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Development of porphyrin-based fluorescent sensors and sensor arrays for saccharide recognition

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ABSTRACT

Saccharide sensing is a very meaningful research topic as saccharides are involved in many biological activities. However, it is challenging to design molecular sensors for saccharides because this family of compounds is hydromimetic in aqueous solutions and shares a similar chemical structure. In this review, research progress in the development of porphyrin-based saccharide sensors is described with representative examples. We focus on using porphyrin as the signal reporter because porphyrins exhibit unique advantages in high chemical stability, long emission wavelength, and multiple structural modification strategies. Reported literature results have been classified into mainly two sections according to the general working principles of the porphyrin sensor molecules. In the first section, recognition unit, design strategy and sensing performance of traditional porphyrin-based selective saccharide sensors are discussed. While in the second section, development of porphyrin-based sensor arrays for pattern recognition of saccharides has been summarized. Looking through the design strategy and sensing performance of reported achievements, it is reasonable to anticipate a bright future for designing practical porphyrin-based saccharide sensors.

1. Introduction

Saccharides are essential substances of life. They play many key roles in life activities by providing energy and carbon resources [1]. The development of reliable and quantitative methods to measure and visualize target saccharides in biological systems is meaningful for early diagnosis of saccharide metabolism related diseases [2]. For example, measurement of the blood glucose concentration is a key parameter to evaluate the healthy status of a diabetic patient [3]. However, such an important family of compounds not only exists in many forms in our body but also shares a similar and complicated chemical structure [4]. It is therefore a challenging work to design reliable and convenient tools for saccharide recognition [5,6].

In addition to expensive instrument-based analytical methods, the development of small molecule-based fluorescent sensors is meaningful due to their advantages of low cost, high accuracy and practical convenience [7]. Small molecule sensors were proven to be suitable for sensing of versatile kinds of analytes [8,9]. In this respect, the development of fluorescent sensors for saccharide sensing has also attracted much attention [10]. Organic fluorophores including AIEgens [11,12], pyrene [13], coumarin [14], rhodamine [15], and *N,N*'-diphenyl-dihydrodibenzo[*a,c*]phenazine (DPAC) [16] have been used to design fluorescent sensors for saccharide sensing.

Among commonly used fluorophores, porphyrin can be considered as an outstanding one since it was selected as the "pigment of life" by the nature [17,18]. To be specific, a tetrapyrrolic architecture can be found in the chemical structures of chlorophyll and heme, which were essential for corresponding life activities of plant and human being. Actually, porphyrin was also selected by scientists of different research fields due to its inherent advantages [19–21]. Firstly, with a conjugated and aromatic structure, porphyrins are chemically stable, which is important for long-term usage of the material. Secondly, the *meso*-, β-positions and even inner NH of a porphyrin molecule can be functionalized to afford the desired structures. Thirdly, porphyrins exhibit a long fluorescence emission wavelength that can even extend into the near-infrared region. Such a long emission wavelength is beneficial for biological applications so as to avoid auto-fluorescence signals from living tissues [22]. With these merits, porphyrin can be considered

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as a promising fluorophore for the development of small-molecule sensors for saccharide sensing.

In this review, the discussion on recent research progress in the development of porphyrin-based saccharide fluorescent sensors was divided into mainly two sections. The first section was focused on the design strategies, synthesis and sensing performance of porphyrin-based selective saccharide sensors. In the second section, porphyrin-based sensor arrays for differential saccharides sensing were discussed with representative examples.

2. Porphyrin-based selective saccharide sensors

Saccharides are all polyols and each of their hydroxyl group exhibits almost the same hydrogen bonding ability. The difficulty for recognition of a specific saccharide in non-polar organic solvents lies in how to arrange the hydrogen bonding sites in the sensor molecule [23]. In comparison to saccharide recognition in non-polar organic solvents, selective binding of saccharides in aqueous solutions became especially difficult. This was a result of the "hydromimetic" nature of saccharides, as the hydrogen bonding strength of water-saccharide was almost equal to that of sensor-saccharide [24]. Even the nature occurring saccharide binding proteins, saying lectins, were just able to bind saccharides with binding constants of around 10^3 L/mol [25]. Obviously, it is very challenging to design molecular sensors for selective binding of a given saccharide in aqueous solutions. It is therefore easy to understand why glucose oxidase (GOx), an enzyme to oxidize glucose into gluconic acid, was still widely used in designing novel blood glucose sensors [26]. In this respect, porphyrins were also used as building blocks to synthesize nano-materials with peroxidase-like catalytic activities (nanozymes [27]) and then combined with GOx enzyme and colorimetric substrates for glucose sensing [28–30].

In despite of the difficulties, there are mainly two approaches to achieve the goal of effective saccharide binding in water. One of them intends to arrange hydrophobic and CH-π interactions in addition to hydrogen bonding to mimic the binding mode of lectins. The core idea is to build a full complementary binding interaction system between the target saccharide and the sensor molecule [31]. For example, a bicyclic cage with a suitable cavity to mimic lectin was reported by Davis and co-workers, which could bind glucose effectively in water with a constant of about 18000 L/mol [32]. For this approach, porphyrins have a relatively large molecule size, making them more suitable for binding of large saccharides such as oligosaccharides. Another approach was based on the interaction of the 1,2-diol moiety of saccharides with boronic acids to form dynamic five-membered boronate ester bonds [33,34]. As the formation of boronate ester bonds can be easily achieved in water, boronic acid was considered as an ideal recognition unit to design saccharide sensors [35]. In this regard, the introduction of boronic acid to the porphyrin fluorophore would be a promising way to afford selective saccharide sensors.

