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CRITICAL REVIEW

Sensitive and specific detection of saccharide species based on fluorescence: update from 2016

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Abstract

Increasing evidence supports the critical role of saccharides in various pathophysiological steps of tumor progression, where they regulate tumor proliferation, invasion, hematogenic metastasis, and angiogenesis. The identification and recognition of these saccharides provide a solid foundation for the development of targeted drug preparations, which are however not fully understood due to their complex and similar structures. In order to achieve fluorescence sensing of saccharides, extensive research has been conducted to design molecular probes and nanoparticles made of different materials. This paper aims to provide in-depth discussion of three main topics that cover the current status of the carbohydrate sensing based on the fluorescence sensing mechanism, including a phenylboronic acid-based sensing platform, non-boronic acid entities, as well as an enzyme-based sensing platform. It also highlights efforts made to understand the recognition mechanisms and improve the sensing properties of these systems. Finally, we present the challenge of achieving high selectivity and sensitivity recognition of saccharides, and suggest possible future avenues for exploration.

Keywords Saccharide detection · Fluorescence assay · Phenylboronic acid · Nanoparticles · Glucose oxidase

Introduction

Saccharides, also known as carbohydrates, are crucial for sustaining life by serving as the main source of energy for most living systems and as fundamental building blocks for oligo-/polysaccharides, DNA, RNA, ATP, glycans, glycolipids, glycopeptides, and glycoproteins. Ranging from basic monosaccharides (e.g., glucose, galactose, mannose, ribose, sialic acid), to critical glycans composed of several to tens of monosaccharide units, and complex polysaccharides consisting of hundreds to thousands of monomers, saccharides perform a wide variety of functions, including primary metabolic fuel supply in life and storage of genetic information, as well as roles in cancer occurrence and viral infection [1, 2]. Notably, saccharides play a significant role in various disease conditions, and glucose detection has a primary application in diabetes diagnosis and management [3]. The number of diabetes patients worldwide, according to data from the International Diabetes Federation (IDF), currently exceeds 500 million, with an estimated increase to 650 million by 2030. Consequently, there is high demand for less invasive techniques enabling continuous glucose monitoring [4–8] to prevent hypo-/hyperglycemia, which can cause severe complications [9]. Furthermore, abnormal glycosylation of proteins, such as the high sialic acid expression at the end of *N*-linked glycans or core fucosylation, has been implicated in several major diseases and cancers, with glycoproteins serving as clinical medicine biomarkers. Most cancer biomarkers identified to date are glycoproteins, of which the most well known are CA125, AFP, and CA50. In addition, sialylated glycans also mediate the entry of some

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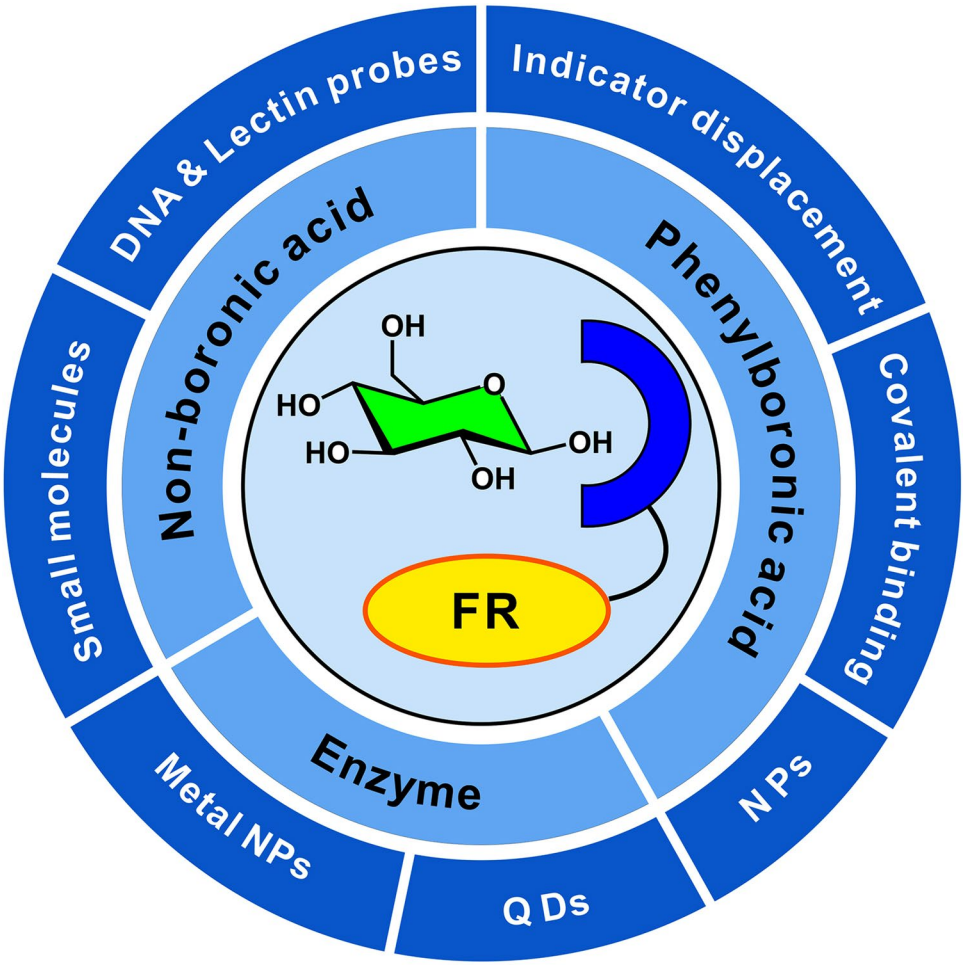

Scheme 1 Illustration of fluorescence sensing systems for saccharides

human viruses, such as the influenza viruses and the Middle East respiratory syndrome coronavirus, into host cells; in particular, different linkage isomers of glycans can lead to distinctly different biological effects [10–12]. The aforementioned examples highlight the enormous significance of saccharides and glycans in biological systems, although their precise recognition, identification, and comprehensive analysis remain exceptionally challenging.

From the perspective of chemical structure, saccharides exhibit three-dimensional spatial complexity. For instance, even simple saccharides such as glucose are governed by a balance between cyclic and linear structures. Furthermore, different monosaccharides, such as glucose, galactose, mannose, and *N*-acetyl-glucosamine, differ solely in the orientation of a single hydroxyl or substituent group. Additionally, glycans consist of a variety of saccharide units with different linkage/epimerism forms or branched structures, which endow glycans with great diversity, making them more complex than DNAs and proteins. Nature has evolved biochemical tools such as various glycosidase or glycosyl transferase enzymes to produce exquisitely complicated and precise glycan structures, while the recognition and diagnostic tools have remained inadequate [13]. Fluorescence sensing approaches have attracted increasing attention due to their intrinsic advantages, including easy sample preparation, low cost, high sensitivity, quick response time, noninvasive and nondestructive nature, real-time analysis, and diverse signal output modes [14–16]. These advantages provide considerable research potential in saccharide detection.

This review aims to describe the current endeavors in saccharide detection based on fluorescence methods. Based on the probe designs and their sensing mechanisms, such efforts can be classified into three primary categories: boronic acid-based sensing platform, non-boronic acid entities, and enzyme-based sensing platform (Scheme 1). Finally, we present our perspective on the future prospects in this field. In view of the rapid development of this research field, our focus is primarily on the progress made in saccharide recognition and sensing in the recent 6 years, while previous works can be found in other reviews [17–21].

Boronic acid-based sensing platform

Molecular probes using an indicator displacement mechanism

The indicator displacement assay has been in use since its introduction approximately two decades ago, primarily utilizing a supramolecular system composed of an optical indicator and a synthetic receptor [22]. Upon exposure to an appropriate analyte, the indicator is released, accompanied by a remarkable change in optical spectra, facilitating qualitative and quantitative assay combined with mathematical regression analysis. Compared to reactive molecular chemosensors, indicator replacement analysis boasts several advantages, including simple operation, low cost, flexible design, high sensitivity and accuracy, and high-throughput automated analysis, making it a popular choice for detecting biologically relevant molecules and ions. Because of the high affinity of phenyl boronic acid toward *cis*-1,2 and *cis*-1,3-diol [22–24], saccharide sensing based on an indicator displacement mechanism often involves the boronic acid-appended receptors [25–27].

Anzenbacher et al. developed oxazolidine boronates for high-throughput saccharide detection based on fluorescence resonance energy transfer (FRET) (Fig. 1A) via the combination of two chromophores [28]. Upon addition of D-glucose to S1, comprising L-tryptophanol (donor) and 6,7-dihydroxycoumarin (acceptor), the emission of 6,7-dihydroxycoumarin decreased by 47.2%, whereas L-tryptophanol emission increased by 440% (Fig. 1B and 1C). The sensor's affinity to monosaccharides (fructose > galactose > glucose > mannose) and disaccharides (sucrose > lactose > maltose) was determined by the fluorescence titrations. Principal component analysis (PCA) (Fig. 1D) and linear discriminant analysis (LDA) (Fig. 1E) revealed complete resolution of different saccharide clusters, with monosaccharide and disaccharide well resolved throughout the F1 canonical factor (Fig. 1E). The sensor successfully quantified glucose in the presence of fructose and complex media (urine) without sample pretreatment, and the concentration range of glucose quantification was 0–60 mM (limit of detection [LOD] 0.94 mM). These dual chromophore sensors not only discriminated various analytes but also distinguished different concentrations of analytes present in urine, suggesting their potential application in saccharide detection.

