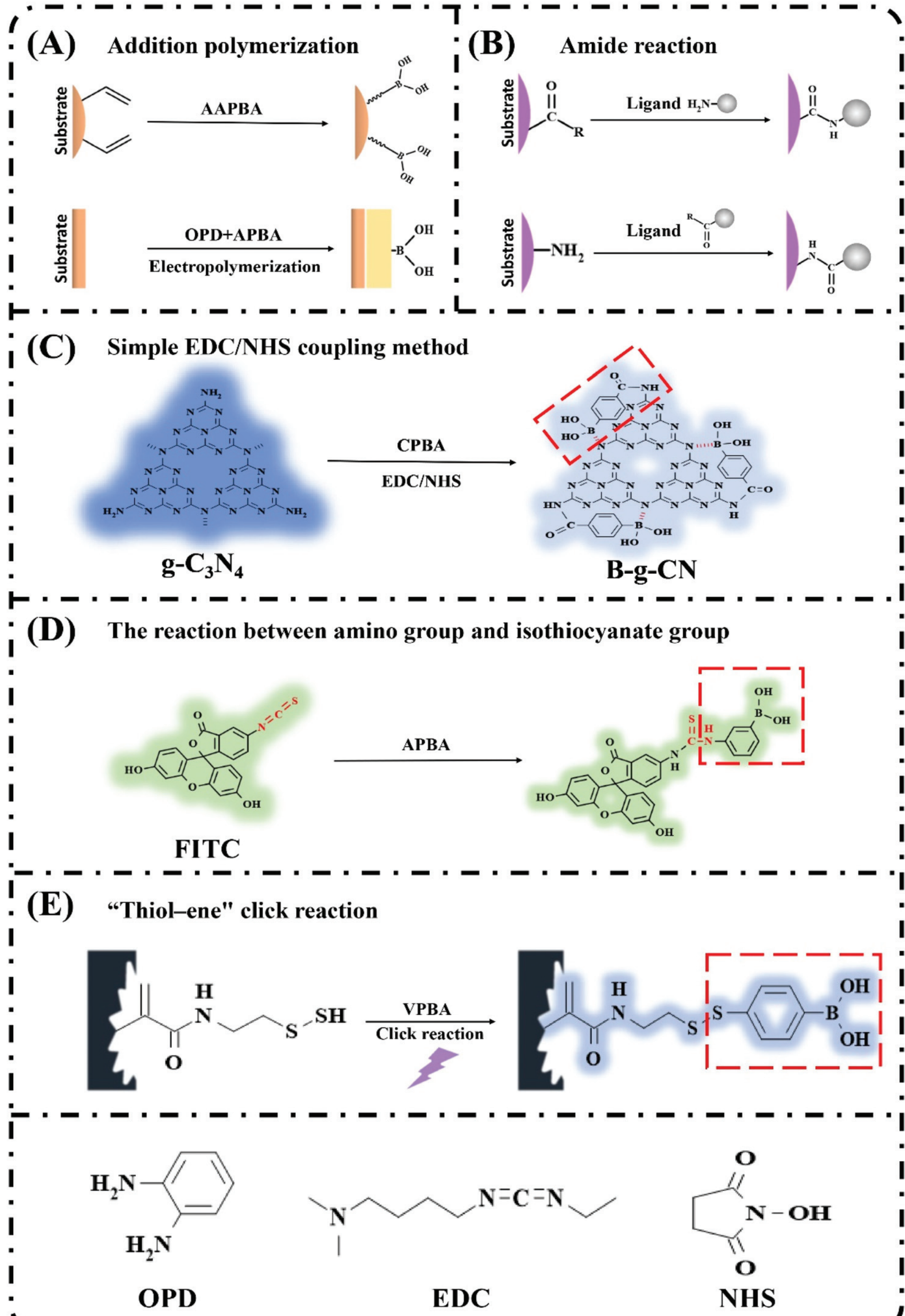


Fig. 2 Summary scheme of chemical reactions of several different grafting ligands: (A) addition polymerization,[30,56,57,67] (B) amide reaction,[58–60,68] (C) simple EDC/NHS coupling method,[69] (D) the reaction between amino group and isothiocyanate group,[59] and (E) "thiol–ene" click reaction.[70]

**2.2.3 Electrostatic interactions.** In all the BAMs using MPBA as the boronate affinity ligand, in addition to the MPBA's affinity for Au and Ag, there is also an electrostatic effect in the MPBA grafting method. Chang and co-workers[78] modified MPBA on the surface of Mn-doped ZnS QDs because there are more metal ions on the surface of the QDs than sulfide ions. Moreover, AMPBA was also immobilized on the surface of Au NPs by electrostatic interaction.[79]

As a basic constituent in the fabrication of BAMs, many factors need to be considered in the selection of boronate affinity ligands, such as the properties of the ligands, their combination methods with the substrate or functional material, and so on. Currently, only a small range of boronate affinity ligands are used in glycoprotein detection, and more effort needs to be made to develop new practical ligands with high selectivity in this field.

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# 3. Functional materials utilized in BAM-based sensor synthesis

### 3.1 Platforms for supporting

Some BAMs are decorated on a plate, which offers a platform for sensing of glycoproteins. The following materials are used as supporting platforms: electrodes,[56,58,64,72,75] GO,[80] polymers including glass and PS,[68,73] and paper chips.[6] The common function of these materials as platforms is to support the BAMs and provide a reaction substrate and platform. In addition, sensors using different support materials have different functions, advantages, and disadvantages. For example, there are electrode platforms for direct conduction, paper chips with excellent chemical modification properties, and PS with chemically stable properties.

**3.1.1 Electrodes.** Electrodes, such as the GCE and the Au electrode, are the traditional supporting materials for electrochemical biosensing. Most of the sensor substrates are prepared similarly by applying various modifying materials on the working electrode to improve and strengthen its electron transfer ability, sensitivity, and stability. Different studies have worked on different modification methods and detection assays.