2.1. Boronic acid as the recognition unit

By introducing a boronic acid unit to the porphyrin core, the afforded boronic acid appended porphyrin would be able to interact with saccharides to form corresponding sensor-saccharide boronate complex, which should induce either aggregation state or photophysical property changes of the porphyrin fluorophore [36,37].

Research on the development of boronic acid appended porphyrin sensors for saccharide recognition was pioneered by the Shinkai group [38,39]. As an early example, two phenylboronic acid units were functionalized at β-positions of the porphyrin to afford the sensor molecule **P2B** (Fig. 1a), which was initially in the aggregation form with quenched fluorescence in DMSO-water mixed solvent. Upon addition of D-fructose, fluorescence emission intensity of the solution enhanced significantly. This was due to the formation of the **P2B**-sugar boronate complex, whose solubility in tested solvent was much better than that of **P2B** itself, resulting in deaggregation of the porphyrin molecule and recovery of its fluorescence.

With a cooperative binding strategy, boronic acid appended zinc porphyrin sensor **ZnP1B** (Fig. 1a) was designed by the Shinkai group for selective binding of glucose-6-phosphate (G6P) [40]. In this molecule, the boronic acid was incorporated to interact with the 1,2-diol moiety in saccharides, while an additional zinc ion coordinated at the inner core was used to bind the phosphate moiety in G6P. It was determined that sensor **ZnP1B** was selective to G6P over glucose-1-phosphate, suggesting that an appropriate distance between the boronic acid and zinc recognition units was important. With a similar strategy, a diboronic-acid-based porphyrin sensor **ZnP1B-Py** (Fig. 1a) was synthesized taking the advantage of self-assembling property of zinc porphyrin with pyridine ligand at the axial position, which was able to form a ternary complex with different monosaccharides and resulted in significant spectral changes [41].

It was obvious that the distance between the two fixed binding sites determined the saccharide selectivity of the sensor. With a larger distance between two boronic acid binding sites, a porphyrin receptor **P2B2** (Fig. 1a) was reported by Anslyn, Sessler and co-workers for the detection of five kinds of ginsenosides [42]. Ginsenosides were used in clinic for treatment of a variety of diseases, whose structures share a gonane steroid nucleus with different sugar substitutions. It was believed that the glycosylation patterns of a ginsenoside significantly influenced its biological activity. Therefore sensing of ginsenosides was meaningful for their quality control. The titration of **P2B2** with tested ginsenosides resulted in enhancement of the fluorescence emission intensity. The binding stoichiometry was determined to be 1:1 between **P2B2** and ginsenosides. It was discovered that the binding strength became apparently stronger by increasing the number of saccharide units and was influenced by the protopanaxtriol substitution pattern. The authors proposed a bifunctional binding mode between **P2B2** and the ginsenosides, which was consist of both the interactions between saccharide moiety and the boronic acid units and hydrophobic interactions between the porphyrin moiety and steroid core of ginsenosides.

Compared to porphyrin sensors with two position-fixed boronic acid units, the development of methods to modulate the distance between two boronic acids in a dynamical way was meaningful for improving the saccharide binding strength of the sensor [43]. As an example, Shinkai *et al.* designed a porphyrin molecule **ZnP2B** (Fig. 1a) with two boronic acid units modified at the axial position, which were linked to the porphyrin core through two ethynyl groups. Through rotation of the ethynyl group, distance between the two boronic acids could vary from 0.1 nm to 2.4 nm. This property enabled the sensor to adjust its conformation to bind saccharides in a dynamic way, as compound **ZnP2B** could bind both mono- and oligosaccharides to form corresponding 1:1 complexes with association constants in a range of 10^2-10^3 L/mol.

In fact, manipulation of the spatial distribution of the boronic acids within a porphyrin sensor would also be an effective way the enhance the sensor's ability to bind one kind of monosaccharide selectively over the others with only configuration differences [44]. In this example, a μ-oxo porphinatoiron(III) dimer **FeP4B-dimer** (Fig. 1b) was discovered to be act as a "sugar tweezer" for selective binding of D-glucose and D-galactose. Porphyrin dimer **FeP4B-dimer** was obtained by simply adjusting the pH value of its monomer solution (**FeP4B**) to 10.5. The authors revealed that **FeP4B-dimer** was able to bind D-glucose with two of its eight boronic acid groups. The reason for the high selectivity was due