Because of its satisfactory water solubility and unique photophysical properties [29, 30], the anionic dye 8-hydroxypyrene-1,3,6-trisulfonic acid trisodium salt (HPTS) is extensively utilized as an optical indicator in

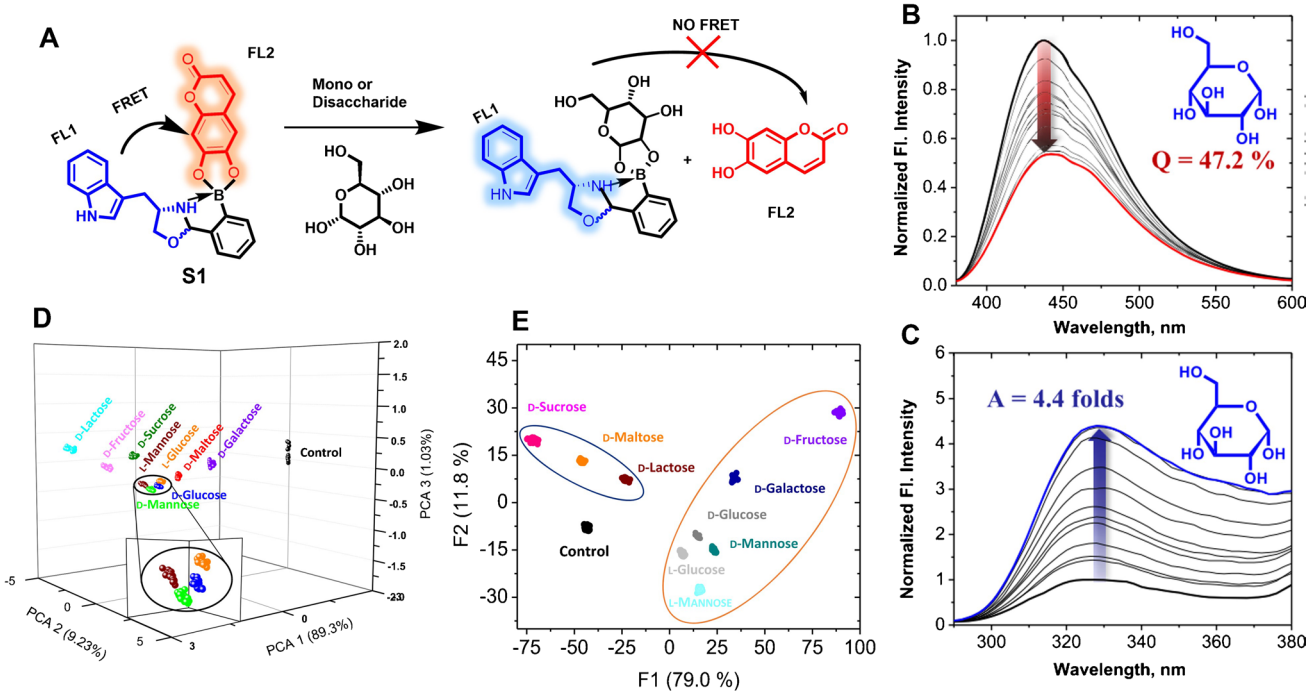

Fig. 1 **A** FRET-based saccharide sensing based on dual chromophore oxazolidine boronate. **B** and **C** Fluorescence spectra of S1 upon addition of D-glucose related to 6,7-dihydroxycoumarin (λex = 370 nm) (B) and L-tryptophanol (λex = 280 nm) (C), respectively. **D** Principal component analysis (PCA) of mono- and disaccharides in acetonitrile/water (98/2). **E** Qualitative linear discriminant analysis (LDA) of mono- and disaccharides in acetonitrile/water (98/2). Reproduced with permission [28]. Copyright 2021, American Chemical Society (ACS)

saccharide sensing [23, 26, 31]. In this process, HPTS reversibly binds to a synthetic receptor (quencher) via electrostatic interaction and π-π stacking interaction. By utilization of HPTS, Feng et al. reported pyridine analogue-modified boronic acid as quencher/connector in two-component ensembles [31]. The quenchers they developed were found to display better sensitivity and selectivity for monosaccharides compared to the previously reported boronic acid-functionalized benzyl viologens (BBVs) [32]. This was ascribed in part to the shorter distance between positive charge N^+ and negative charge B^-, as shown in Fig. 2. Their results suggested that the number of the positive charges and boronic acids of the quencher had an impact on the monosaccharide detection. Among the nine pyridinium analogue-appended boronic acids, the receptor TCTB (containing three positive charges and three boronic acid groups)/HPTS (20/1, mole ratio) exhibited the best sensitivity toward D-glucose. In addition, this two-component probe demonstrated highly selective detection for forsythoside A, with LOD of 1.0×10^{-5} mol/L.

Unlike other receptors that require complicated and multistep synthesis processes, a simple chemosensor was fabricated through the in situ mixing of off-the-shelf reagents, namely esculetin or 4-methylesculetin coupled with 3-nitrophenylboronic acid (3-NPBA) [33]. This two-component system enabled qualitative and quantitative detection of phosphorylated saccharides with a fluorescence "turn-on" response (Fig. 3A). Using the indicator displacement assay, the system was able to simultaneously detect and classify 14 different types of saccharides with a 100% success rate (Fig. 3B) by linear discriminant analysis (LDA), including glucose-6-phosphate (G6P) and fructose-6-phosphate (F6P). Moreover, this chemosensor array system was successfully applied to monitor the glycolytic activity of hiPS cells, wherein two spiked clusters demonstrated that up/down responses of canonical factors 1 and 2 (F1 and F2) were dependent on Glc and F6P levels (Fig. 3C and 3D). This simple sensing system, which does not require any organic synthesis, holds potential for application in biomarker detection.

Minami et al. presented a novel 96-well paper microtiter plate for simultaneous classification of 12 saccharides [34], which utilized a paper-based chemosensor array device (PCSAD) constructed of four types of catechol dyes and 3-nitrophenylboronic acid via dynamic covalent bonds (Fig. 4A). The saccharide detection method involved an indicator displacement assay by competitive boronate esterification, and the resulting colorimetric changes were applied for qualitative, semi-quantitative, and quantitative analyses (Fig. 4B and 4C). The qualitative linear discriminant analysis, with a classification rate of 100%, enabled the discrimination of all 12 saccharides, while the semi-quantitative analysis demonstrated successful classification of fructose in the presence of glucose. Furthermore, the concentration of fructose in a mixture was precisely predicted by regression analysis, utilizing the support vector machine (SVM) algorithm (Fig. 4D).

In addition to small molecules, conjugated polymers have been utilized as indicators for saccharide discrimination. A straightforward nine-element library array was constructed using three different boronic acid-functionalized quencher molecules (*o*-, *m*-, *p*-BV^{2+}) and three anionic conjugated polymers (PAE 1–3) [35]. The binding of PAEs to *p*-BV^{2+} was determined to be the strongest using the Stern–Volmer formalism, which was approximately five times that of *m*- and *o*-BV^{2+}. Furthermore, among the three PAEs, PAE 1

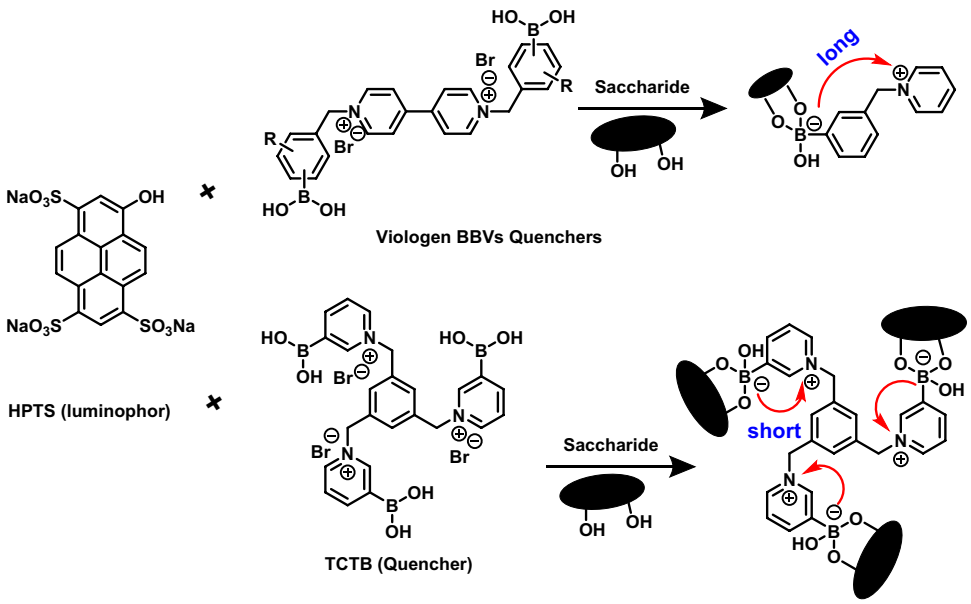

Fig. 2 Comparison of quenching effect by boronic acid-appended benzyl viologens (BBVs) and pyridinium analogue. Reproduced with permission [31]. Copyright 2019, Elsevier

