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Straightforward synthesis and crystal structures of the 3-piperazine-bisbenzoxaboroles and their boronic acid analogs

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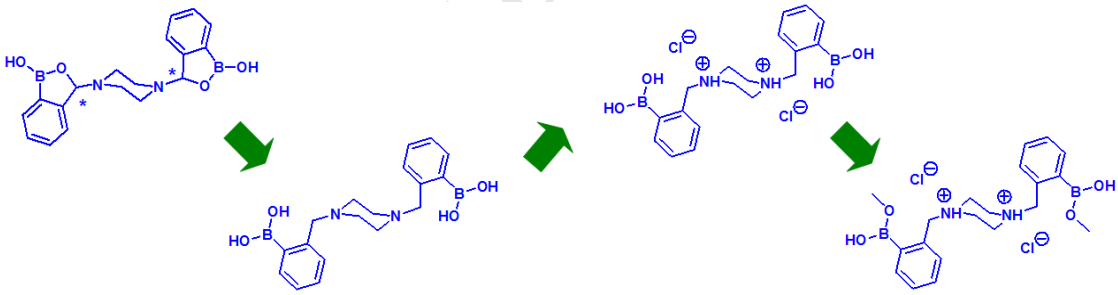
Keywords: benzoxaborole, diboronic, bisboronic, monoester, piperazine, boronic acid

Abstract

The straightforward synthesis of a highly biologically active 3-piperazine-bisbenzoxaborole and its fluorine analog has been described. The obtained bisbenzoxaboroles have been used in the synthesis of their phenylboronic acids analogs. One diboronic acid has been also isolated as hydrochloride salt as well as its methyl monoester. All the described compounds display unique molecular architectures, which have been determined by X-Ray measurements.

Graphical abstract



1. Introduction

Benzoxaboroles emerged lately as compounds that possess interesting properties and have many applications in organic synthesis, medicine and materials science.[1] Recent development in benzoxaborole chemistry is connected first of all with their biological action. Libraries of benzoxaboroles have been investigated as antifungal agents and screened for antitrypanosomal activity, resulting in several new leads.[2] The formation of the tetrahedral adduct via a dative bond has been postulated as the mechanism by which benzoxaboroles act as enzyme inhibitors.[3] The

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first 3-amino-substituted benzoxaborole was reported several years ago[4] and some of its physicochemical properties have been recently studied.[5] Further studies enabled the synthesis of several other 3-amino-substituted benzoxaboroles.[6] A recent contribution describes sugar receptor activity of those compounds.[7] The biological action of several 3-amino-substituted benzoxaboroles and other phenylboronic compounds has been also evaluated.[8]

The boronic acid moiety, which is able to reversibly form complexes with hydroxyl compounds, can be responsible for binding to specific biomolecules.[9] The proximity of the nitrogen atom increases the affinity of the boronic acid towards hydroxyl compounds, enabling their binding at physiological pH.[10]

The introduction of a second boronic unit into the receptor scaffold is used to achieve selective sugar binding.[11-14] Diboronic acids have also been used in materials science e.g. in the formation of self-healing polymers[15] or selective membrane transport of sugars.[16] Diboronic acids are especially valued due to their higher affinity towards glucose in comparison with fructose.[11,17,18] This fact is of crucial importance in the development of glucose sensors for use in the diagnosis and management of diabetes, a disease that is emerging as a major global health concern. The diversity of the reported compounds is large, yet only one crystal structure of the diboronic acid sugar receptor has been reported.[19]

The piperazine scaffold is frequently found in biologically active compounds, perhaps thanks to its high affinity to various receptors.[20-26] The piperazine-containing potent anticancer drug (Imatinib) is the first to be found to act by inhibiting a specific enzyme rather than by killing all of the rapidly dividing cells.[27] Similar action is displayed by the recently developed boronic anticancer drug Bortezomib, inhibiting the Proteasome 26S receptor.[28] Despite the potential importance of molecules that combine piperazine and boronic scaffolds, only a few such phenylboronic derivatives have been obtained and studied so far.[29] The present contribution describes the straightforward synthesis of several species containing two benzoxaborole or phenylboronic acid units linked to a piperazine scaffold placed at *ortho* position.