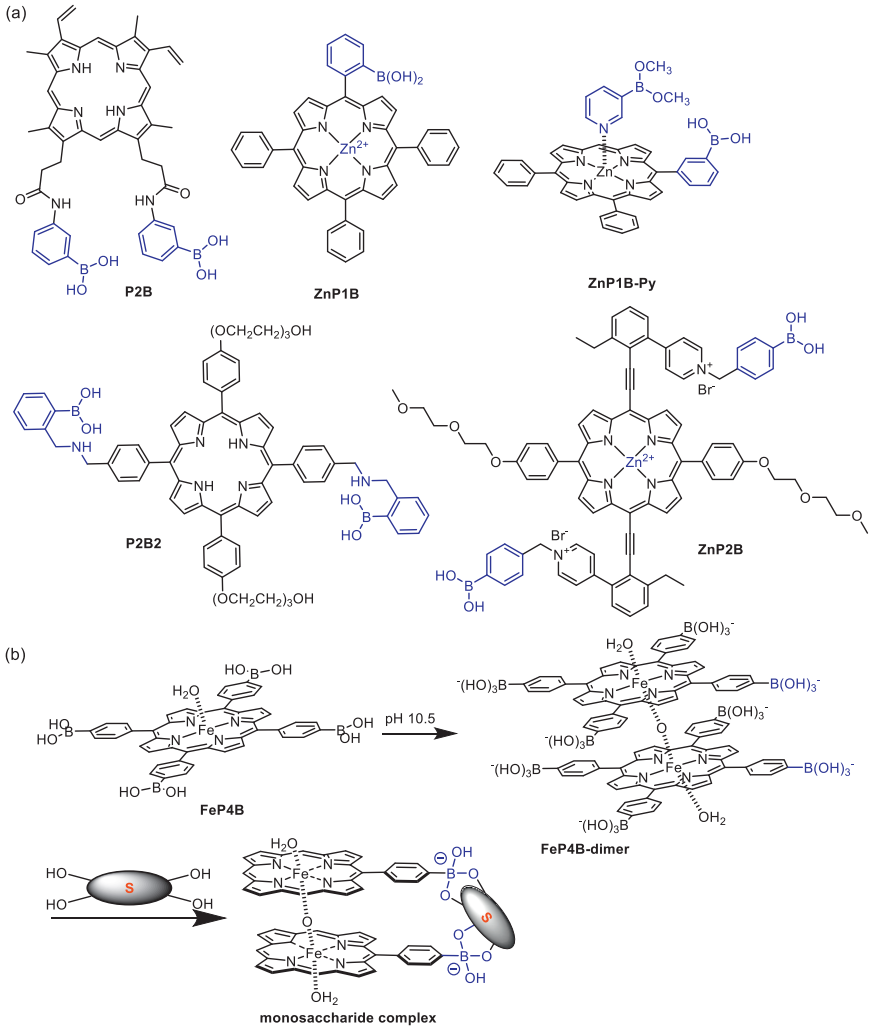

Fig. 1. (a) Chemical structure of boronic acid appended porphyrins for saccharide sensing. (b) Formation of the μ-oxo porphinatoiron(III) dimer **FeP4B-dimer** and its saccharide binding mode. Some boronate units were omitted for clarity.

to the fact that the distance between two porphyrin planes (3.8 Å) in **FeP4B-dimer** was comparable to the size of monosaccharides (3.0 Å). The binding constants of **FeP4B-dimer** with D-glucose and D-galactose were calculated to be as large as 1.51×10^5 L/mol and 2.43×10^4 L/mol, respectively, which even reached the level of corresponding specific enzymes.

2.2. Monosaccharide sensing with other recognition units

As mentioned above that effective binding of saccharides in water requires complementary binding interactions between the sensor and saccharide molecules. From this point of view, groups that could afford corporative hydrogen bonding, metal coordination, and hydrophobic interaction sites could be used as an effective recognition unit for target saccharide. However, compared to the formation of boronate complex, hydrogen bonding and hydrophobic interactions were relatively weak. Therefore, the fluorescence signal output of a porphyrin sensor upon the addition of saccharide could also be ascribed to their altered aggregation states but not the formation of a new porphyrin-saccharide complex. As Davis *et al.* have reported that the titration of tetraphenylporphine tetrasulfonate (TPPS) with glucose was accompanied with vivid UV-visible spectral changes, while no ^{1}H NMR signal changes can be detected [45]. Therefore, the in-deep mechanism for the spectral changes should be proved by all possible measurements.

By simply introducing phosphonate groups as the hydrogen bond acceptors, Kral *et al.* reported two water soluble compounds **P2P** and **P4P** (Fig. 2) for saccharide recognition [46,47]. The titration of **P2P** and **P4P** with monosaccharides such as α-D-glucose, α-D-arabinose, D-mannose, D-fructose, D-ribose, D-trehalose, D-maltose and α-D-lactose in 95% water resulted in significant UV-vis absorption changes. The binding stoichiometry was determined to be 1:1 for both **P2P** and **P4P** to bind tested monosaccharides with the binding constants calculated to be $0.6 \times 10^4 \sim 2.5 \times 10^4$ L/mol.

A number of urea groups are rich in hydrogen bonding acceptors and donors, making them possible to be used as recognition sites to bind saccharide -OH groups. Compounds **P4U1**-**P4U4** (Fig. 2) were synthesized by Bonar-Law and co-workers through introducing four identical amino acid esters to the *meso*-positions of the porphyrin core using urea group as the linker [48]. In this design, urea functionalized porphyrins could bind target saccharides through multiple hydrogen bonding interactions. Upon titration of **P4U1**-**P4U4** with pyranosides such as galactoside, glucoside and mannoside in dichloromethane solution, vivid red-shift and changes in intensity of the porphyrin Soret absorption band can be detected. The binding constants between **P4U1**-**P4U4** with tested