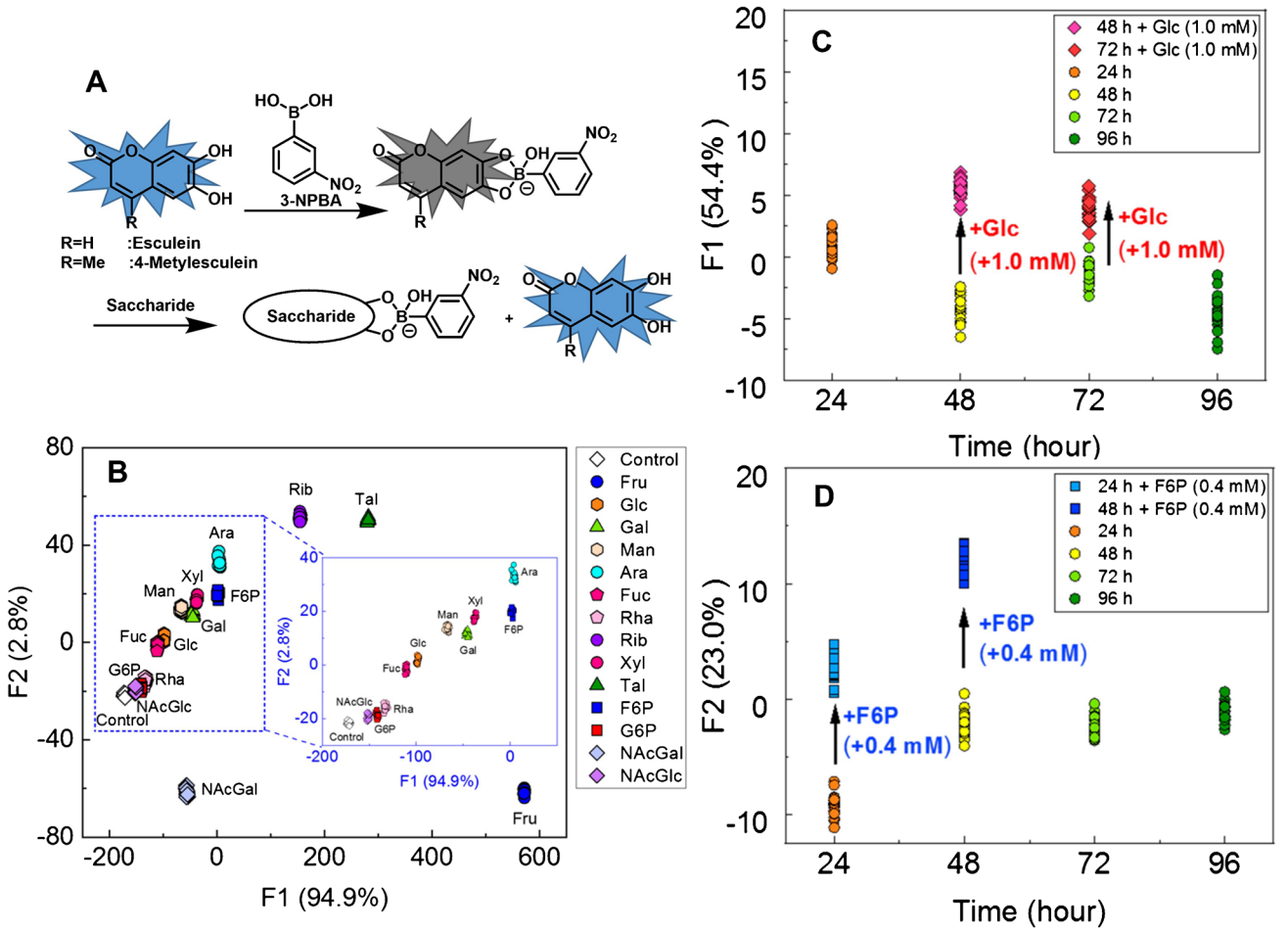

Fig. 3 **A** Illustrated scheme for the easy-to-prepare chemosensor array fabricated with off-the-shelf reagents. **B** LDA result of the qualitative assay with 100% correct classification against 15 types of clusters (14 saccharides and a control). **C** and **D** Indirect monitoring of the glycolytic activity of hiPS cells using the chemosensor array system. Reproduced with permission [33]. Copyright 2019, ACS

exhibited the strongest binding to the quencher. The use of the two-component probes enabled a displacement assay for differentiating nine different saccharides. Specific saccharide binding induced the release of the conjugated polymers, leading to differential fluorescence turn-on. Nonetheless, their assay was not sufficiently sensitive for detecting glucose levels in blood.

Molecular probes using direct covalent interactions

Because of the high binding affinity of phenylboronic acid for *cis*-diols, various fluorophores with appended boronic acids have been designed for direct carbohydrate binding [36]. In this regard, molecules with vibration-induced luminescence (VIE) [37] and aggregation-induced luminescence (AIE) [38] properties were explored for glucose detection. Galan et al. synthesized a VIE-based fluorescence receptor (Fig. 5A) that formed dynamic covalent bonds with glucose, resulting in remarkable fluorescence enhancement (Fig. 5B) [37]. Notably, the emission response of this *N*,*N*′-diphenyldihydro dibenzo[a,c]phenazine (DPAC) derivative probe to each saccharide appeared different. This allowed the discrimination of similar monosaccharides, including D-glucose, D-galactose, and D-fructose, found in blood (Fig. 5C). Their proposed interaction of receptor 1 with monosaccharides formed pseudomacrocyclic complexes at a stoichiometry of 1:1, and fluorescence color change was visible to the naked eye (Fig. 5D). Their findings indicated the potential of VIE receptors for the quantification of carbohydrates in biological samples.

Inspired by wearable electronics, a smart contact lens has been developed for glucose monitoring [5, 6, 8]. A reference fluorescent dye (e.g., rhodamine) was fused with a selective fluorescent probe that could bind with glucose, within a hydrogel network of poly(2-hydroxyethyl methacrylate) (PHEMA) (Fig. 6A) [39]. Glucose levels were then able to be measured by capturing fluorescent color images of contact lenses with a smartphone and converting the data

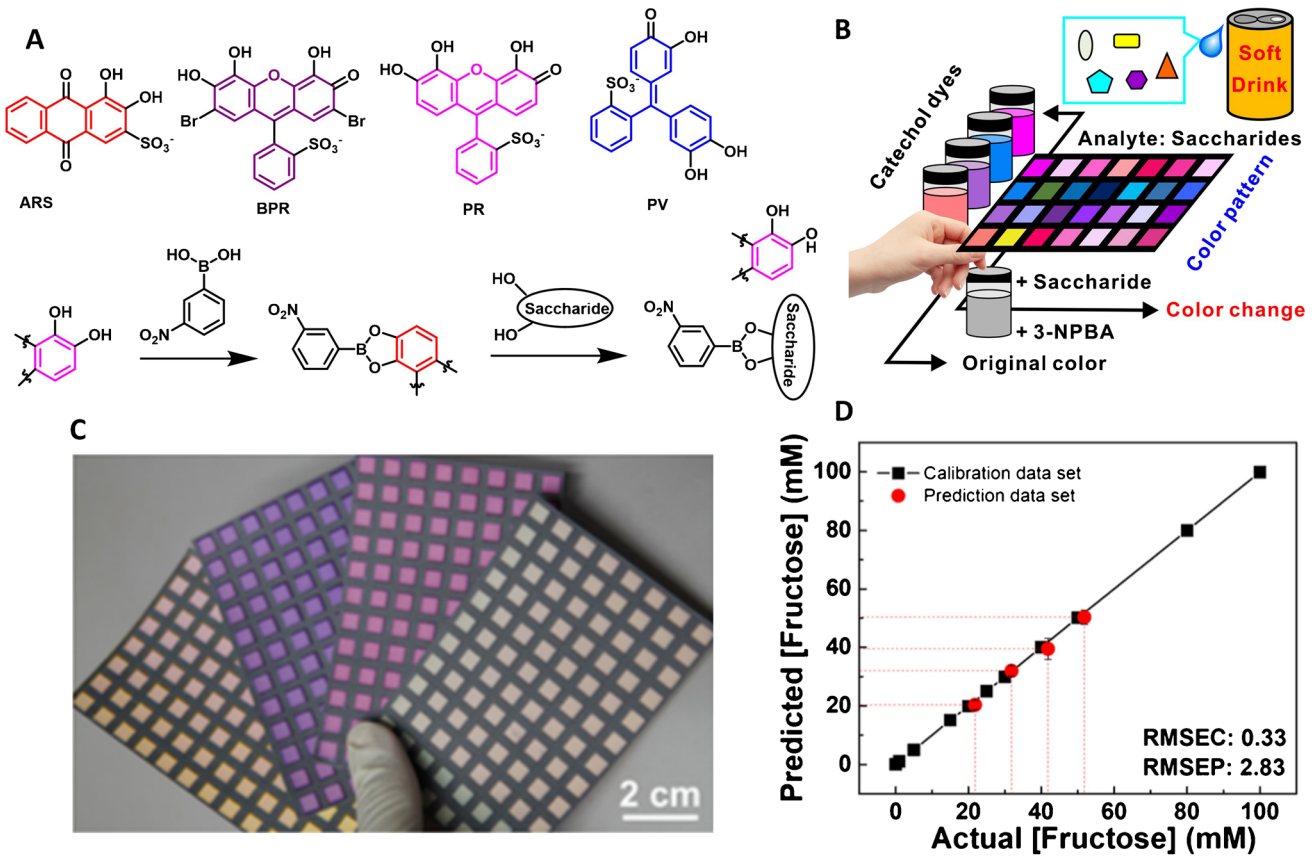

Fig. 4 **A** Structures of the catechol dyes and 3-nitrophenylboronic acid, and the mechanism of saccharide detection based on IDA. **B** Protocol overview of saccharide detection using the PCSAD. **C** Photograph of the fabricated PCSAD. (D) Results of the SVM regression for fructose in a soft drink. Reproduced with permission [34]. Copyright 2021, ACS