For example, Song and Yoon[64] constructed a gold electrode based on a titanium primed (20 nm Ti) Si wafer, and the electrode was modified with DMSO, DSTP, and dendrimeric boronic acids. Quantitative measurement for the target was performed using an enzymatic backfilling assay. Ai and his workmates[56] proposed a novel biomimetic sensor using a GCE as the supporting platform, which was modified with a graphene–Au NPs nanocomposite, *o*-phenylenediamine, and APBA, and then synthesized a MIPs layer. The detection of BSA, the target glycoprotein, was realized *via* measurement of the electrochemical oxidation signal of FcHT@Au NPs. The preparation process is shown in Fig. 3A. You and co-workers[75] demonstrated quantitative detection of HRP based on BASA. The GCE was decorated with chitosan, GO-Au NPs, and VPBA, and later the MIPs layer was composed. As a sandwich-type sensor, the signal tag $SiO_2$@Au/FcHT/MPBA was seized by the target glycoprotein HRP on the surface of the modified GCE for further electrochemical detection.

**3.1.2 Graphene oxide (GO).** GO is a kind of two-dimensional honeycomb lattice carbon nanomaterial with a single layer structure, which has the characteristics of a huge surface area and potential for chemical modification, and it has been recently considered as ideal candidate as supporting material

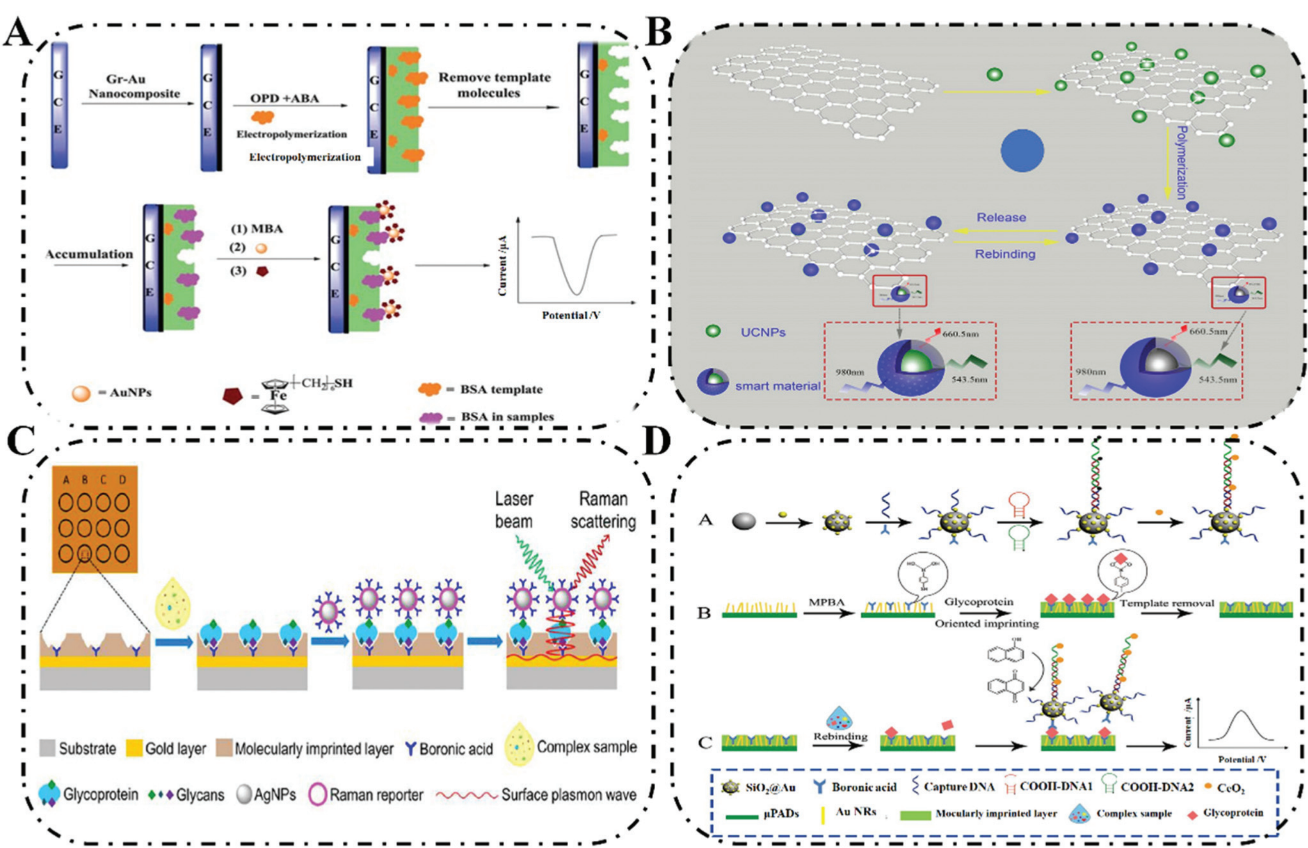


Fig. 3 Some boronate affinity sensors using different supporting platforms. (A) Schematic diagram of an electrochemical sensor using a GCE as the platform. Reproduced from ref. 56 with permission from the Royal Society of Chemistry. (B) Preparation of a boronate affinity fluorescent material with GO as the support matrix. Reprinted from ref. 80, Copyright, 2016, Elsevier. (C) Schematic diagram of a sensor array with glass as the substrate. Reprinted from ref. 83, Copyright, 2016, American Chemical Society. (D) Preparation of microfluidic electrochemical paper chip based on boronate affinity. Reprinted from ref. 6, Copyright, 2019, American Chemical Society.

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for MIPs.[81,82] Wang and co-workers[80] made use of GO as a supporting matrix to present a fluorescent sensor based on BAMs for detecting glycoproteins. This sensor showed good recognition and sensing performance (Fig. 3B). In their work, GO enhanced the mass transfer and acted as the support material. GO has also been used in many BAMs and plays a very important role as a modifying material.