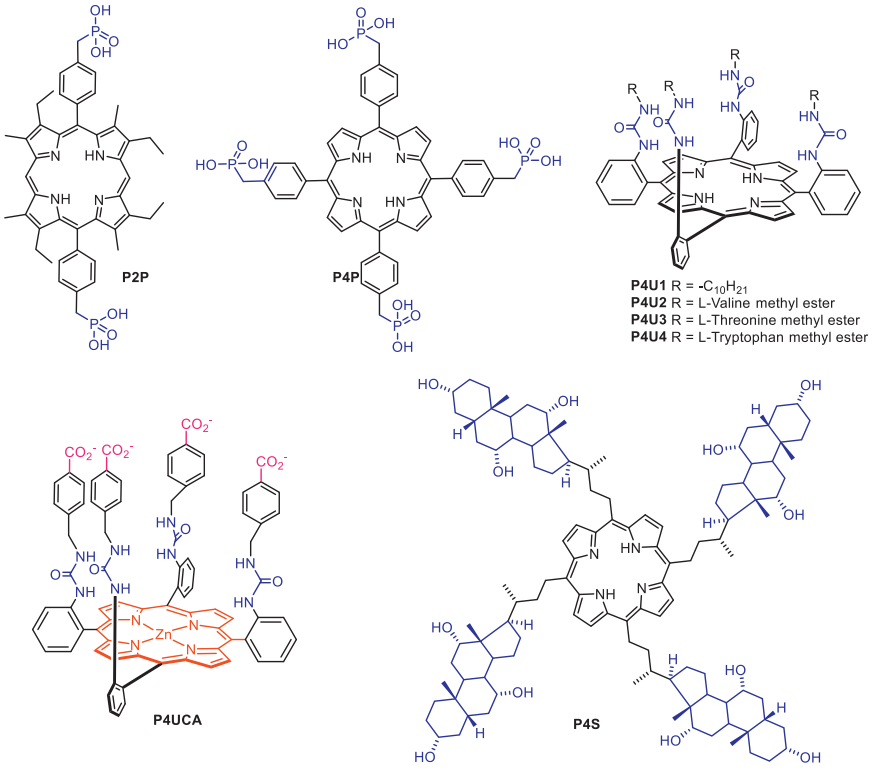

Fig. 2. Chemical structures of porphyrin-based selective saccharide sensors with other recognition units.

pyranosides were calculated to be in a range of $3 \times 10^4 \sim 9 \times 10^5$ L/mol.

Following this work, Hong *et al.* [49] reported another urea linked porphyrin receptor **P4UCA** (Fig. 2) for saccharide recognition in aqueous solution [50]. The structure of compound **P4UCA** can be divided into mainly three functional moieties. The zinc-inserted porphyrin plane served as both of the Lewis acid-base interaction site and a hydrophobic interaction site. The urea moieties acted as not only the linker but also were responsible for providing multiple hydrogen bonding sites. At last, the incorporation of carboxylate groups increased water solubility of the sensor and could participate in hydrogen bonding as well as electrostatic interactions. With this three-functional-moiety design strategy, compound **P4UCA** was able to bind amino saccharides including D-glucosamine, D-galactosamine and D-mannosamine with binding constants in a range of 38-430 L/mol in MeOH-H_2O (v/v, 1/3).

2.3. Oligosaccharide sensing

In addition to hydrogen bonding, the incorporation of hydrophobic interaction was also meaningful in designing saccharide sensors. Steroid-substituted porphyrin **P4S** (Fig. 2) was synthesized *via* a condensation reaction of corresponding steroid aldehyde with pyrrole followed by deprotection of the hydroxyl groups [51]. In this molecule, the steroid moiety was incorporated as the saccharide binding site. To avoid aggregation of the sensor molecule, a mixed solvent containing 50% aqueous 2-propanol was used as the test media. It was determined that sensor **P4S** was able to bind saccharides and introduce vivid UV-vis spectral changes. In addition, sensor **P4S** exhibited a higher selectivity toward oligosaccharides over monosaccharides. The binding mechanism was ascribed to hydrogen bonding and hydrophobic interactions between the steroidal part of the sensor and saccharide molecules.

Similar to steroid structures, bile acid could also provide both hydrogen bonding and hydrophobic interaction sites for saccharide recognition. In the work reported by Kralova, Kral and their co-workers, four bile acid appended porphyrins **P4BA1**-**P4BA4** (Fig. 3) were designed and synthesized for recognition of tumor expressed saccharides [52]. In addition to the bile acid unit, since ammonium group was used as the linker, porphyrins **P4BA1**-**P4BA4** were positively charged molecules. Therefore, porphyrins **P4BA1**-**P4BA4** may bind negatively charged saccharides through hydrogen bonding, hydrophobic and electrostatic interactions. In this study, mixed solvent of MeOH-water (3:7, v/v) was used to investigate the binding interactions between **P4BA1**-**P4BA4** and saccharides including glucose, sialic acid, hyaluronic acid and heparan sulfate. It was determined that the binding of **P4BA1**-**P4BA4** with heparan sulfate was much higher than that of the other tested saccharides. This was ascribed to additional electrostatic interactions between the porphyrin and heparan sulfate, since porphyrins **P4BA1**-**P4BA4** were positively charged while heparan sulfate was negatively charged. Through binding to tumor expressed saccharides, porphyrins **P4BA1**-**P4BA4** were used to image living cancer cells such as A431NS, HeLA, and 4T1 and applied for differentiating transformed (tumor) cells and their untransformed counterparts (Fig. 4). To further investigate the binding mechanism of tetrakis(bile acid)-porphyrin conjugate with saccharides, ESI-FTICR (FTICR: Fourier transform ion cyclotron resonance) mass spectrometry and electron capture dissociation (ECD) experiments was carried out by Kalenius and co-workers [53]. They revealed that at least one bile acid side arm and the porphyrin center in the tetrakis(bile acid)-porphyrin conjugate was responsible for saccharide binding.