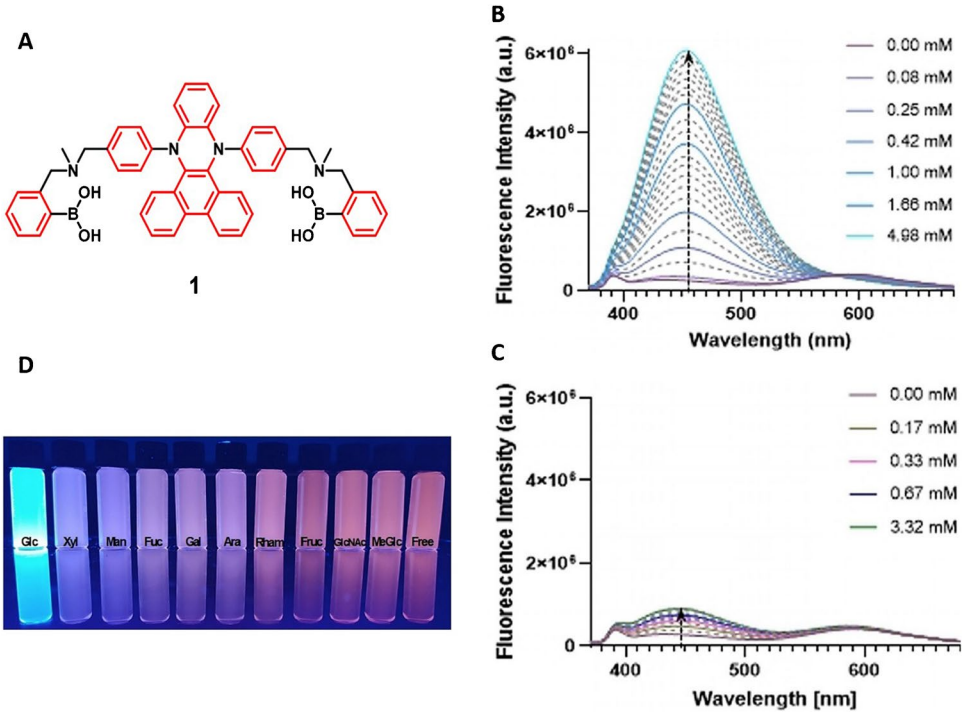

Fig. 5 **A** Chemical structure of DPAC derivative receptor **1**. **B**, **C** Fluorescence emission spectral changes of **1** upon the addition of D-glucose (B) and D-fructose (C), $\lambda_{ex} = 350$ nm, respectively. **D** Fluorescence image of **1** in the presence and absence of various monosaccharides under irradiation with 365 nm UV light. Reproduced with permission [37]. Copyright 2021, Wiley–VCH

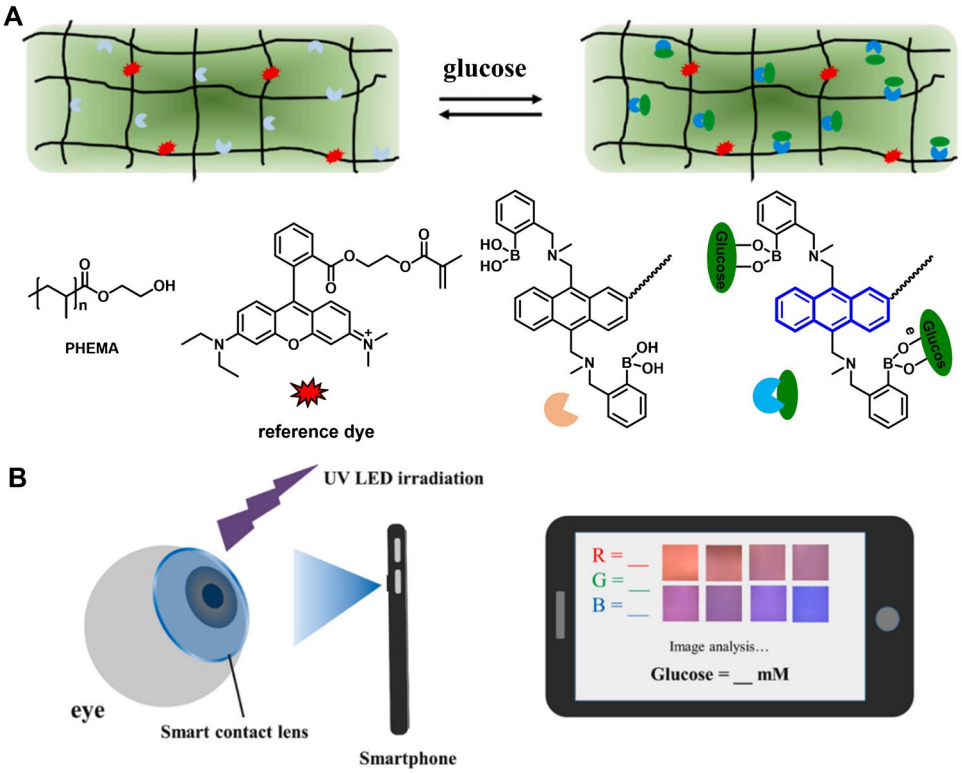

Fig. 6 Schematic illustration of smart contact lenses for monitoring glucose. **A** The network of HEMA hydrogels contains two probes: one as a reference probe for calibration, and the other for glucose binding. **B** Design of the contact lenses for glucose detection through capture of the image and analysis of the RGB value of the image by a smartphone. Reproduced with permission [39]. Copyright 2021, Elsevier

into RGB signals (Fig. 6B). This innovative approach successfully monitored glucose levels ranging from 23 μM to 1.0 mM, which fulfills the requirement for glucose detection in tears. This technology is expected to replace the current methods for painless glucose monitoring, making it a promising new platform for glucose detection.

Cyclodextrin, which is water-soluble, possesses a chiral hydrophobic cavity that allows it to encapsulate small molecules and induce the formation of supramolecular ensembles, which can be used for D-glucose detection [40]. Hayashita et al. used the unique hydrophobic cavity structure of γ-cyclodextrin (γ-CD), and achieved selective saccharide recognition through supramolecular co-assembly. The binding between saccharides and phenylboronic acid groups significantly shortened the distance between two anthracene fluorophores, enabling them to fall into the cavity of γ-CD (Fig. 7A) [41]. In the γ-CD cavity, probe **1** [(4-(anthracen-2-yl-carbamoyl)-3-fluorophenyl) boronic acid] formed a 2:1 supramolecular complex with glucose, exhibiting the evolvement of dimer fluorescence, and the different emission intensity was even visible by the naked eye after addition of various saccharides (Fig. 7B, C). Moreover, the circular dichroism (CD) signal changed significantly after the interaction with different sugar molecules, which led to the selective recognition of the saccharides based on the cotton effect splitting pattern (Fig. 7D). This system demonstrates good application prospects for sugar detection, particularly under neutral pH conditions.

Nanoparticles (NPs) functionalized with boronic acid

Boronic acid-functionalized carbon dots have been developed for glucose sensing, owing to their strong fluorescence, tunable excitation and emission, water solubility, attractive photo-stability, and biocompatibility [42]. With the use of sodium citrate and 3-aminophenylboric acid as precursors, carbon dots (C-dots) were fabricated in one step, with the boronic acid group firmly anchored to the surface (Fig. 8) [43]. The C-dots readily formed a coordination complex with the *cis*-diol group of glucose, resulting in fluorescence quenching in its aggregation state. Furthermore, due to the presence of the *cis*-diol group in glucose, the aggregation of C-dots simultaneously promoted an increase in the resonance light scattering owing to the nonhomogeneous phase size effect. The glucose detection limit was as low as 10 μM in water samples [43], displaying excellent selectivity as compared to other analogues.

Zhou et al. synthesized dual-emission quantum dots by hybridizing red-emitting CdTe quantum dots (r-QDs) with green-emitting CdTe QDs (g-QDs), as illustrated in Fig. 9A and B [44]. The fabricated QDs were functionalized with 3-aminophenylboric acid (APBA) for selective glucose detection via boronic acid-*cis*-diol chemistry. The fluorescence of g-QDs was found to be quenched upon glucose binding, while the emission of the r-QD remained constant, which worked as a reference, resulting in ratiometric fluorescence

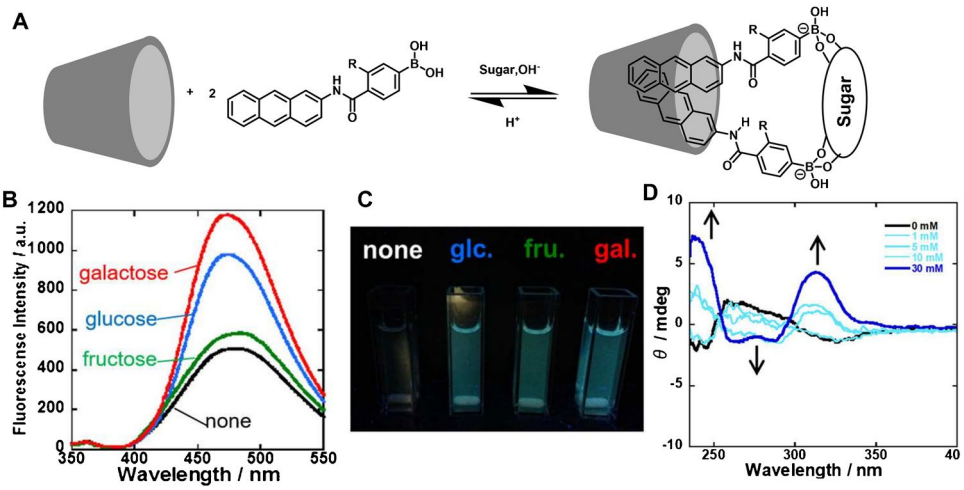

Fig. 7 **A** Possible saccharide response mechanism of [4-(anthracen-2-yl-carbamoyl)-3-fluorophenyl] boronic acid/γ-CD complex. **B** Comparison of fluorescence spectra of 1/γ-CD complex with various saccharides. **C** Fluorescence image of 1/γ-CyD complex solution before and after the addition of various sugars at pH 7.4 under UV irradiation. **D** Induced circular dichroism spectral changes of 1/γ-CD complex responding to the addition of glucose with different concentrations. Reproduced with permission [41]. Copyright 2019, Frontiers Media SA

detection. Continuous changes in the fluorescent intensity and color were visible to the naked eye in response to different concentrations of glucose (Fig. 9C). The linear detection range was 0.1–2.0 mmol L^{-1}, with a limit of detection of 4.5 μmol L^{-1}. The proposed probes showed superior visual detection performance compared to conventional ones, as revealed in Fig. 9D. Moreover, the sensor demonstrated practical utility by detecting glucose in human serum samples.