**3.1.3 Polymers including glass slides and PS plates.** Glass is a kind of amorphous inorganic non-metallic material that is generally made of a variety of inorganic minerals as the main raw materials and a small amount of auxiliary materials. Its main components are silica and other oxides, and it is a very common transparent material with a mature preparation process. Some studies[73,79,83] combined boronate affinity technology, photolithography imprinting technology, SERS, *etc*., constructing a new series of probes with broad prospects on glass to identify and detect glycoproteins. As shown in Fig. 3C, Tu and co-workers developed a new PISA strategy based on a bare glass slide. They synthesized the Au and the MIPs layers on glass, which can specifically capture the target glycoproteins. After the target glycoprotein was bound to the substrate, the Raman nanotags were added and combined with the captured glycoprotein; the sensor then performs the Raman detection.[83]

Because of the good absorbability to proteins and other macromolecules, PS 96-well Microplates are generally used in ELISA.[84] Bi and Liu[68] combined boronate affinity technology and ELISA for the detection of glycoproteins using modified PS 96-well microplates as the support platform. Firstly, the microplate wells were treated with $H_2SO_4/HNO_3$ mixture solutions and APTES to generate an amino-PS surface, and then the amino-PS plates were modified with FPBA by amide reaction. In addition to supporting materials, polymers such as polydopamine and polyaniline also serve as functional monomers for polymerization. [68,85,86]

**3.1.4 Microfluidic paper chips.** Microfluidic paper chips use paper to replace the traditional substrate materials, such as silicon, glass, electrodes, graphene/graphene oxide, or polymers. Through treatments such as wax spray printing, wax melt soaking, photolithography, and other processing technologies, paper can be given a certain structure of hydrophilic/hydrophobic microchannel network and used to construct analysis devices, known as μPADs.[87] By constructing a microfluidic channel on the paper chip, the sample can flow by capillary force in the designed channel without an external force, thus the channel automatically drives the sample to be tested. As the base material for analysis, paper has the advantages of low cost, good biocompatibility, biodegradability, good chemical properties, and environmental friendliness. At the same time, paper-based sensors have been shown to have excellent performance for detecting metal ions,[88] pesticide residues,[89] biomolecules,[90] bacteria,[91] and so on. A diverse range of μPADs have been designed in recent decades.[92,93] Based on the above conditions, Sun and co-workers prepared a paper-based boronate affinity electrochemical sensors in two steps, as shown in Fig. 3D.[6] (a) The $SiO_2$@Au/dsDNA/$CeO_2$ signal tag was prepared; (b) Au NRs were immobilized on the surface of μPADs to improve the electron transport performance of the paper electrode and connect boronate affinity ligands, and then the MIPs layer was synthesized. The MIPs-based paper chip and the signal tag could specifically recognize the target glycoprotein from complex samples. After dropping the sample onto the paper chip, the signal tag is added, and DPV measurement then qualitatively and quantitatively determines whether the target glycoprotein is present.

### 3.2 Nanoparticles

Nanoparticles are used in the synthesis of BAM-based sensors as the reaction substrate, the intermediate medium, the signal materials, and so on. There are four main kinds of nanoparticles, namely Au NPs, Ag NPs, magnetic nanoparticles, and $SiO_2$ nanoparticles. In addition, PGMA microspheres are also used as the reaction substrate.[60] This part mainly discusses the four main kinds of nanoparticles as follows.

**3.2.1 Au NPs.** Au NPs, a kind of metal particle with good conductivity, have the advantages of good biocompatibility, the possibility of radius controllability, electrocatalysis, stability, and so on.[94,95] Owing to their excellent electrical conductivity, a number of studies on boronate affinity electrochemical sensors utilized Au NPs as the modification material to accelerate electron transfer and optimize the performance of the working electrode. Especially, combining their conductivity with their affinity for sulfydryl, thiol and amino groups, Au NPs are often used as "the bridge for connection" in the sensors. Like the signal tag of an electrochemical sensor based on BASA, Au NPs link to the amino-modified $SiO_2$ nanoparticles and the MPBA with a sulfhydryl group for synthesizing $SiO_2$@Au/FcHT/MPBA as an intermediate medium.[75] In addition, when Gr-AuNPs film, a combination of GO and Au NPs, was modified on a working electrode, the Au NPs were found to be dispersed on the border of the GO and played an active role in preventing the GO from aggregating.

As of now, Au NPs have three main functions in BAM-based sensors: first, improving the conductivity and electron transfer efficiency of electrochemical sensors to optimize the electrode performance; second, connecting other materials as an intermediate medium; and third, when used with GO, they are dispersed around the GO to prevent the GO from aggregation by electrostatic repulsion.

**3.2.2 Ag NPs.** For the detection of glycoproteins with BAM-based sensors, to date only Ag NPs have been modified by boronate affinity ligands and used for the fabrication of SERS probes to provide SERS-active surfaces. In addition to the above-mentioned as a SERS probe material, in a study by Xie and co-workers,[76] Ag NPs were polymerized into an integrated film to increase the cross section, and then bonded to MPBA through its thiophile affinity to accept glycoprotein.

**3.2.3 Magnetic nanoparticles.** Magnetic nanoparticles is a general term for microsphere materials with magnetism.[96] So far, three kinds of magnetic nanoparticles have been used in the synthesis of BAM-based sensors, and they are $Fe_3O_4$, Ag@MagPMMS, bacterial magnetic particles, and a kind of

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commercial carboxyl-modified MNBs (the author did not describe the specific type). $Fe_3O_4$ has been widely utilized as a molecular imprinting substrate by degrees because of its virtues of low cost, easy separation, and easy synthesis.[57,97–99] Taking advantage of the good conductivity of $Fe_3O_4$, $Fe_3O_4$@Au NPs served as the substrate for electrochemical-response NPs and showed a good effect in the detection of glycoproteins. Salimi and co-workers[74] first tried to prepare a magnetic boronate affinity SERS substrate using a type of porous microsphere [poly(HPMA-Cl-*co*-EDMA)] with bifunctional character as the starting material. The utilization of the magnetic substrate contributed to the easier separation of tags after specifically binding to the glycoprotein.

**3.2.4 $SiO_2$ nanoparticles.** $SiO_2$ nanoparticles with the merits of easy synthesis and low cost are extensively used as the basal material for MIPs, similar to $Fe_3O_4$. $SiO_2$ has been widely used as a good substrate in core–shell structures because of its controllable particle size, easy surface modification and good biological affinity.[100,101] In BAM, $SiO_2$ nanoparticles have been used as the "core" of the core–shell structure; firstly, particles were modified by grafting groups, and then modified by the "shell", such as Fig. 3D.

### 3.3 Fluorescent materials

To date, traditional fluorescent dyes, QDs, QBs, FNCs, UCNPs, g-$C_3N_4$, and a boronate affinity ligand with its own fluorescence have been used as fluorophores for BAMs. Some boronate affinity ligands in Table 1 have been bonded to several fluorescent materials with different properties; in the presence of a glycoprotein that was specifically recognized by the BAM, the FL of the BAMs changed to some extent. Therefore, based on the fluorescence response of boronate affinity fluorescent materials to specific glycoproteins, they can realize the sensing and detection of glycoproteins. Several fluorescent materials for glycoproteins have been synthesized according to the above principles and are shown in Table 2.