In biology, natural carbohydrate-binding proteins usually provide a suitable "pocket" to meet the full complementarity saccharide binding requirement. Therefore, it is reasonable to design a molecular cage for effective saccharide binding [54]. To provide a suitable cavity to encapsulate saccharides, bisporphyrinic sandwich compounds were synthesized by Kral and Schmidtchen *et al.* for effective saccharide sensing in highly competitive media (95%

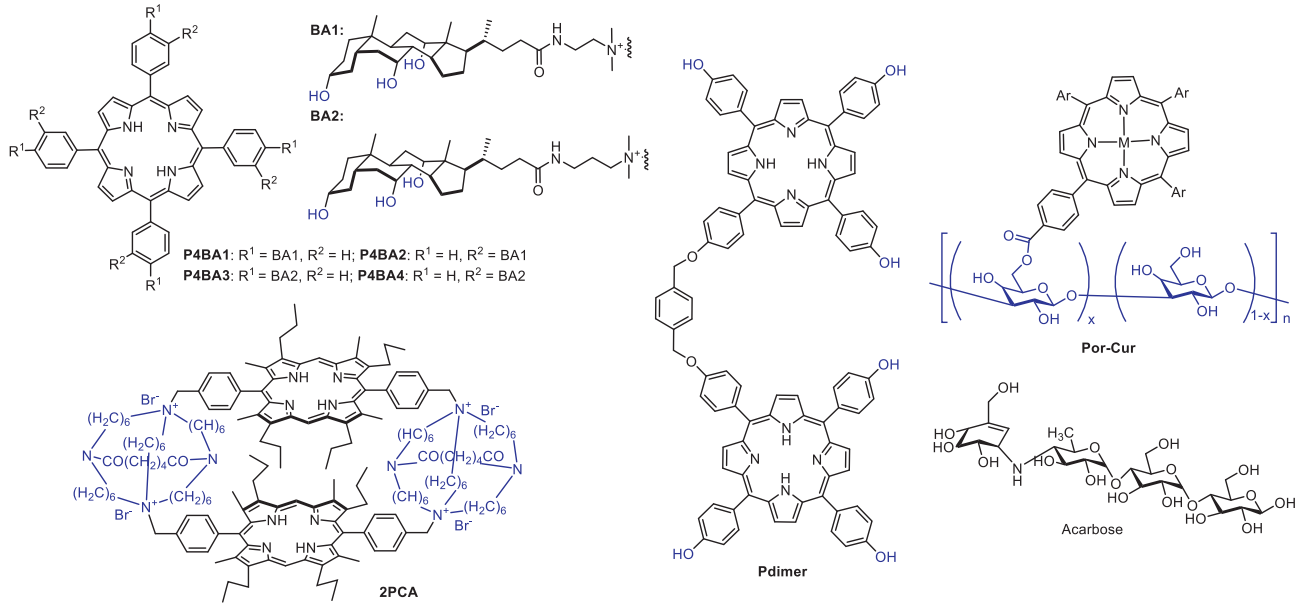

Fig. 3. Chemical structures of porphyrin-based fluorescent sensors for oligosaccharides.

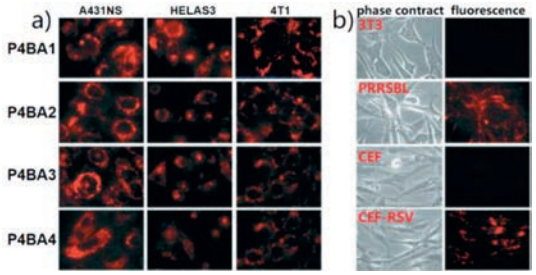

Fig. 4. (a) Fluorescent imaging of living cancer cells (A431NS, HeLaS3, 4T1) using **P4BA1**-**P4BA4**. (b) Imaging of transformed (tumor) cells (PRRSBL and CEF-RSV) and their untransformed counterparts (3T3 and CEF) using **P4BA2**. Reproduced with permission [52]. Copyright 2008, The Royal Society of Chemistry.

water) [55]. For example, macrocyclic porphyrin sandwich compound **2PCA** (Fig. 3) was synthesized by reaction between corresponding macrotricyclic amide and bis(bromomethyl)porphyrin. Investigations revealed that compound **2PCA** exhibited higher binding ability to a trisaccharide saying maltotriose than mono- and disaccharides. The binding stoichiometry between **2PCA** and maltotriose was determined to be 1:1 with a logK_a up to about 4.72. The binding strength between sensor **2PCA** and maltotriose was a result of matched hydrophilic and hydrophobic host-guest interactions between the sensor and saccharide molecule.

Using *p*-xylene as the linker, porphyrin dimer **Pdimer** (Fig. 3) was synthesized by Ye *et al.* for saccharide sensing [56]. Different from a molecular cage with a cavity of fixed size, porphyrin dimer **Pdimer** exposed a hydrogen bonding "cleft" for saccharide using its six phenolic hydroxyl groups. UV-vis and fluorescence emission titration experiments revealed that **Pdimer** was able to bind a variety of monosaccharides and oligosaccharides in DMSO, accompanied with vivid spectral changes. Job plot data indicated a 1:1 binding stoichiometry between **Pdimer** and D-glucose. The binding constant for **Pdimer** with maltotriose (~2000 L/mol) was determined to be much higher than that of monosaccharides (~170 L/mol) such as glucose and fructose. This oligosaccharide binding selectivity was possibly due to the large binding surface area of compound **Pdimer**.