Sialic acids, a group of nine-carbon carboxylic monosaccharide, are vital to physiological and pathological

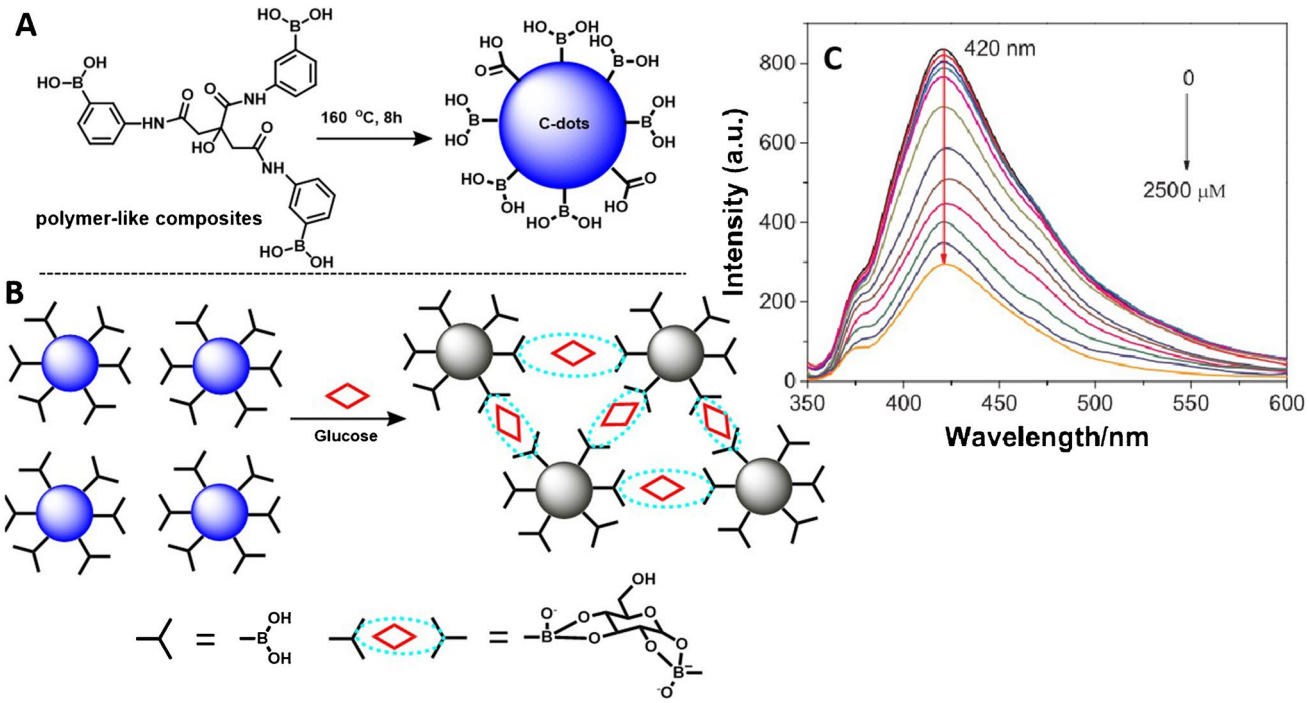

Fig. 8 **A** One-step fabrication of boronic acid-functionalized C-dots. **B** Working principle for glucose sensing with fluorescence quenching. **C** Fluorescence spectra of glucose titrating C-dot aqueous solution. Reproduced with permission [43]. Copyright 2018, Elsevier

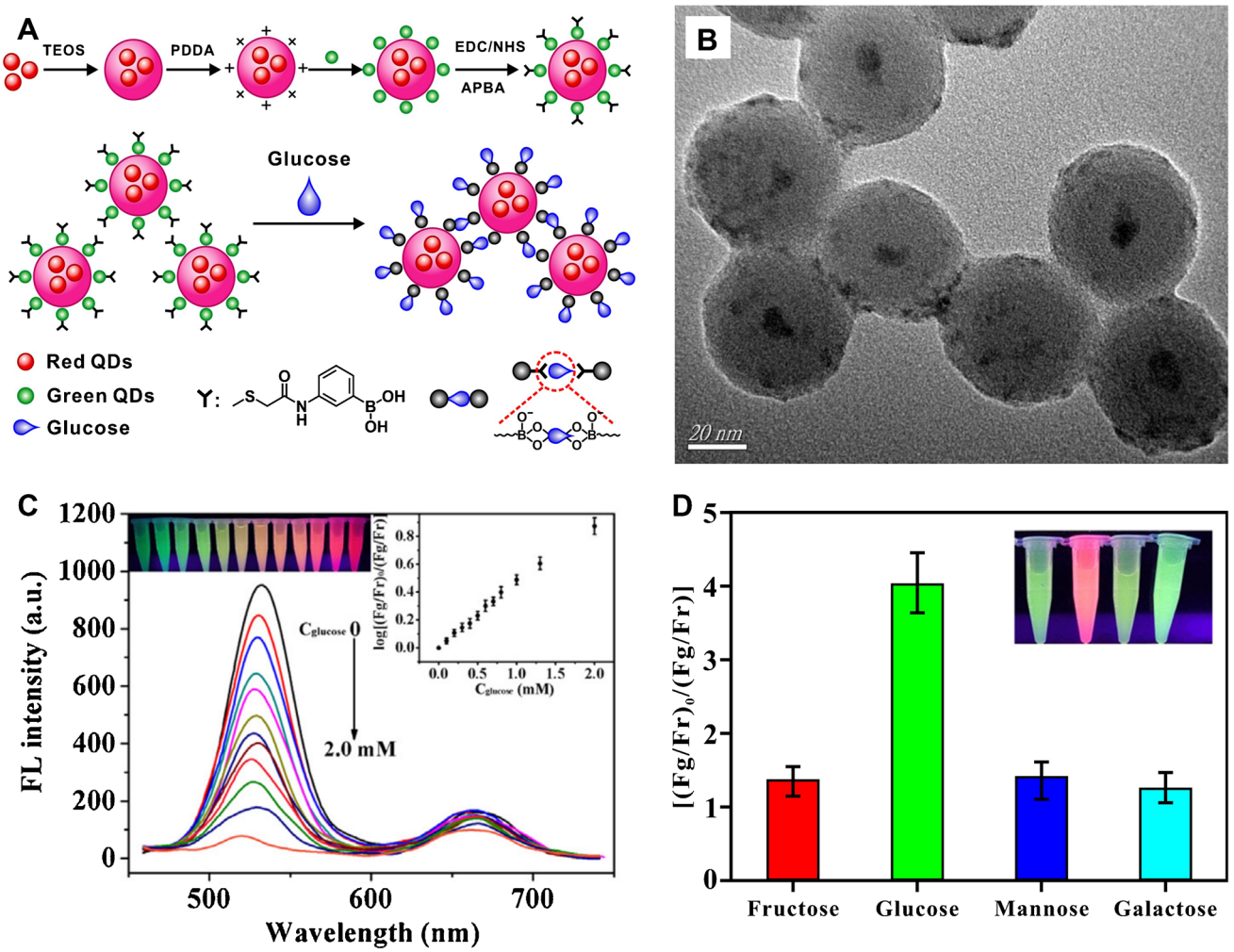

Fig. 9 Schematic illustration of preparation of r-QDs@SiO_2@g-QDs@APBA ratiometric fluorescence probe and the sensing mechanism toward glucose. **B** TEM image of the hybridized QDs. **C** Fluorescence spectra, linear relationship. and the corresponding photographs of the hybridized system responding to glucose with different concentrations. **D** Selectivity of the hybridized QDs toward different monosaccharides. Reproduced with permission [44]. Copyright 2016, Elsevier

processes. Gold nanobipyramids (AuBPs) are noteworthy for their unique plasmonic properties, ease of functionalization, and high biocompatibility. In a study by Ng et al., polydopamine-coated AuBPs were modified using phenylboronic acid-substituted distyryl boron dipyrromethene (BDP) [45], achieving sensitive and selective detection of sialic acid on the surface of cancer cells through a dual response of fluorescence enhancement and surface-enhanced Raman scattering. By anchoring the photosensitive response BDP units on the surface, the photodynamic activity of the nanostructures were activated upon interaction with sialic acid, thereby bringing about the selective photo-eradication of cancer cells. This approach could be applied to the development of other nanomaterials and nano-photosensitizers for cancer diagnosis and photodynamic therapy.

Non-boronic acid entities

Small-molecule carbohydrate-binding agents

Biomimetic carbohydrate-binding agents (CBAs), which are artificial small molecules designed for molecular recognition of carbohydrates through non-covalent interactions, have exhibited notable effectiveness in recognizing carbohydrates in physiological media, thereby opening up new biological applications [46]. According to Roelens et al., the design of CBAs is based on three basic concepts: the pre-organization/adaptivity of the receptor structure [47], the nature of the binding interaction, and the receptor chirality [48]. The authors developed a macrocyclic receptor by integrating carbazole, anthracene, and water-soluble phosphonate units

(Fig. 10A) [49], exhibiting remarkable affinity toward the α anomer of fucose, with over 30-fold α/β selectivity. Isothermal titration calorimetry (ITC) measurements showed that the binding interaction was driven by enthalpy, attributable to extensive hydrogen bonding. The authors suggested that the carbazole unit might be an alternative to natural lectins, with potential therapeutic applications. Moreover, inspired by this idea, they designed an acyclic receptor with similar subunits (Fig. 10B), considering its ability to accommodate disaccharides more effectively than its macrocyclic counterpart [50]. This tweezer-like receptor displayed unprecedented affinity for *N*,*N*′-diacetylchitobiose (GlcNAc2), the core glycosidic fragment of viral *N*-glycans, with an affinity of 160 μM. The interaction between the receptor and disaccharides induced an adaptive architecture. This high affinity and selectivity was attributed to hydrogen bonding and CH–π interactions, as further revealed by molecular modeling calculations with a 3D description of the binding pattern. Acyclic receptors, unlike cyclic or cage-shaped structures, could be a promising tool for carbohydrate recognition owing to their adaptive structure and easy synthesis and structural modification.