Zhang and co-workers[30] first developed a kind of fluorescence nanosensor to recognize and detect glycoproteins. CdTe NCs were coated with octadecyl-*p*-vinylbenzyldimethylammonium chloride and then copolymerized by the monomers *N*-isopropylacrylamide and VPBA in the presence of HRP; after releasing the glycoproteins, the imprinted 3D caves and the recognition sites of the boronate affinity ligands provided higher specificity for the detection of HRP (Fig. 4A). Similarly, Mn-doped ZnS QDs, UPNPs, and QPBA have also been used as fluorescent materials and used to prepare a series of substrates to efficiently detect glycoproteins. In a study by Wang and co-workers,[69] g-$C_3N_4$ nanosheets were decorated with VPBA using the EDC/NHS coupling approach, and the B-g-CN nanosheets had the feature of Wulff-type boronic acid. The B-g-CN nanosheets not only showed ability for glycoprotein detection but also for cell imaging. In addition to the above studies, a new boronate affinity fluorescent material of sandwich format was successfully proposed to detect HRP,[59] which had multiple glycosylation sites. Boronic acid-decorated $SiO_2$ particles had oriented surface imprinting by using HRP as the template. When detecting HRP, the HRP bound to the MIPs specifically; only the HRP@MIPs could absorb APBA-FITC and emit a fluorescent signal (Fig. 4B). Similarly, QBs, a QD-embedded luminescent bead, served as a fluorescent tag to detect hCG.[102]

## 4. Advanced technologies

There are many unique and advanced technologies, including boronate affinity ELISA, one-step PIMs of click reaction, boronate affinity SERS, and boronate affinity sandwich assays. They are all based on boronate affinity, but the innovation is that for the first time they have incorporated a technology, or they have used a new test method, or they have come up with a new concept.

### 4.1 Boronate affinity ELISA

ELISA, which has both a highly specific immune response and an amplification effect of the enzymatic reaction, is generally used for qualitative or quantitative detection of antigens, antibodies, or other proteins.[103–105] With the development of ELISA, it exhibits several merits, including but not limited to rapid analysis, high specificity, high sensitivity, and environmental friendliness; it is one of most widespread tests in clinical diagnostics.[106–108] Bi and Liu[68] proposed a new method based on a boronate affinity ELISA and oriented surface molecular imprinting for glycoprotein detection, which showed good responsiveness and linearity in the detection of HRP and AFP. The research first made use of HRP as a model target to design the assay, optimize the imprinting conditions of polymerization pH, ratio of APS, concentration of aniline, and polymerization time, and then investigate the properties of the synthetic ELISA sensor. The boronate affinity-based oriented

Table 2 Boronate affinity fluorescent materials

| Fluorescent category | Name | Boronate affinity ligands | Target | Fluorescence change | Ref. |
| --- | --- | --- | --- | --- | --- |
| FNCs | CdTe NCs | VPBA | HRP/OVA | Quenching | 30 |
| QDs | Mn/ZnS QDs | MPBA | TRF | Enhancement | 78 |
| | Mn/ZnS QDs | AAPBA | HRP/TRF | Enhancement | 67 |
| QBs | QBs | 4-APBA | HCG | Enhancement | 102 |
| UCNPs | UCNPs | VPBA | HRP | Quenching | 80 |
| Boronate affinity ligand with its own fluorescence | QPBA | QPBA | HRP | Enhancement | 60 |
| g-$C_3N_4$ | g-$C_3N_4$ | CPBA | IgG | Enhancement | 69 |
| Traditional fluorescent dye | FITC | APBA | HRP | Enhancement | 59 |

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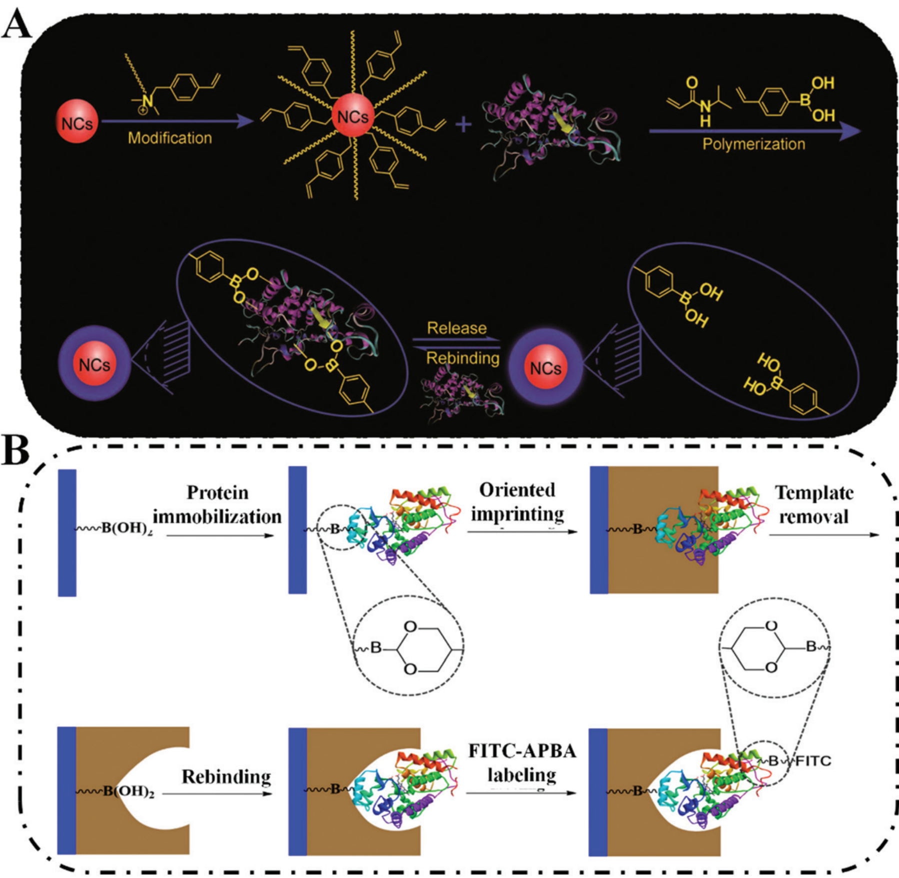


Fig. 4 Some boronate affinity sensors using fluorescence materials. (A) Assembly of BAMs with NCs as fluorescent material. Reprinted from ref. 30, Copyright, 2014, John Wiley and Sons. (B) Preparation of sandwich boronate affinity imprinting material with FITC fluorescent probe. Reprinted from ref. 59, Copyright, 2019, MDPI.