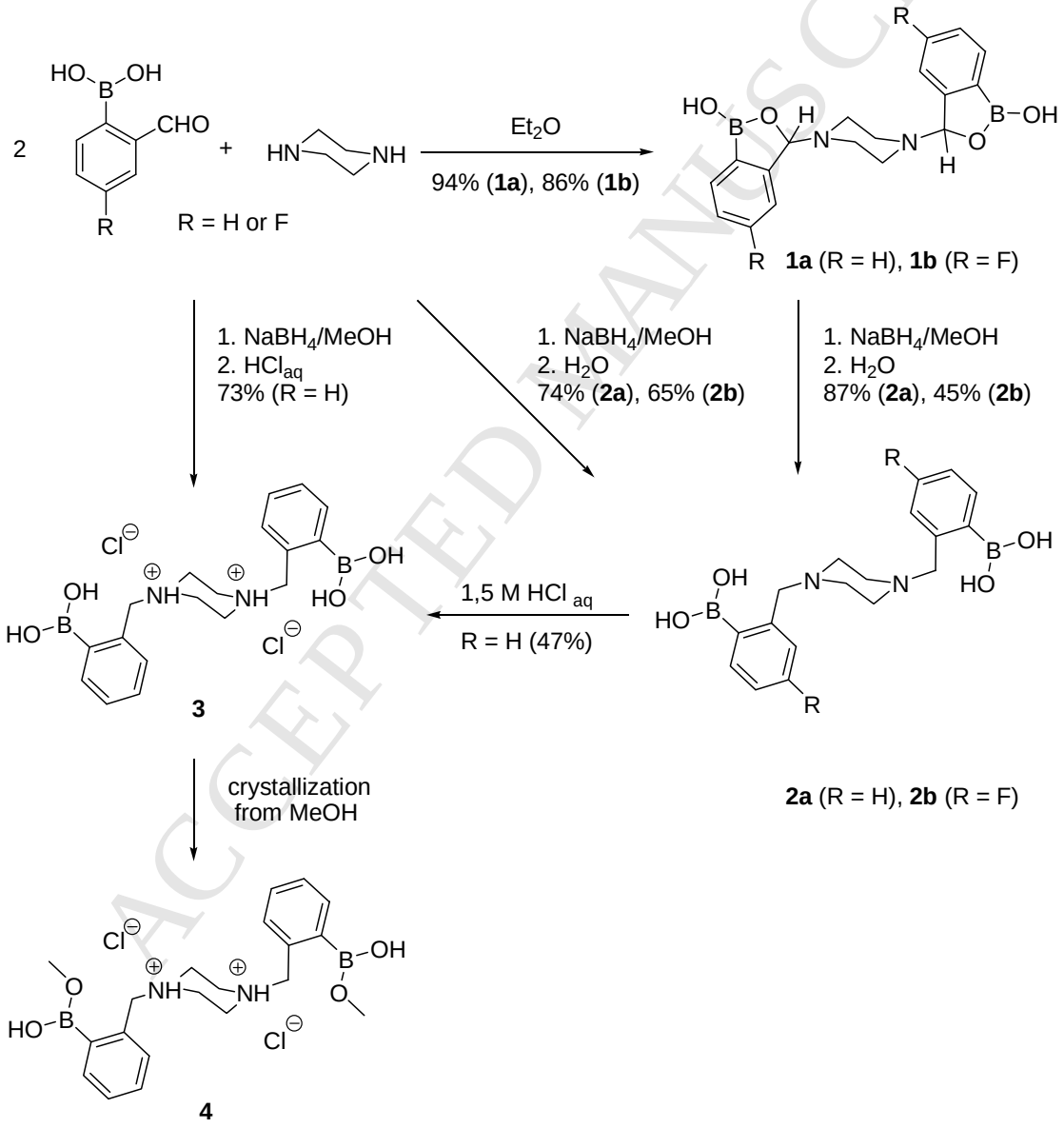
2. Results and discussion

Current work deals with the straightforward synthesis, molecular structure and spectroscopic investigation of piperazine derivatives of phenylboronic acids.

2.1. Synthesis

Compounds **1** – **4** have been obtained by relatively simple synthetic methods (Scheme 1). Molecules **1a** and **1b** contain two oxaborole functions that may lead to useful properties.

Compound **1a** indeed has recently shown an exceptional biological action against *Mycobacterium luteum, Aspergillus niger* and *Candida tenuis*, no details of its synthesis or characterization data have been yet reported.[8] Compounds **1a** and **1b** have been obtained by the amination of 2-formylphenylboronic acid or its fluorinated analog with piperazine. Very low solubility of **1a** and **1b** in the employed reaction solvents' mixture (diethyl ether or diethyl ether/THF) caused precipitation of the products. It allowed for the removal of the products from the reaction mixtures, driving the reaction to completion. The application of a drying agent, essential in the synthesis of other 3-amino-substituted benzoxaboroles was not needed in this case.[6,30]



Scheme 1. Synthesis of compounds **1a-4**, **1b** and **2b**.

Benzoxaboroles **1a** and **1b** contain two asymmetric carbon atoms and according to the 2^n rule, four different diastereomers are possible (Figure 1). The ^{1}H NMR spectra of **1a** and **1b** measured in DMSO-d_6 show two sets of signals of equal intensity, corresponding to two pairs of enantiomers. After several days at room temperature, the spectra did not alter, which proves high stability of **1a** and **1b** in DMSO solution. Signals corresponding to the diastereomers are indistinguishable in the spectra recorded in CD_3OD.