Helical foldamer-type hosts have garnered attention as artificial hosts for saccharide recognition owing to their ability to form a hydrogen bond network with multiple hydroxyl groups of saccharides [51]. Inouye et al. designed oligomers consisting of pyridine-acetylene-aniline units wherein the amino groups of the aniline acted as a hydrogen-bonding donor, creating a push–pull hydrogen bonding with the hydroxy groups of methyl *β*-D-glucoside (Fig. 11A) [52]. Density functional theory (DFT) calculation suggested that a helical structure with conformational stability was formed. A combination of several experiments, including ^{1}H nuclear magnetic resonance (NMR), UV/Vis, circular dichroism, and fluorescence titration, revealed that the interaction between the oligomer and methyl *β*-D-glucoside in nonpolar solvents possessed a high affinity constant ($K_a = 10^4$ to 10^5 M^{-1}). Meanwhile, the oligomer remained stable under alkaline conditions, but this catalyst lacked regioselectivity during the acylation of octyl glycoside (Fig. 11B).

Numerous studies have displayed a close relationship between abnormal sialylation of specific proteins and various cancers, highlighting its clinical potential as a potent cancer biomarker [53]. However, while glucose sensors have been studied extensively [54, 55], sialic acid sensors remain relatively scarce [56–59]. In response, Qing and co-workers designed a series of fluorescent sensors using dipeptides [Pro-Asp (PD), Asp-Pro (DP), Asp-Ala (DA), Asp-Asp (DD), Pro-Ala (PA), and Ala-Asp (AD)] to detect sialic acid species [60], mimicking the lectin-carbohydrate binding model [61]. The sensors showed sensitive and differential responses to six typical SA species, despite interference from 300-fold D-glucose or other sugars, providing a novel fluorescence sensing matrix for rapid and efficient discrimination of different SA species. Reversed-phase liquid chromatography (RPLC)–fluorescence detection (FD)–mass spectrometry (MS) was used to differentiate *N*-glycan sialic acid linkages, and this kind of platform might be an additional or orthogonal method to current analytical approaches [62].

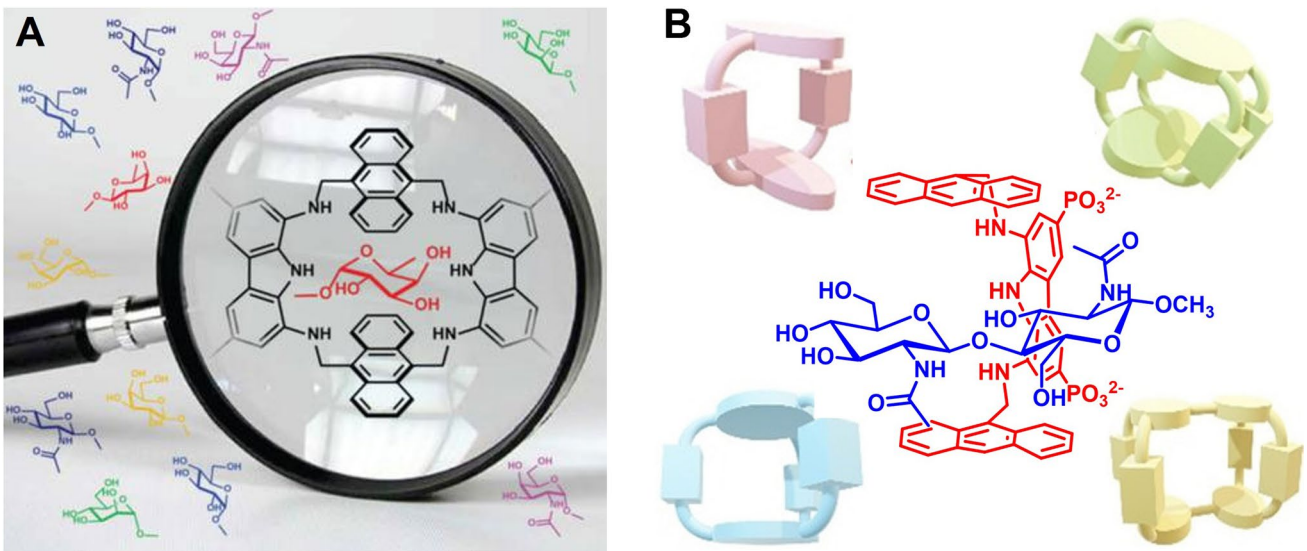

Fig. 10 **A** Selective binding of cyclic receptor toward fucose. Reproduced with permission [49]. Copyright 2018, Wiley–VCH. **B** Schematic illustration of tweezer-like acyclic receptors for disaccharide binding over cyclic and cage-shaped receptors. Reproduced with permission [50], Copyright 2021, Wiley–VCH

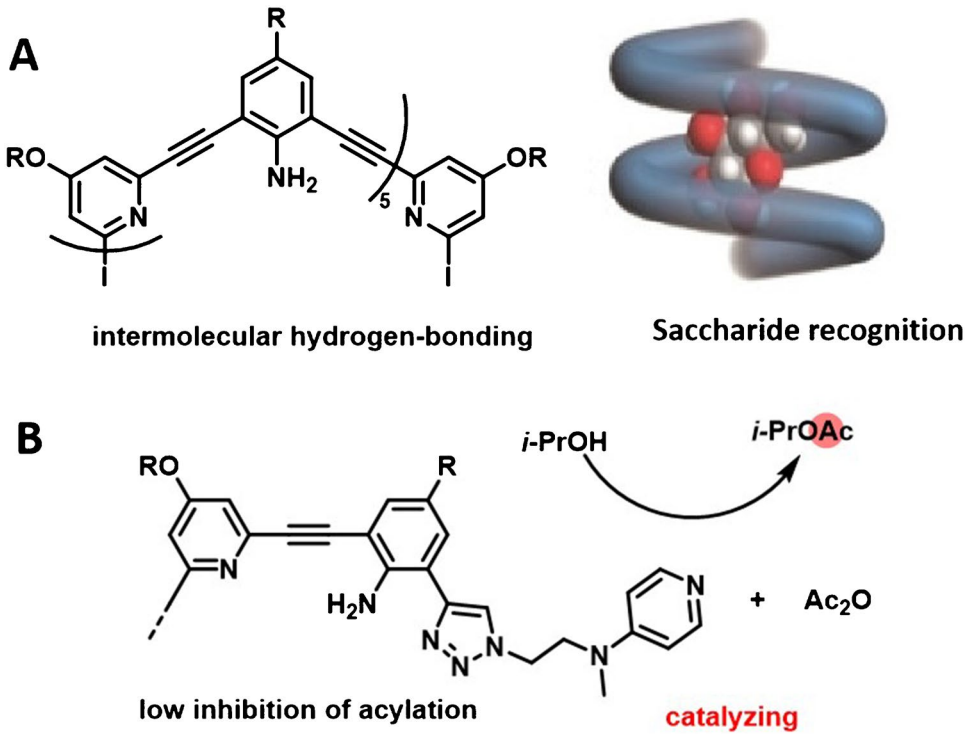

Fig. 11 **A** Saccharide recognition based on pyridine-acetylene-aniline oligomer. **B** Activity of the oligomer as acylation catalyst. Reproduced with permission [52]. Copyright 2020, Wiley–VCH

DNA and lectin-based probes

In addition to artificial small molecules that act as carbohydrate-binding agents via non-covalent bonding, DNA and lectin have also been explored [63]. Glycosylation, a prevalent post-translational modification of proteins and lipids in eukaryotic cells, has been associated with neurological diseases and brain cancers due to abnormal cell surface glycan expression [64]. A recent study by Gao et al. presented a label-free imaging method for cell surface glycans using DNA/silver nanoclusters (AgNCs) via hybridization chain reaction (HCR) and fluorescence-guided photothermal therapy [65]. This system utilized a dibenzocyclooctyne (DBCO)-functionalized DNA and two hairpin structures of DNA/AgNC probes (Fig. 12), along with functional groups that were built on the cell surface for the click reaction through metabolic glycan labeling. The DNA length was subsequently increased to absorb more AgNCs for signal amplification through HCR, resulting in a detection limit as low as 20 cells in 200 µL of binding buffer. Furthermore, its photothermal properties enabled efficient killing of cancer cells and inhibited tumor growth under imaging guide, highlighting its potential in biomedical applications.

Exosomal surface glycans play important roles in both microvesicle protein sorting and exosome-cell interactions. To illustrate, Feng et al. established an exosomal array for glycan signatures, which was achieved through lectin recognition-mediated in situ rolling circle assembly of fluorophore-labeled DNA, as depicted in Fig. 13 [66]. The approach, which focuses on tumor-associated glycans such as sialic acids, fucose, and truncated *O*-glycans, has successfully uncovered specific exosomal glycan characteristics when compared to their parent cells. By incorporating the large-scale microarray technique, this method presents a high-throughput profiling of exosomal glycome, which could fuel the development of exosome-derived glycan-based biomarkers and drug targets that are considerably more accessible than those of cell surface glycans.