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surface imprinted 96-well microplate for detecting HRP was produced step by step as follows: (a) the phenylboronic acid-modified 96-well microplate was made by using FPBA as the boronate affinity ligand; (b) add the template glycoprotein HRP to combine with the solid-phase carrier in alkaline pH, and then imprint orientally; (c) remove the template in acid solution to exposed 3D caves, which allow the specific recognition of HRP. The boronate affinity-based oriented surface imprinted 96-well microplate for detecting AFP was prepared using the same procedure as above, except that the glycoprotein template was AFP. The HRP and AFP ELISAs were similar to the common sandwich ELISA. The process is shown in Fig. 5A, including some major steps: (1) incubation of the sample in the MIP-coated well; (2) blocking the remaining area of the MIP layer with BSA; (3) incubation with HRP-labeled anti-AFP IgG; (4) staining with TMB solution; and (5) measurement of the absorbance at 650 nm.

### 4.2 One-step PIMs of click reaction

PIMs are a means of chemical modification, usually decorating the 3D specific binding cavities of MIPs with functional materials for extra functions.[109] There is no doubt that PIMs can be endowed with characteristics such as fluorescence, specificity, and sensitivity *via* the addition of functional materials. Click reactions, with a variety of advantages like high yield, no by-products, high selectivity, and mild reaction conditions, have been increasingly developed in the past few years.[110] Zhao and co-workers[70] designed and synthesized a novel fluorescence sensor based on PIMs and click reaction. The preparation process is described as follows and shown in Fig. 5B. The functional monomer MDTA with an exchangeable moiety and light fluorescence was polymerized while regarding MBAA as the cross-linker, and the template glycoprotein was imprinted. After removal of the template, MDTA's disulfide bond could be reduced by tris(2-carboxyethyl)phosphine hydrochloride, leaving exposed thiol groups, thus, MIPs could be modified with a functional group by linking to the exposed thiol groups. A mild "thiol–ene" click reaction was used for introducing the boronate affinity ligand, VPBA, to the MIPs; and VPBA can not only specifically recognize the target glycoprotein but also contains a large conjugated $\pi$ bond for improving the fluorescence property of the MIPs as a fluorescence reporter. The fluorescence of the synthesized compound is quenched in the presence of the target glycoprotein. The combination of PIMs and click chemistry enlarges the available properties of modified MIPs and provides wide application prospects.

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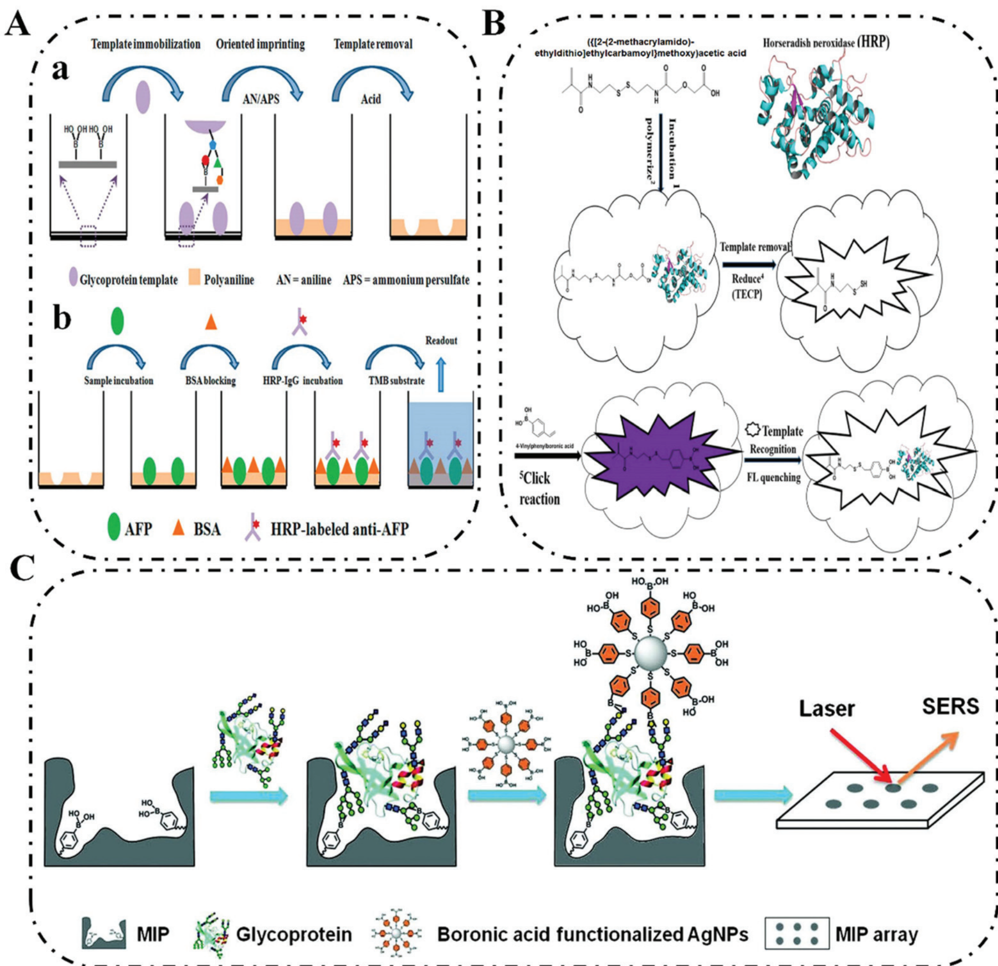


**Fig. 5** (A) The preparation process (a) and detection steps (b) of a boronate affinity ELISA. Reprinted from ref. 68, Copyright, 2014, American Chemical Society. (B) One step post implying modification of click reaction. Reprinted from ref. 70, Copyright, 2017, Elsevier. (C) The figure emphasizes both SERS and BASA. Reprinted from ref. 73, Copyright, 2014, John Wiley and Sons.

