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A Brief Overview of Recent Advances in the Applications of Boronic Acids Relevant to Glycomics

Simone MI[1]*, Houston TA[2]*

[1]Discipline of Chemistry, School of Environmental and Life Sciences, University of Newcastle, Newcastle, NSW 2308, Australia
[2]Institute for Glycomics and School of Natural Sciences, Gold Coast Campus, Griffith University, QLD 4222, Australia

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Boron acids (boric, $B(OH)_3$, boronic, $RB(OH)_2$, or borinic, R_2BOH) have been utilised in a wide range of applications, including as reaction promoters and catalysts [1-4] as dyes,[5] as support for derivatisation and affinity purification of diols, sugars and glycosylated proteins,[6] as sensors for carbohydrates,[7-8] as protecting or activating groups in carbohydrate synthesis,[9-12] as separation or membrane transport tools,[13-15] and as a pharmacophore in medicinal chemistry.[16-17] Here, the authors would like to focus on the most recent advances (mainly the past 5 years) in the applications of boronic acids important to the "glycosciences" and related fields.

Fluorescence-based saccharide sensing using boronic acid-based entities has been investigated for nearly 25 years[18-21] because it is recognized that boronic acids have the potential to afford semi-invasive or non-invasive monitoring of carbohydrate levels in a variety of medical conditions, including cancer and diabetes. Glucose-level monitoring is of paramount importance to limit the long-term consequences of diabetes mellitus (e.g. damage to the heart, eyes, kidneys, nerves and other organs caused by malign glycation of vital protein structures).[22] A number of challenges still require improvement, including increased discrimination between monosaccharides, functioning under physiological conditions and sensor stability towards photobleaching or oxidation. [23,24] The relative binding constants (K) of monosaccharides with boronic acids reveal glucose to be a weak boronic acid binder,[25] and D-fructose a strong binder which presents a problem in the development of glucose-selective artificial receptors. This issue has been partially ameliorated by the utilization of diboronates. However, these bulkier sensors tend to be less water soluble than their monoboronate counterparts. [23-24] Increasing the sensor's water solubility profile, whilst still retaining the low pKa values for binding at neutral pH, has been achieved by introduction of a pyridiniumboronic acid unit in the sensor molecule [26-27].

Recent advances in this field include the bisanthracene diboronic acids (e.g. 1, figure 1) developed by Wang and co-workers,[28] which showed that the careful balance of orientation and distance between the two boronic acids results in sensors, such as 2, that can bind selectively to D-glucose over D-fructose ($K = 1472\ M^{-1}$ vs. $34\ M^{-1}$). Variation of the spacer allowed binding of the important carcinoma antigen sialyl Lewis X directly on the cell-surface, marking the first time an oligosaccharide was successfully targeted in such a manner. [29-30] The Houston group has reported a fluorescent receptor 3 for free sialic acid (Neu5Ac) that operates by a unique divergent fluorescence response for this monosaccharide over glucose. [31] Wang also described the enhanced binding profiles of three representative sugars (D-glucose, D-fructose and D-sorbitol) to a series of water-soluble isoquinolinylboronic acids. In particular, at physiological pH, 4 and 5 showed greater binding affinities with D-glucose of 42 and 46 M^{-1} respectively, which are much higher than those observed with phenylboronic acid (5 M^{-1}).[32] Peters has described a diboronated MRI contrast agent based on 6 that can recognize sialic acid residues on cell surfaces. [33] Examples of FRET systems are the series of viologen-based optical sugar sensors developed by Singaram and co-workers that are capable of operating in aqueous solution at pH 7.4 and are highly sensitive to D-glucose in the physiological range. [34-35] In the absence of sugar, 7 and 8 form a photo-inactive complex; however, upon addition of D-glucose (which binds to 7 with K of 37 M^{-1})[36] the fluorescence of pyranine is regained. This phenomenon was ascribed to the conversion of the dicationic viologen into a neutral zwitterionic species and resulted in the loss of electrostatic interaction between 7 and 8, with the release of fluorescent 8. "Click-Fluor" systems developed by James and co-workers represent a further novel class of boronic acid-based saccharide sensors possessing a triazole moiety (synthesized via a click reaction) three-carbons away from the boron atom. [37] These compounds have been shown to exhibit a nontypical binding preference with sample saccharides, provide an additional fluorophore (the triazole) and can provide great diversity in sensor architecture thanks to the wide availability of acetylene units.

A number of electrochemical and optical sugar sensors based on phenylboronic acid and its derivatives have been developed,[38] including holographic glucose sensors;[39] and ferrocene-modified polyboronic acids (PBAs) used as redox-active additives in solution for the voltammetric determination of sugars, in which the redox potential and/or current are dependent on the sugar concentration [40-42]. PBA-modified electrodes have been successfully used to detect sugars and to immobilize glycoenzymes through potentiometric and voltammetric responses (e.g. Okano's glucose-sensitive Pt-electrode coated with a PBA-bearing polymer film;[43] glucose- and mannose-sensitive Au/3-hydroxyphenylboronic acid electrode [44]. Willner's immobilization of apo-flavoenzymes via the covalent bond between the PBA-modified electrode and cofactor FAD[45-46]; Fernandez' [50] immobilized horseradish peroxidase via covalent bonds between its glycan chains and a PBA SAM-modified electrode [47]).