Enzyme-based sensing platform

Novel metal nanoparticles

Enzymatic glucose sensors have garnered significant attentions due to their selectivity, simplicity, and sensitivity. In recent studies, novel metal nanoclusters have been developed for the detection of the oxidation product of glucose by the glucose oxidase enzyme (GOx) [67, 68]. Bovine serum albumin stabilized Au nanoclusters (BSA-AuNCs) and 1,2-bis [4-(3-sulfopropoxy)phenyl]-1,2-diphenylethylene (BSPOTPE) sodium were employed as the fluorescence detection probe and reference probe, respectively [69]. BSPOTPE, as an AIE molecule, has low emission on its own but displays high emission between 400 and 550 nm after incubation with BSA-AuNCs. The BSPOTPE/BSA-Au NCs hybrid system demonstrated ratiometric detection to glucose (Fig. 14). As the product of GOx-catalyzed glucose

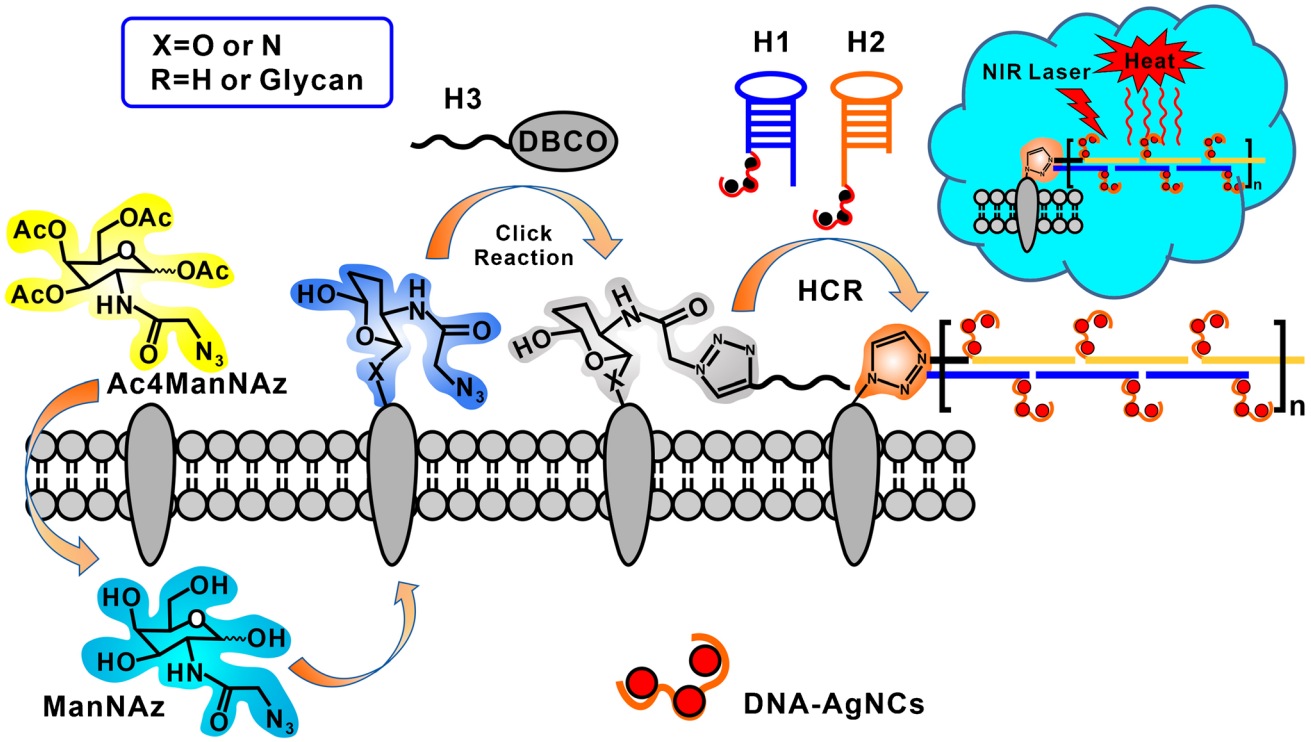

Fig. 12 Illustration of DNA/AgNCs and HCR-based theranostic nanoplatform for label-free fluorescence imaging of cell surface glycans and fluorescence-guided photothermal therapy. Reproduced with permission [65]. Copyright 2018, ACS

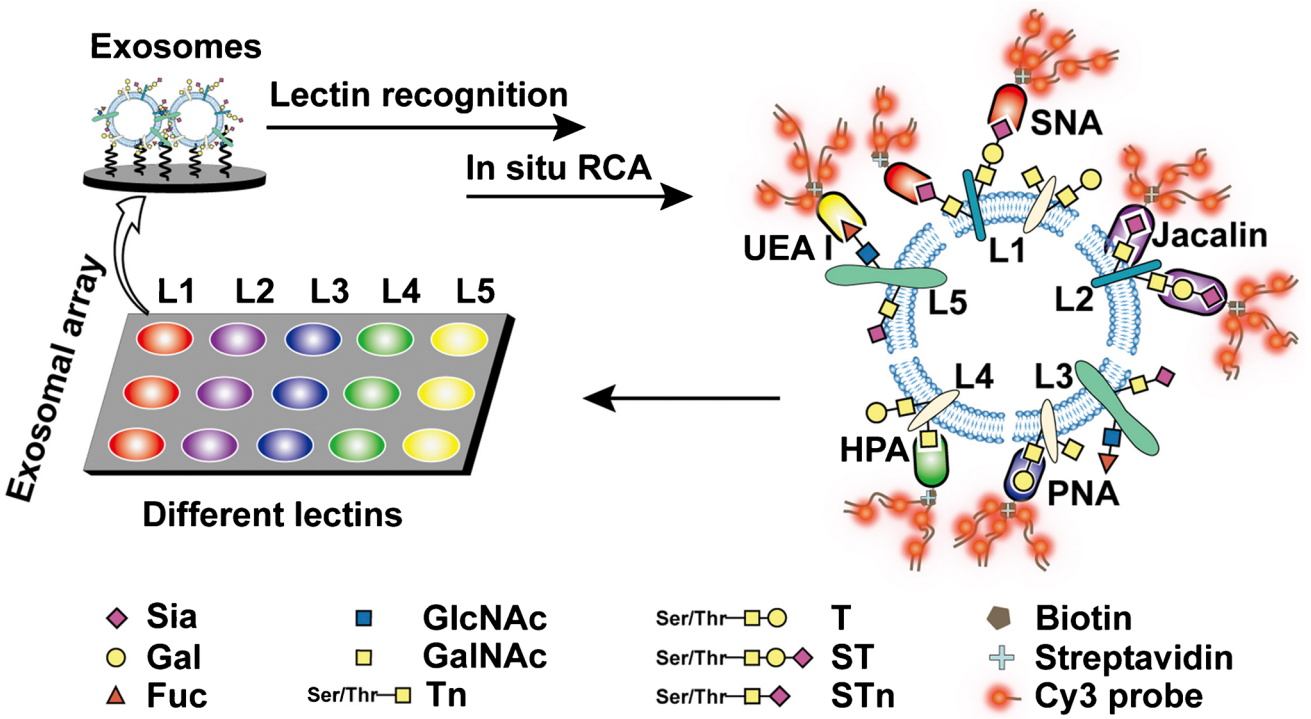

Fig. 13 Lectin-mediated in situ rolling circle amplification (RCA) on an exosomal array for detection of cancer-related exosomal glycan pattern. Reproduced with permission [66]. Copyright 2018, Elsevier

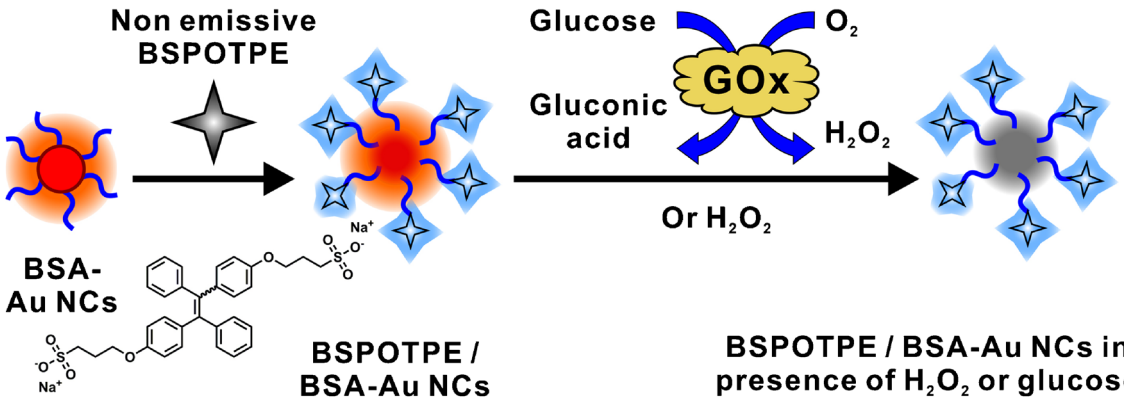

Fig. 14 Fabrication of BSPOTPE/BSA-AuNC probe and its glucose sensing strategy. Reproduced with permission [69]. Copyright 2020, Elsevier

oxidation, H_2O_2 oxidized BSA-Au NCs and induced emission quenching between 550 and 800 nm, but it did not affect the emission of BSPOTPE. The hybrid system exhibited a linear detection range of 1–8 mM based on the ratio of the two emission bands. Additionally, the system exhibited bright red or bright cyan light with concentrations of glucose lower than 3 mM or higher than 7 mM, respectively.

Lin et al. reported a fluorescence amplification strategy for intracellular glucose detection based on silver nanocubes (AgNC) [70]. According to their proposed sensing mechanism, the AgNC was oxidized into Ag^+ by H_2O_2, which was generated from GOx-catalyzed glucose oxidation, as depicted in Fig. 15. Simultaneously, the generated Ag^+ induced a remarkable emission enhancement of its fluorescence probe (FP, i.e., 3′,6′-bis(diethylamino)-2-(2-iodoethyl) spiro[isoindoline-1,9′-xanthen]-3-one), strongly amplifying the signals. Their AgNC−GOx/Ag^+-FP complex system appeared to be sensitive and specific to glucose, as further verified in five different cell lines.