### 4.3 Boronate affinity SERS

The full name for SERS is surface-enhanced Raman spectroscopy, which is a high sensitivity spectroscopic technique based on the enhanced Raman scattering when molecules are close to SERS-active surfaces for molecular characterization, identification, and detection.[111] At present, SERS probe materials with strong SERS-active surfaces include three kinds of frequently used nanostructured metals, Au NPs, Ag NPs, and Cu NPs. For the development of SERS in molecular detection, the key problem is whether the target molecules can specifically bind to SERS probes or not. It has been noted that the trait of boronate affinity between boronic acids and glycans contributes to the construction of SERS probes in glycoprotein detection, and several studies have reported that boronate affinity SERS has been successfully applied to glycoprotein detection in real samples. Ye and co-workers[73] first took advantage of boronate affinity SERS to detect HRP and AFP. They designed a kind of sandwich assay called BASA, which will be described at length in next section; the boronate affinity MIPs arrays were prepared by photolithography to specifically combine target glycoproteins, and the boronic acid-modified Ag NPs as SERS probes were designed to tag onto the captured glycoproteins and enhance their Raman scattering. Similarly, Salimi and co-workers[74] proposed a double-site sensor based on BASA and SERS using Ag@MagPMMS as the SERS tag and boronic acid-modified Ag NPs as the SERS probe. The SERS probe and tag for the detection of target glycoproteins enhanced the intensity of the SERS signal and generated "hot spots" because of plasmon coupling between Ag NPs and Ag@MagPMMS. Different to the above studies, boronate affinity Ag nanofilms were structured as both a Raman reporter and a glycoprotein acceptor.[76] Various glycoproteins have their own distinctive Raman spectrum and fingerprint, and SERS enhances the Raman spectrum signal intensity. Combined with boronate affinity, this new method, *i.e.*, boronate affinity SERS, showed higher specificity and sensitivity, and great prospects in glycoprotein detection. Based on boronate affinity SERS, Liu and co-workers proposed an upgraded version called PISA strategy,[112] including dual MIP-based PISA,[113] orthogonal dual aptamer-based PISA,[114,115] and

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MIP-based PISA array.[83] Particularly, PISA can achieve ultra-sensitive detection of glycoproteins by the additional amplification mechanism between substrate and tags,[79] and it actually holds great prospects for development. At present, the selection of a probe and a label with an active SERS surface is a little monotonous, so there is still a lot of room for development in this field.

### 4.4 Boronate affinity sandwich assay (BASA)

The concept of BASA was first proposed by Ye and co-workers.[73] They explained that the BASA was based on MIPs and SERS and depends on the special formation of boronate affinity MIPs, the target glycoprotein, and boronate affinity SERS probes (Fig. 5C). A target glycoprotein is specifically recognized and bound to the boronate affinity MIPs substrate; after unwanted substances are removed, the captured glycoprotein causes the SERS probe of the boronate affinity Ag NPs to generate the SERS signal.

Besides, You and co-workers[75] showed a new type of BASA, which consisted of MIPs with a boronate affinity modified electrode as the substrate, target glycoproteins and an electrochemical boronate affinity tracing tag. Similarly, the target glycoprotein that was specifically captured by the MIPs was labeled with the tracing tag to produce an electrical signal. The two detection modes are similar, but there are some innovations in the detection method, substrate, and probe preparation, *etc*. In addition to the above studies, which have been proposed as BASA, more broadly speaking, numerous boronate affinity detection methods for glycoproteins also belong to BASA.[6,56,58,59,72,74] These studies have different substrates, different signal tags and different detection methods for specific recognition of glycoproteins; however, their common characteristics are that the detection format is based on a sandwich assay, and the basements or signal tags are modified by some materials with some functions and BAMs with the action of specific binding with glycoproteins. The detection limits of this method can reach picogram or picomole per millilitre levels. Thus, in the field of glycoprotein sensing and detection, BASA can be broadly defined as electrochemical, SERS or other tests using the properties of BAMs and sandwich-type experiment mode, which consists of a target glycoprotein, substrate and label (either the substrate or the label is modified by a boronate affinity ligand).

Most BASAs not only show the sensitivity and specificity of BAMs, but also have lots of advantages compared to sandwich immunoassays, which require hours or even overnight for incubation, such as cost efficiency, stability, and speed. BASA has provided double recognition sites and high sensitivity and selectivity for glycoproteins, and offered a promising and developing direction. However, the preparation process for most boronate affinity BASA sensors is complex, which may affect the overall efficiency compared with a one-step reaction. Therefore, boronate affinity BASA need to be improved to obtain better utilization.

## 5. Applications

In addition to their good applications in the detection of some enzymes, antibodies, and other glycoproteins, BAM-based sensors also show great potential in disease diagnosis and prognosis, and the recognition and imaging of glycoproteins in biological cells. Table 3 details applications of BAM-based sensors in the detection of various glycoproteins.

### 5.1 Disease diagnosis or disease prognosis

Most clinical biomarkers are glycoproteins, and abnormal glycosylation is a very important feature in the occurrence of disease.[5] At present, boronate affinity sensors for the detection of clinical biomarkers AFP, $HbA_{1c}$, IgG, PSA, and hCG have been reported, and good responses were obtained. AFP is a well-known biomarker of liver cancer; the concentration of AFP is closely related to the size of the tumour but it is the same in the early stages of liver cancer. $HbA_{1c}$, a glycosylated protein that is formed by a nonenzymatic reaction between glucose and hemoglobin β-chains, is an important biomarker for diabetes and it has become an important indicator for the long-term monitoring of blood glucose in diabetic patients. The abnormal increase or decrease of IgG is related to some diseases, such as liver disease and nephrotic syndrome. PSA is a tumour marker of prostate cancer. The PSA level is low in the serum of healthy men and increases in the serum of men with prostate disease. However, benign prostatic hyperplasia, obesity or other factors can also lead to its promotion, so it is not accurate to judge the disease based on PSA levels.[116] hCG is usually used to indicate pregnancy and related diseases, but it is also a biomarker of many cancers, such as prostate cancer and breast cancer.[117] Therefore, BAMs have broad prospects in the detection of a variety of glycosylated proteins.