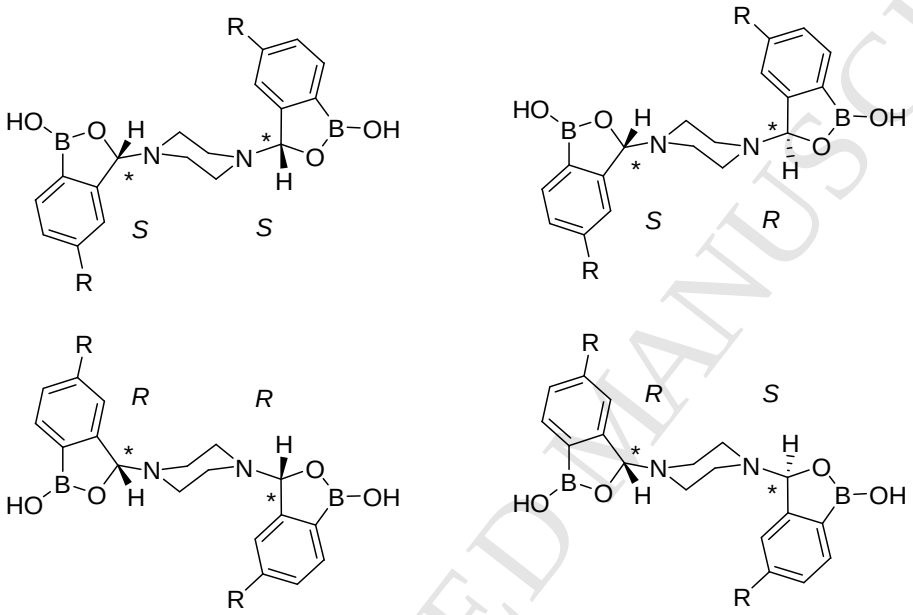


Fig. 1. Diastereomers of **1a** and **1b**.

The reduction of benzoxaboroles **1a** and **1b** with $NaBH_4$ in methanol and subsequent hydrolysis with water afforded the corresponding diboronic acids **2a** and **2b** in high yields. A one-pot amination-reduction protocol for **2** followed by hydrolysis with water resulted in remarkably lower yield of **2b**. In contrast, in the case of **2a** the one-pot protocol provided a higher yield of the product than the synthesis via benzoxaborole reduction. Changing the hydrolysing agent from water to aqueous hydrochloric acid results in a high yield (73%) of diboronic acid hydrochloride salt (**3**), a single crystal of which has been obtained by crystallization from a water:acetonitrile mixture. Crystallization of **3** from methanol resulted in its methyl monoester (**4**).

2.2. X-Ray studies

Benzoxaboroles usually form dimeric units in the solid state.[1,6,31-33] It was of interest to determine if this pattern will be present also in the obtained bisbenzoxaborole. Single crystals of **1a** were obtained by crystallization from dimethyl sulfoxide (DMSO). Molecules of **1a** crystallize in the centrosymmetric space group symmetry of the triclinic system (Table S1 in ESI) with a half of the bisbenzoxaborole molecule (**1a**) and one DMSO molecule in the asymmetric unit. Hence, the molecule of **1a** generated by crystallographic inversion center is an *R,S*-isomer in the solid state (Figure 2).

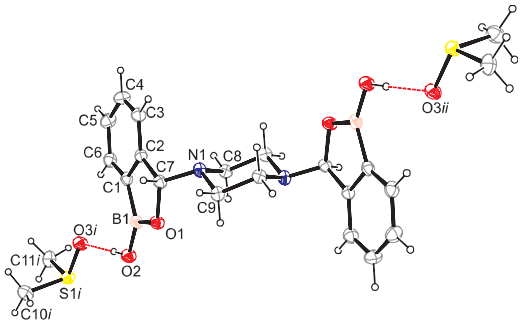


Fig. 2. Molecule of **1a** with O-H…O hydrogen bonded DMSO molecules (dashed lines). Ellipsoids with 50% probability and atom numbering scheme are given.