Curdlan, making up with (1,3)-linked-β-D-glucose repeating units, is a linear glucan that usually forms random coils in DMSO but changed into triple-helices and globules in aqueous solution. By introducing porphyrin as the signal reporter to the curdlan molecule, a porphyrin-based sensor **Por-Cur** for acarbose (a drug for type-2 diabetes) was reported by Fukuhara, Inoue and coworkers (Fig. 3) [57,58]. In this work, the presence of acarbose resulted in significant circular dichroism (CD) signal changes through the formation of globule curdlan-saccharide co-aggregates. The sensitivity of **Por-Cur** to detect acarbose was determined to be 200 μmol/L.

From these limited examples, it can be concluded that porphyrin was a promising fluorophore for designing selective saccharide sensors. Through the incorporation of a suitable recognition unit, porphyrin-based sensor molecules can effectively bind target mono- and oligosaccharides in even aqueous solutions.

3. Porphyrin-based sensor arrays for pattern recognition of saccharides

From above examples it can be found that the design of a complementary receptor for mono-, di- and trisaccharides requires not only well manipulation of the hydrogen bonding, hydrophobic and C-H···π interactions between the sensor and saccharide molecule but also incorporation of a suitable sized cavity to accommodate the target saccharide. However, this idea was only available to saccharides with a limited molecular size, as a polysaccharide should be too large to design a cavity that big enough to encapsulate it.

As a member of the saccharide family, glycosaminoglycans (GAGs) are a series of similar linear polysaccharides that exhibit versatile biological activities. Among various GAGs, heparin is much different from the others because it has a highly sulfated chemical structure and bears the highest negative charge density among all known large biomolecules [59]. Heparin was able to bind antithrombin III and activate its anticoagulation activity. As a result, it is widely used in clinics as an anticoagulant, especially for anticoagulation treatment in surgery and blood dialysis [60]. However, as the chemical structure of heparin was large and too complicated to be synthesized in a fully artificial way, production of such an important anticoagulant drug still requires extraction of it from biological tissues [61,62]. Following the synthetic difficulty,