A variety of chromophores and fluorophores [48-49] can be coupled to PBA to afford colorimetric sensing systems for sugars. In this area azobenzene dyes have been most frequently used for the preparation of colorimetric sugar sensors, in which the absorption wavelength and intensity of the dye are dependent on the type and

***Corresponding author:** Simone MI, Discipline of Chemistry, School of Environmental and Life Sciences, University of Newcastle, Newcastle, NSW 2308, Australia, Tel: +61249854037, Email: michela.simone@newcastle.edu.au
Houston TA, Institute for Glycomics and School of Natural Sciences, Gold Coast Campus, Griffith University, QLD 4222, Australia, Tel: +617 5552 7051; Email: t.houston@griffith.edu.au

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concentration of added sugars. [50] These dyes have been used in solution or immobilized in films, hydrogels,[51] nanospheres, and quantum dots (QDs). QDs-based sensors have been successfully applied for continuous monitoring of glucose in cells. Recent examples include Singaram's glucose sensing system,[52] composed of CdSe/ZnS QDs, whose fluorescence intensity was quenched by viologen-substituted PBA, and enhanced upon glucose addition. Willner produced a sugar sensor that utilizes CdSe/ZnS QDs as a FRET donor to fluorescent dye-modified galactose linked to PBA-functionalized QDs. [53] Zhou determined the intracellular glucose level using PBA-modified CdTe/ZnTe/ZnS QDs, that self-assemble in the presence of glucose [54].

In the fields of host-guest chemistry and self-assembly, a number of boronic acid-containing macrocycles have been produced by condensation of boronic acids with diols assisted by boron-nitrogen interactions. [55] Macrocycles obtained from [4+4]-tetrameric [56] (9, Figure 2), [3+3]-trimeric [57] and [4+2+2]-multicomponent systems 10 [58] have been reported. Iwasawa showed that control over the formation of the [2+2]- versus the [3+3]-macrocycles of a tetraol compound and 1,4-benzenedi(boronic acid) was possible via the use of toluene versus benzene in the reaction solvent. [59] Boroxines, dehydrated cyclic analogues of boronic acids, have also been the object of intense research recently in the development of novel classes of cyclic and linear supramolecular assemblies displaying novel architectures. [60] In this area, recent reports describe the self-assembly of a pentameric boroxine cage from a single component which involves two levels of self-complementary self-assembly [61] and hybrid ring systems, such as Yang's organic-inorganic B_2O_3Al six-membered ring system [62] and Lee's borasiloxane conjugated polymers aimed at the detection of volatile amines. [63] Importantly, boroxine coordination chemistry requires further investigation, especially in the systems where solid-state structures revealed the interplay of more than one intermolecular B-N interactions. Because boroxine ring-formation is a dynamic process, this allows the synthesis of thermodynamic products,[64] facilitates error correction in assembly and production of self-healing materials [65].

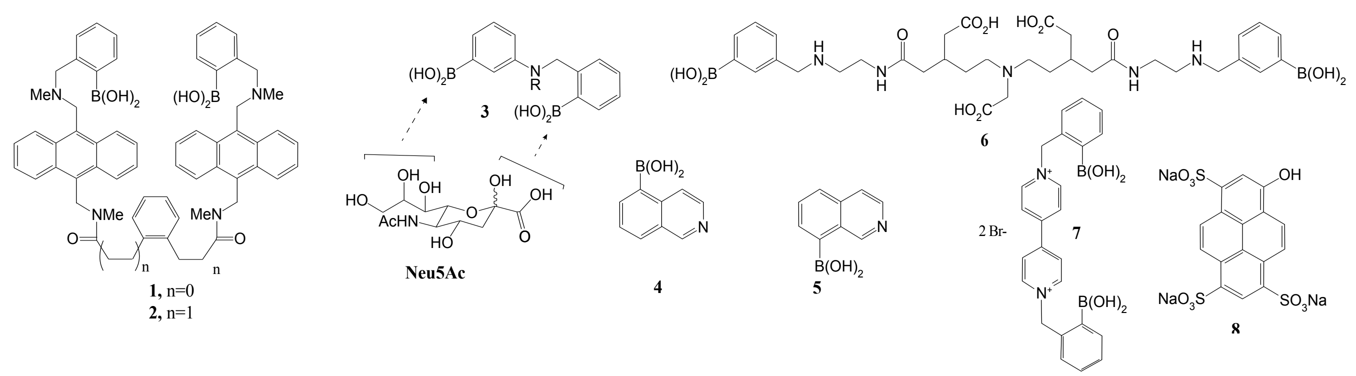

Figure 1: Boronic acids useful for fluorescence sensing and imaging applications.