Quantum dots

As a promising alternative to traditional fluorescent dyes, various quantum dots (QDs) have been explored for glucose detection, including Mg/N-doped carbon QDs (Mg–N-CQDs) [71], carbon dots combined with CdTe QDs [72], silica-coated quantum dot (QD@SiO_2) [73], and cesium-doped graphene QDs (Cs-GQDs) [74]. A dual-emission ratiometric fluorescence probe was constructed through the combination of fluorescein isothiocyanate (FITC) and QD@

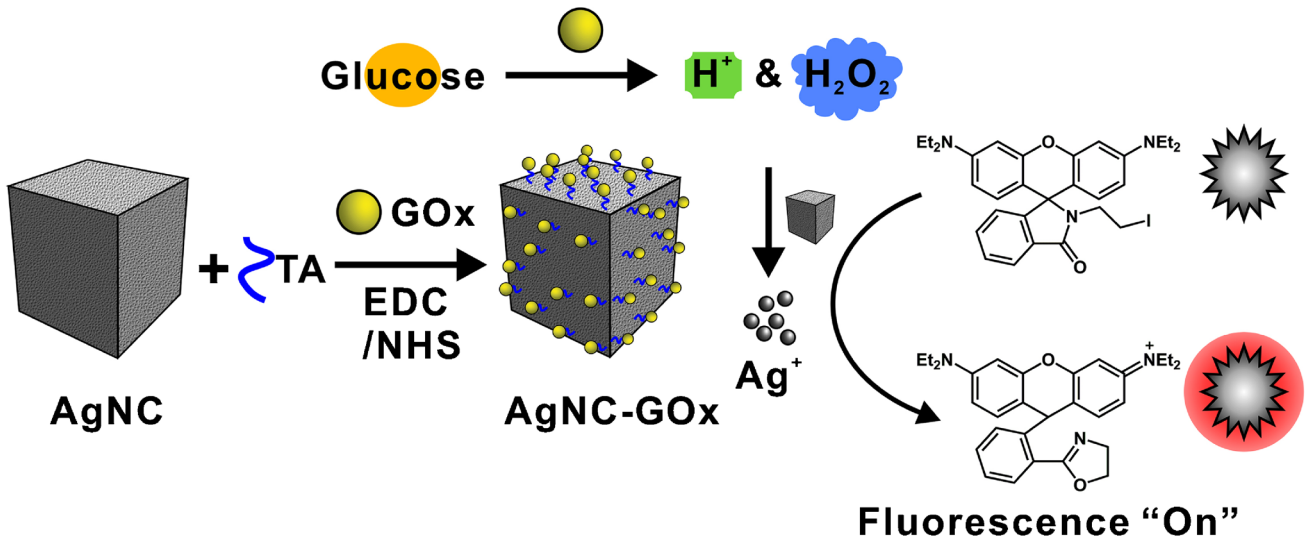

Fig. 15 Schematic illustration of fluorescence amplification strategy of glucose detection mediated by AgNC−GOx/Ag^+-FP. Reproduced with permission [70]. Copyright 2019, ACS

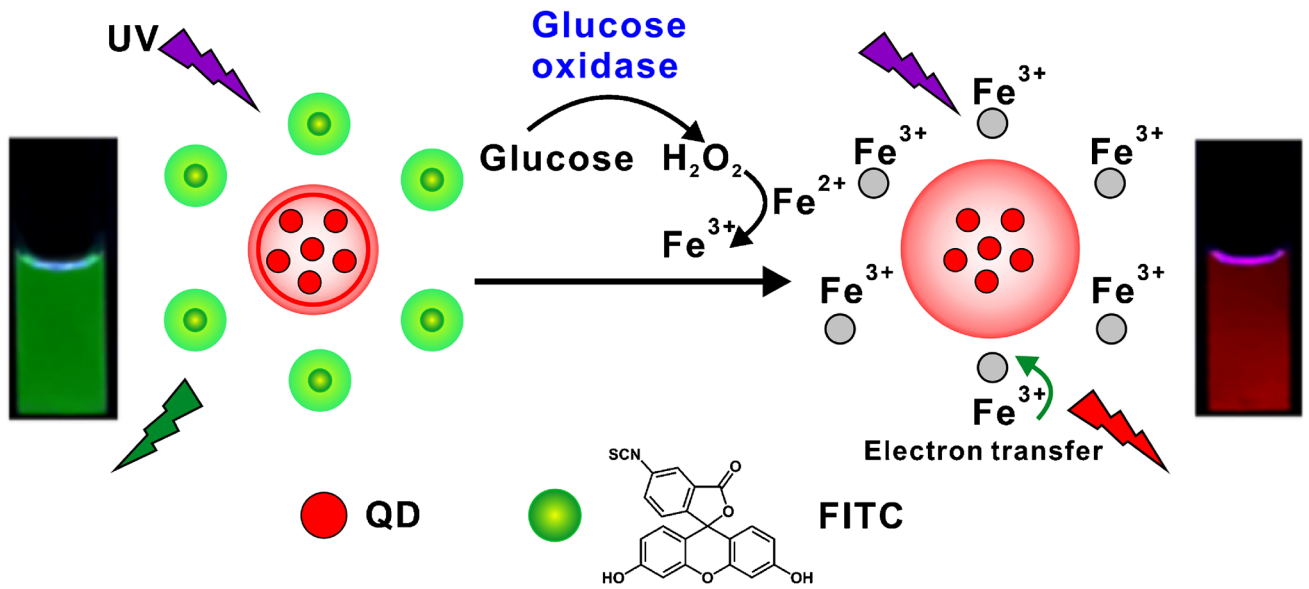

Fig. 16 Illustration of visual glucose determination by quenching green emission of ratiometric fluorescent probe via H_2O_2-induced oxidation of Fe^{2+}. Reproduced with permission [73]. Copyright 2020, Elsevier

SiO_2 [73]. Under the catalysis of GOx, the oxidation product H_2O_2 of glucose oxidized Fe^{2+} to Fe^{3+} ion, resulting in the emission quenching of FITC (Fig. 16). With a wide detection range and continuous fluorescence change, this strategy may facilitate the qualitative and quantitative detection of glucose in blood and fruit juice.

Cesium-doped graphene QDs (Cs-GQDs) were explored as a fluorophore for glucose detection with the GOx enzyme [74]. The prepared Cs-GQDs showed excitation-independent blue fluorescence with a relatively high quantum yield. In the presence of horseradish peroxidase, *o*-phenylenediamine (OPD) was oxidized by H_2O_2 to generate 2,3-diaminophenazine (DAP), a yellow fluorescent compound [71]. By employing the fluorescence resonance energy transfer (FRET) mechanism between DAP and Cs-GQDs (Fig. 17), the system achieved ratiometric detection for H_2O_2 and glucose with detection limits of 25 and 23 nM, respectively. Because of its high sensitivity and selectivity for glucose, this method holds good potential for clinical diagnostics with human serum samples.

Concluding remarks and perspectives

The detection of saccharide plays a crucial role in various biomedical fields [75]. Until now, blood has remained the sole recognized biofluid for diabetes monitoring in daily life. The current invasive wearable blood glucose sensors cause

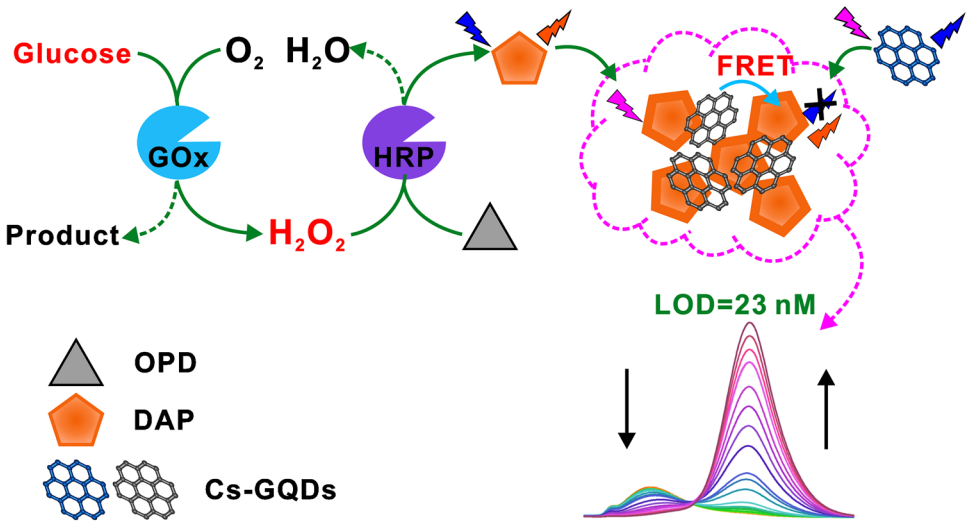

Fig. 17 Illustration of the glucose-sensing mechanism of the Cs-GQD-based ratiometric fluorescence probe. Reproduced with permission [74]. Copyright 2021, ACS

discomfort and raise the risk of infection. As a result, noninvasive wearable point-of-care sensors are being continually developed and improved [76, 77], yet there is still significant room for improving their accuracy, repeatability, wearability, and accessibility for end users [78]. Phenylboronic acid is a well-known saccharide *cis*-diol binder; however, Anslyn et al. proposed an unprecedented mechanism for the interaction of *o*-aminomethyl phenylboric acid and sugars. They found that the fluorescence enhancement was not entirely related to fructose binding, but rather the suppression of the PET process through sensor depolymerization [54]. Thus, the development of boronic acid-based receptors with high selectivity for specific substrates remains challenging, requiring the precise localization of saccharide at the structural and site-specific levels [20].

On the other hand, measurement of the oxidation product catalyzed by the enzyme glucose oxidase presents an alternative approach for saccharide detection [79–81]. Despite the use of both organic and inorganic materials for this purpose, they have been found to suffer from strong interference from various redox-active species, require specialist equipment, and tend to lose accuracy at low glucose concentrations [82, 83]. Porphyrin boxes were utilized to construct monosaccharide channels, which realized size-selective transmembrane transport by impeding the transport of larger saccharides [84]. As an emerging single-molecule tool, nanopores have been designed to identify saccharides due to their ability to detect slight structural differences in monosaccharides [85, 86]. A common and significant challenge across both natural and synthetic receptors is enhancing selectivity toward a specific saccharide target, and researchers are increasingly shifting focus from monosaccharides and disaccharides toward glycans, which have greater biological significance [87, 88]. Accordingly, further development of new saccharide-binding entities will continue to be a top priority in the foreseeable future.

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Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

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