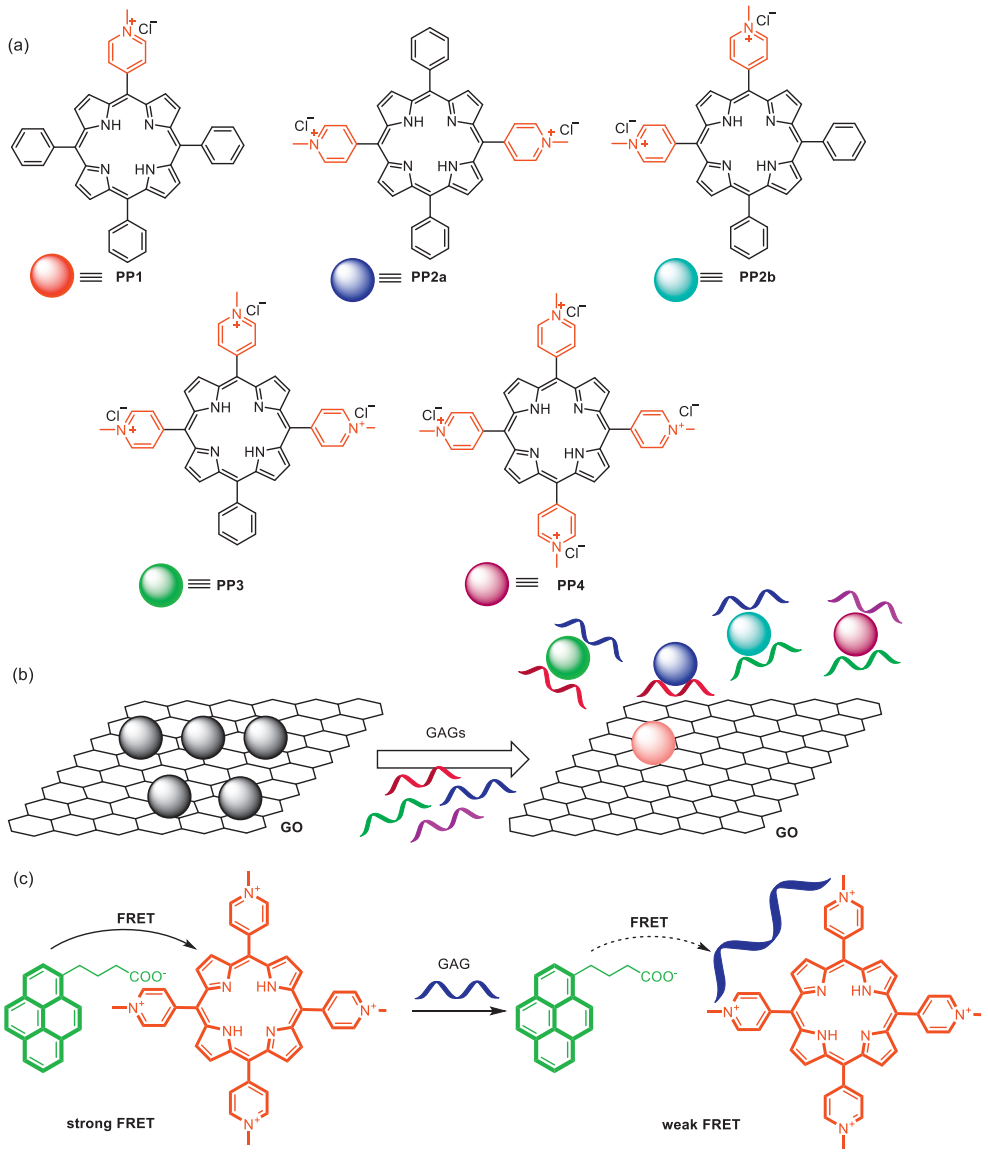

Fig. 5. (a) Chemical structures of porphyrins **PP1**, **PP2a**, **PP2b**, **PP3** and **PP4**. (b) Working principle of the porphyrin-GO sensor array. (c) Working principle of the pyrene-porphyrin sensor array. (a, b) Reproduced with permission [70]. Copyright 2020, American Chemical Society.

the structural complexity of heparin also resulted in the challenge to design selective sensors for it [63].

As an alternative approach, pattern recognition can be applied for discrimination of a large number of similar analytes by mimicking the working principle of human olfactory systems [64]. Since pattern recognition do not require the design of highly selective recognition units, it is very suitable to be applied for detection of analytes with similar and complicated chemical structures [65]. Therefore the design of sensor arrays for pattern recognition of GAGs has attracted much attention [66–69].

Actually, literature reports on the design of porphyrin-based sensor arrays for pattern recognition of GAGs were still rare. Considering that the detection of GAGs should always be accomplished in biological samples such as serum, our group intended to develop saccharide sensor arrays that exhibit long emission wavelength to avoid auto-fluorescence interference from biological backgrounds. Thus five kinds of positively charged porphyrins (**PP1**, **PP2a**, **PP2b**, **PP3** and **PP4**) were designed and synthesized by *N*-methylation of the pyridine substituted porphyrin precursors (Fig. 5a) [70]. The afforded porphyrins were highly fluorescent in aqueous solutions, which can be almost fully quenched through the addition of graphene oxide (GO). The formation of the non-fluorescent porphyrin-GO complexes was ascribed to π-π stacking, hydrogen bonding and electrostatic interactions. In the presence of different GAGs, the GAG molecules would bind the positively charged porphyrins through multiple hydrogen bonds and electrostatic interactions (Fig. 5b). As a result of such multiple interactions, GAG molecules would compete with GO to remove porphyrin from its surface and recover the fluorescence of porphyrins (Fig. 6a). It was determined that with different number and position of the 4-*N*-methyl-pyridyl substituents, five porphyrin-GO complexes showed a cross-response behavior to tested GAGs (Fig. 6b). The designed porphyrin-GO sensor array was successfully applied for discrimination of four kinds of GAGs in 10% serum media. Moreover, as low as 0.1% (wt%) of similar GAG contaminants in heparin can be detected with 100% accuracy.

With the consideration that ratiometric signals could avoid the background interference from fluctuation of the sensor concentration and instrumental factors, above mentioned porphyrins (**PP1**, **PP2a** and **PP4**) were further used by our group as the FRET

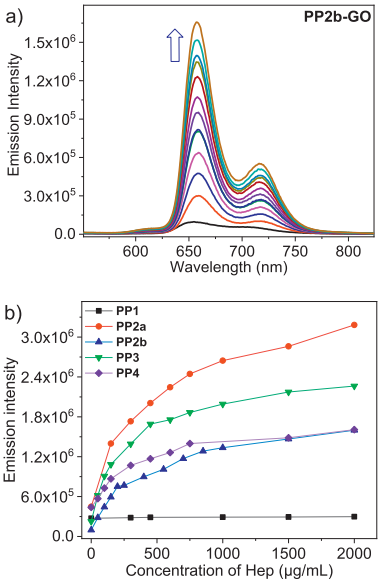

Fig. 6. (a) Fluorescence titration profile of **PP2b-GO** nanocomposites with increasing amount of heparin in buffer. (b) Plots show the fluorescence emission intensity changes of the five nanocomposites upon addition of heparin. Reproduced with permission [70]. Copyright 2020, American Chemical Society.

(Förster resonance energy transfer) energy acceptor to construct a pyrene-porphyrin based FRET sensor array for discrimination of GAGs (Fig. 5c) [71]. In this design, positively charged porphyrins **PP1**, **PP2a** and **PP4** were combined with a negatively charged dye, saying pyrene-1-butyric acid (**Py**), to form three corresponding pyrene-porphyrin complexes. The driving force to form the pyrene-porphyrin complexes was π-π stacking and electrostatic interactions between **Py** and the porphyrins. Upon the addition of GAGs to the solution of pyrene-porphyrin complexes, GAGs were able to bind porphyrins through hydrogen bonding and electrostatic interactions, which would influence the stability of corresponding pyrene-porphyrin complexes and result in changes in the FRET fluorescence signal. As porphyrins **PP1**, **PP2a** and **PP4** were functionalized with different numbers of 4-*N*-methyl-pyridyl substituents, their binding strength with GAGs were different from each other. The pyrene-porphyrin ratiometric sensor array was determined to be cross-reactive toward tested GAGs. It was applied for accurate discrimination of GAGs such as heparin, chondroitin sulfate, dextran sulfate and hyaluronic acid in a concentration range of 2-100 μg/mL. Besides, it was worth pointing out that the ratiometric fluorescence signal of the pyrene-porphyrin sensor array response to GAGs can be even distinguished by naked eyes.