However, the limitation of the application of BAM-based sensors in disease diagnosis and prevention lies in the gap between its development and the needs of frontier medical research. In addition to those mentioned above, there are still many glycoproteins that have not been studied as target glycoproteins to make boronate affinity sensors, such as fucosylated haptoglobin, which is regarded as a biomarker of pancreatic cancer. Moreover, the performance of some glycoproteins that have been studied as clinical biomarkers is not good enough, such as AFP. AFP is a marker of liver cancer but has little effect on early detection of the disease.[116]

If the research in this field can keep up with the development of medical science and meet the requirements of high accuracy in clinical diagnosis, BAMS can definitely be used to detect clinical biomarkers in time to prevent the occurrence of some diseases, such as cancer, diabetes and so on. Then BAMs will see great development in disease prevention. PEI-modified magnetic GO nanocomposites were synthesized and applied to the enrichment of glycoproteins from human plasma under physiological conditions, as shown in Fig. 6. Compared to other BAMs under alkaline conditions, not only were more glycoproteins detected and the enrichment selectivity improved but also more low abundance and labile glyco-

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Table 3 Application of BAMs in the detection of various glycoproteins

| Category | Biomarkers | The range of detection | Linearity ($R^2$) | Detection limit | Samples | Analytical methods | Ref. |
|---|---|---|---|---|---|---|---|
| Enzyme | ALP | 1–10 000 U/L | 0.991 | $3.1 \times 10^{-12}$ M | Human serum | Raman spectroscopy | 79 |
| | HRP | 0–100 ng $mL^{-1}$ | 0.990 | — | — | Ultraviolet absorption method | 68 |
| | | 0–10 μM | — | — | Human urine | Fluorescence spectrometry | 30 |
| | | 0–10 μM | 0.991 | 0.66 μM | — | Fluorescence spectrometry | 80 |
| | | 0.05–0.1 μM | — | 0.02 μM | Human serum | Fluorescence spectrometry | 60 |
| | | 0.3–0.7 μM | — | $1.44 \times 10^{-10}$ M | — | Fluorescence spectrometry | 67 |
| | | 0.1–10 mg $mL^{-1}$ | — | — | — | Fluorescence spectrometry | 59 |
| | | 0.1 ng $mL^{-1}$–100 mg $mL^{-1}$ | — | — | — | Raman spectroscopy | 73 |
| | | 1 pg $mL^{-1}$–100 ng $mL^{-1}$ | 0.996 | 0.57 pg $mL^{-1}$ | Human serum | Electrochemistry | 75 |
| | | 0.01–0.30 mg $mL^{-1}$ | 0.9976 | 0.005 mg $mL^{-1}$ | — | Electrochemistry | 57 |
| Clinical biomarkers | AFP | 0–50 ng $mL^{-1}$ | 0.93 | — | Human serum | Ultraviolet absorption method | 68 |
| | | 1 ng $mL^{-1}$–10 mg $mL^{-1}$ | 0.99 | — | Human serum | Raman spectroscopy | 73 |
| | | $10^{-12}$–$10^{-8}$ M | 0.938 | $10^{-12}$ M | — | Raman spectroscopy | 76 |
| | | 1 pg $mL^{-1}$–100 ng $mL^{-1}$ | 0.990 | $1.5 \times 10^{-14}$ M | Human serum | Fluorescence spectrometry | 79 |
| | $HbA_{1c}$ | 2.5%–15% per total hemoglobin | — | — | — | Electrochemistry | 64 |
| | | 0.05–100 μg $mL^{-1}$ | 0.99 | — | Hemolysates of human red blood cells | Raman spectroscopy | 74 |
| | | 10–$10^4$ ng $ml^{-1}$ | — | — | — | Luminescence detection | 71 |
| | IgG | 1.0–10 μg $mL^{-1}$ | — | 2.2 nM | Human urine | Fluorescence spectrometry | 69 |
| | | 0.03–0.2 μg $mL^{-1}$ | — | 52 pM | | | |
| | PSA | 152 fM–3.65 pM | 0.999 | 50 fM | — | Electrochemistry | 72 |
| | | 0.5 pg $mL^{-1}$–0.2 ng $mL^{-1}$ | — | 0.2 pg $mL^{-1}$ | Human serum | Electrochemistry | 77 |
| | TRF | 0.10–10.0 μM | — | $5.69\times10^{-9}$ M | Fetal bovine serum | Fluorescence spectrometry | 78 |
| | | 0.4–0.9 μM | — | $3.36 \times 10^{-10}$ M | Fetal bovine serum | Fluorescence spectrometry | 67 |
| | HCG | 2.0–$10^5$ mIU $mL^{-1}$ | 0.9385 | 0.19 mIU $mL^{-1}$ | Human serum | Fluorescence spectrometry | 102 |
| Other glycoproteins | Avidin | 157 fM–4.40 pM | 0.999 | 75 fM | — | Electrochemistry | 72 |
| | BSA | $10^{-11}$–$10^{-5}$ g $mL^{-1}$ | 0.998 | $7.5 \times 10^{-12}$ g $mL^{-1}$ | Diluted human blood plasma | Electrochemistry | 56 |
| | Con A | — | — | 15.56 nM | — | Surface plasmon resonance | 118 |
| | Erythropoietin | — | — | $2.9 \times 10^{-14}$ M | Human urine | Raman spectroscopy | 83 |
| | OVA | 0–10 μM | — | — | — | Fluorescence spectrometry | 30 |
| | | $10^{-10}$–$10^{-4}$ mg $mL^{-1}$ | 0.989 | $2 \times 10^{-11}$ mg $mL^{-1}$ | Egg whites of chicken and quail | Electrochemistry | 58 |
| | | 1 pg $mL^{-1}$–1000 ng $mL^{-1}$ | 0.991 | 0.87 pg $mL^{-1}$ | Egg white chicken | Electrochemistry | 6 |

proteins were detected, demonstrating the great potential of nanocomposites in deep-coverage glycoproteome analysis.[119]

### 5.2 Recognition and imaging of glycoproteins in biological cells

BAMs combine with fluorescent materials, which can be applied to recognition and imaging of glycoprotein living cells. Wang and co-workers[69] regarded HeLa cells as the model living cell and their proposed B-g-CN nanosheets were used as fluorescent probes to study the imaging of endogenous and exogenous glycoproteins. After the cells were treated with different concentrations of glycoprotein, B-g-CN was used to detect the exogenous target glycoprotein and a clear cell image was obtained, thus showing that this probe can be applied in imaging. However, at present, there is not much research on the use of BAMs for glycoprotein recognition and imaging of living biological cells. In contrast, a large number of fluorescent BAMs have been proposed for cell imaging to recognize cell membrane glycans, usually using QDs,[120,121] traditional fluorescent dye,[122,123] and conjugated polymers[124,125] as fluorescence donors. QDs are characterized by controllable size emission wavelength, great photostability, broad excitation and narrow emission, compared with traditional fluorescent dyes.[126] Meanwhile, conjugated polymers have the obvious advantages of superior brightness, tuneable emission spectra, and good photostability.[127] These BAMs probes are increasingly being used in living cell imaging and they provide an effective reference for the development of recognition and imaging of glycoproteins in biological cells.