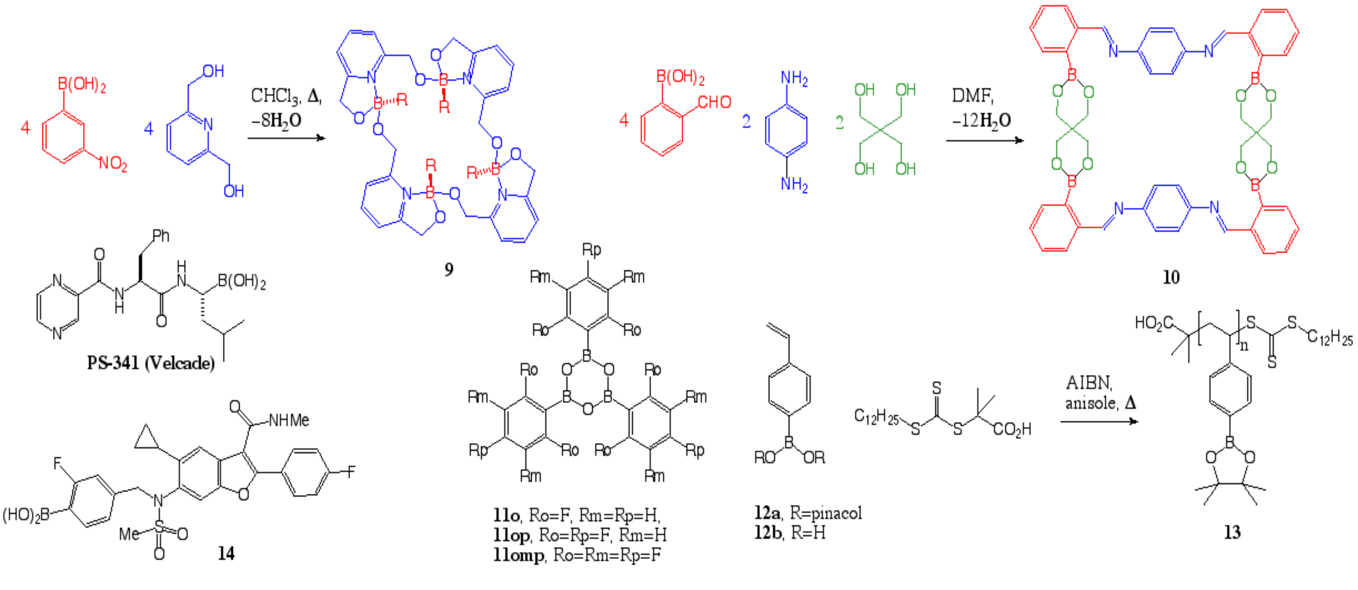

Figure 2: Diverse applications of boronic acids.

Boron-based anion receptors have found application for selective binding of fluoride anions in lithium ion batteries [66-67]. Nair and Reddy have recently investigated a series of perfluorinated aryl boroxines (11o, 11op and 11omp, Figure 2) through ab initio theory, fluoride binding studies and ionic conductivities to systematically fine-tune their binding efficiencies and found them to perform comparably to the state of the art PFPB anion receptor [68]. Polymerisation of p-vinylphenylboronic acid has long been known;[69-70] however, only recently Cambre and Sumerlin reported the first synthesis (by RAFT) of well-defined, water-soluble boronic acid/acrylamido block copolymers (e.g. 13) aimed at sensing and delivery applications [71].

The boronic acid moiety continues attracting increasing attention as a critical pharmacophore to the medicinal chemistry of biologically active molecules. Peptide boronates have been very successfully employed in the inhibition of the proteasome allowing them to act as anticancer agents [72]. These compounds selectively induce apoptosis in proliferating cells whilst concomitantly inhibiting angiogenesis. [73-74] The most notable example in this area is represented by Bortezomib, PS-341 (Velcade®),[75-77] marketed as an anticancer agent for multiple myeloma. [78-80] Its mechanism of inhibition occurs via the formation of a covalent bond between the boron with the active site threonine to afford a tetrahedral adduct. [75-77] Some of the attractive properties of these borylated agents is their tendency to slow binding kinetics to their biological targets,[81] their circumvention of a number of resistance mechanisms, such as the rapid secretion from cells by the MDR pump and their chemical stability. Within an antiviral context, a series of potent inhibitors of the NS5B polymerase have been obtained through design optimization with clinical trial candidate 14 which targets the inhibition of the polymerase RNA replication cycle initiation step with a dissociation half-life of >40 hours with the GT1b 316N protein and showed a statistically significant reduction in serum HCV ribonucleic acid (RNA)[82]. This will undoubtedly open the door to new uses for boronic acids in medicinal chemistry. From the diversity highlighted here, many future applications across a range of fields can be expected from the humble fifth element.

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