With a purpose to increase the discrimination sensitivity of the saccharide sensor array, our group designed a coumarin-porphyrin FRET complex named **4Esculetin-BAAP** for pattern recognition of 7 kinds of monosaccharides (Fig. 7) [72]. Complex **4Esculetin-BAAP** was synthesized through the formation of boronate ester bonds between esculetin and a boronic acid appended porphyrin. Looking into the chemical structure of **4Esculetin-BAAP** complex, four esculetin molecules were incorporated as the FRET energy donor while only one porphyrin acted as the energy acceptor. With an improved FRET energy donor to acceptor ratio, the FRET efficiency between esculetin and porphyrin within the complex was determined to be about 93.9%, apparently higher than the control molecule with only two esculetin energy donors. By dissolving **4Esculetin-BAAP** in PBS solutions with different pH values, a three-component sensor array **4EBSA** was constructed for discrimination of 7 kinds of monosaccharides including glucose, fructose, mannose, galactose, glucose-6-phosphate, fructose-2-phosphate and fructose-6-phosphate even in a visualized way (Fig. 7). Due to an enhanced FRET efficiency, sensor array **4EBSA** was successfully applied for discrimination of tested saccharides in diluted serum samples with a sensitivity of 0.01 mmol/L.

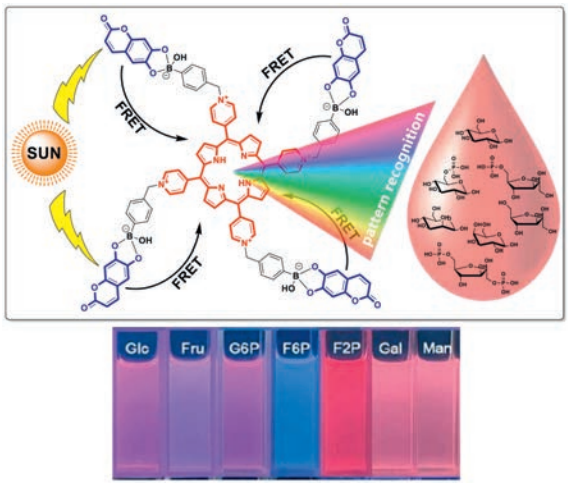

Fig. 7. Top: working principle of coumarin-porphyrin complex **4Esculetin-BAAP** for pattern recognition of monosaccharides; down: visual detection of monosaccharides using **4Esculetin-BAAP** in pH 7.4 PBS buffer. Reproduced with permission [72]. Copyright 2023, Elsevier B.V.

Looking through above examples, porphyrins can be considered as ideal building blocks to construct supramolecular fluorescent sensors for saccharide recognition. In addition, the example of **4Esculetin-BAAP** complex suggested that it is meaningful to increase the energy donor to acceptor ratio when designing FRET sensors, which could improve the energy transfer efficiency and sensitivity of the sensor.

4. Conclusions

In this review, the research progress in the development of porphyrin-based fluorescent sensors and sensor arrays for saccharide recognition was discussed with representative examples. We focused on using porphyrin as the fluorescence signal reporter because porphyrins exhibit some unique merits such as high chemical stability, long emission wavelength and multiple structural modification strategies. Generally, porphyrins were successfully applied for designing saccharide molecular sensors through two approaches.

One approach was to incorporate a suitable recognition unit to the porphyrin fluorophore to achieve highly selective fluorescent saccharide sensors. The difficulty for this approach lies in the fact that saccharides are hydromimetic in aqueous solutions and they share similar chemical structure. Therefore it was better to design a full complementary interaction system to increase the binding constant, where hydrogen bonding interactions should be integrated with hydrophobic, CH-π and electrostatic interactions. Among the commonly used recognition units for saccharide, boronic acid could be considered as an outstanding one, as it was able to form dynamic covalent bonds with the 1,2-diol moiety of saccharides. With the assistance of another saccharide bind unit substituted at a reasonable distance, boronic acid appended porphyrins could even exhibit a saccharide binding ability that equal to natural occurring saccharide binding proteins.

Another approach to achieve the purpose of practical saccharide sensing was to construct porphyrin-based sensor arrays for pattern recognition of saccharides. Since the working principle of a sensor array do not require the design of a highly selective recognition unit for the target saccharide, it is reasonable to pay more at-

tention in the design of cross-reactive sensor arrays for saccharide recognition. However, the construction of a saccharide sensor array needs the design of several cross-reactive sensory units, which could significantly increase the production cost. It should therefore consider a balance between the cost and practical application needs.

In conclusion, porphyrins have been successfully applied for designing fluorescent sensors and sensor arrays for saccharide recognition. Considering that the number of literatures that focused on this topic was relatively limited, research on the development of porphyrin-based saccharide molecular sensors is still at an initial stage. It is obvious that the future development of both porphyrin-based saccharide sensors and sensor arrays will still rely on supramolecular approaches such as the indicator displacement assay. Therefore, one consideration is to use porphyrins as the building blocks to construct novel supramolecular structures such as molecular cages and metal-organic frameworks (MOFs) with suitable or even dynamic inner space to recognize and accommodate the target saccharide. We believe that these excellent literature results would inspire the further development of novel porphyrin-based fluorescent saccharide sensors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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