## 6. Conclusions and perspectives

Research on BAMs has made great progress in the past decade. Using BAMs as a sensor to identify and detect glycoproteins has the characteristics of low sample requirements, high sensitivity, and high specificity, but their use is still limited. Firstly, at present, the glycoproteins that have been studied include only a few enzymes and some biomarkers, and there are not many types. Secondly, the specificity of some sensors is very low and they are not only responsive to the target glycoprotein,

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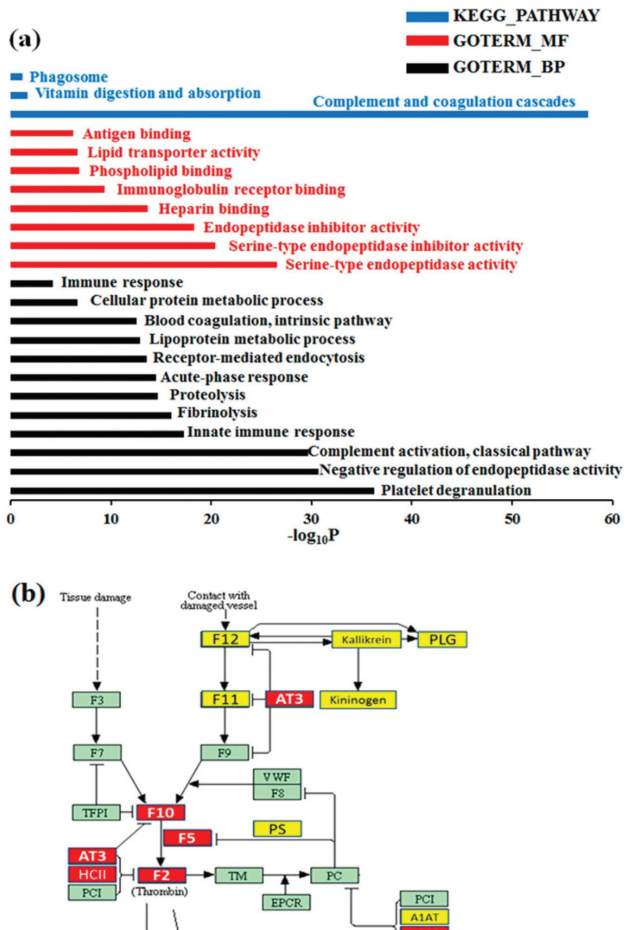


Fig. 6 (a) GO term enrichment analysis of biological processes, molecular function, and KEGG pathway using DAVID program. (b) Identification of glycoproteins associated with complement and coagulation cascades pathway under physiological conditions. Reprinted from ref. 119, Copyright, 2018, American Chemical Society.

which can easily affect the detection results, resulting in false-positive results. Finally, the syntheses of some sensors using BAM-based sensors are complex, time-consuming, and high cost, which cannot provide convenience for the actual detection of glycoproteins, and maybe they can only be used in simulated laboratory studies. Although the research progress is limited, the advantages and potential of BAM-based sensors are limitless. The limitations just prove that there is still much room for further research in the detection of glycoprotein with BAM-based sensors.

Moreover, with the further study of BAM-based sensors in glycosylated diseases and their biomarkers, the applications in clinical diagnosis and prognosis will develop. The research on the detection of glycoproteins using boronate affinity will enter a new stage. We hope and believe that this field of study will gradually overcome its limitations and shortcomings and see significant development.

## Abbreviations

| | |
|---|---|
| AFP | α-Fetoprotein |
| Ag NPs | Ag nanoparticles |
| Ag@MagPMMS | Ag shell-coated magnetic, monodisperse polymethacrylate microspheres |
| ALP | Alkaline phosphatase |
| APS | Aniline to ammonium persulfate |
| APTES | 3-Aminopropyltriethoxysilane |
| Au NPs | Au nanoparticles |
| BAMs | Boronate affinity materials |
| BASA | Boronate affinity sandwich assay |
| B-g-CN | Boronic acid-decorated g-$C_3N_4$ |
| BSA | Bovine serum albumin |
| Con A | Concanavalin A |
| Cu NPs | Cu nanoparticles |
| DPV | Differential pulse voltammetry |
| EDC | 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride |
| EDMA | Ethylene dimethacrylate |
| ELISA | Enzyme-linked immunosorbent assay |
| FcHT | 6-Ferrocenylhexanethiol |
| FITC | Fluorescein isothiocyanate |
| FL | Fluorescence intensity |
| FNCs | Fluorescent nanocrystals |
| g-$C_3N_4$ | Graphitic carbon nitride |
| GCE | Glassy carbon electrode |
| GO | Graphene oxide |
| Gr | Graphene |
| $HbA_{1c}$ | Glycosylated hemoglobin |
| hCG | Human chorionic gonadotropin |
| HPMA | 3-Chloro-2-hydroxypropyl methacrylate |
| HRP | Horseradish peroxidase |
| IgG | Immunoglobulin G |
| MBAA | *N*,*N*′-Methylenebis(acrylamide) |
| MIP | Molecular imprinted polymer |
| MNBs | Magnetic beads |
| MDTA | ({[2-(2-Methacrylamido)-ethyldithio]ethylcarbamoyl}methoxy)acetic acid |
| NHS | *N*-Hydroxysulfosuccinimide |
| OVA | Ovalbumin |
| OPD | *o*-Phenylenediamine |
| PAMAM | Poly(amidoamine) |
| PGMA | Poly (glycidyl methacrylate) |
| PIMs | Post-imprinting modifications |
| PISA | Plasmonic immuno-sandwich assay |
| PS | Polystyrene |
| PSA | Prostate-specific antigen |
| QDs | Quantum dots |
| QBs | Quantum dot nanobeads |
| SERS | Surface-enhanced Raman scattering |

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| | |
|---|---|
| SPR | Surface plasmon resonance |
| TRF | Transferrin |
| UCNPs | Upconversion nanoparticles |
| μPADs | Microfluidic paper-based analytical devices |

## Conflicts of interest

The authors have declared no conflict of interest.

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