The boron atom has a flat trigonal coordination and deviates only by 0.006(2) Å from the plane defined by O1O2C1 atoms. Similarly to the other structurally characterized benzoxaboroles,[4,6,31-33,35-42] the fused six-(phenyl) and five-(borole) membered ring is flat with the largest deviation from the l.s. plane being only 0.033(1) Å. The length of C7–N1 bond linking the borole unit with the piperazine ring is equal to 1.435(3) Å. The piperazine ring shows a chair conformation with benzoxaborole moieties in an equatorial disposition. The relevant orientation of the piperazine unit and the plane containing fused aromatic moiety is almost perpendicular (the dihedral angle equals to 81.87(5)º). Moreover, the boronic group is positioned *trans* towards the nitrogen lone electron pair with torsion angle C1C2C7N1 amounting to 127.2(2)º. Therefore, the O-H group is pointing outside the molecule and achieving the *anti* conformation. This rare conformation in benzoxaborole crystals is forced here by the presence of the solvent molecule containing a relatively strong hydrogen bond acceptor. In **1a**, instead of typical dimeric $R^2_2(8)$ O-H…O hydrogen bond motif,[4,6,31,32,35-37,40-42] the boronic hydroxyl group interacts with oxygen atom of the DMSO molecule. The resultant O(1)–H(1)…O(3) bond is almost linear (the distances O…O, H…O and the O–H…O angle equal to 2.711(2), 1.88 Å and 179º, respectively) and form a finite structure with

the *D*(3) graph descriptor[43] (Figure 2). It is worth mentioning that such an *anti* conformation has previously been observed only in one benzoxaborole derivative, namely 3-ethyl-1-hydroxy-3-(4-hydroxybenzoyl)-2,1-benzoxaborolane,[38] where the boronic O-H donor bounds to the carbonyl oxygen acceptor present in the substituent. Since there are no other strong hydrogen bond donors in **1a**, the numerous weaker interaction are responsible for 3-D structure formation. Single crystals of **2a** were obtained by crystallization from dimethyl sulfoxide. Molecules of **2a** crystallize in $P2_1/c$ space group symmetry of the monoclinic system (Table 1 in ESI). Similarly to **1a**, the molecules of **2a** are generated by an inversion center (Fig. 3).

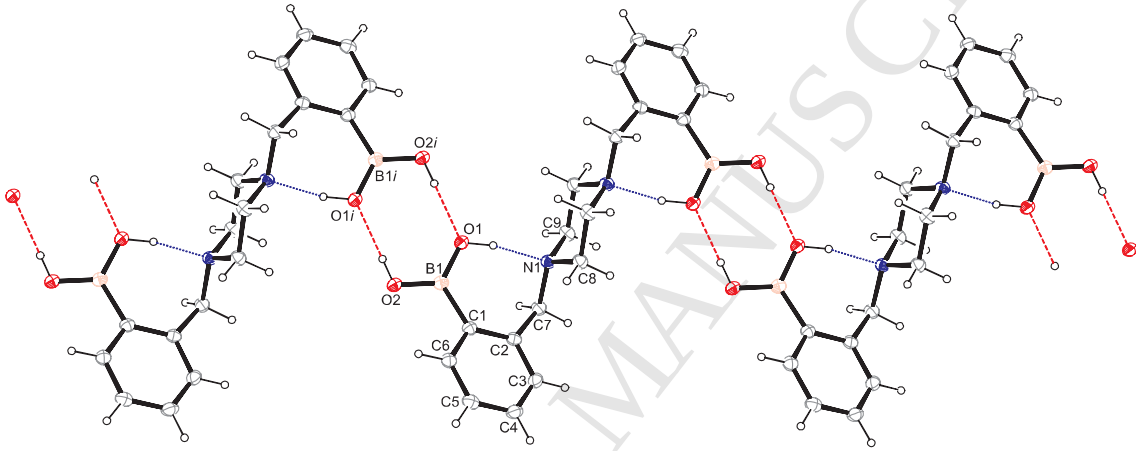


Fig. 3. The hydrogen bonded infinite chain structure of **2a**. The 50% probability thermal ellipsoids and atom numbering scheme are shown. Hydrogen bonds are shown as dashed or dotted lines.

No solvent molecules or solvent accessible voids were detected. The boron atom is in trigonal environment with the deviation from the plane defined by O1O2C1 atoms amounting to 0.018(1) Å. The boronic $B(OH)_2$ moiety is twisted by 25.37(5)º with respect to the phenyl ring and adopts *syn-anti* conformation of OH groups. Such conformation, although frequently observed in crystals of boronic acids, is enhanced here by the formation of intramolecular O–H…N hydrogen bond (H…N and O…N distances equal to 1.80(2) and 2.605(1) Å, respectively, while O–H…N angle equals to 169.2(7)º). The presence of the B-O-H…N intramolecular hydrogen bond was previously observed for other aminomethylphenylboronic acid derivatives characterized by X-ray diffraction methods[10,19,44-49] except for the derivative[50] where charge assisted intermolecular hydrogen bonds with trifluoroacetate anion were detected. Moreover, the presence of such intramolecular H-bond in **2a** forces the twist of the boronic unit on C7–N1 bond (C1C2C7N1 torsion angle equals to 60.8(1)º). Thus, its orientation

towards nitrogen's lone electron pair is *synplanar*, oppositely to **1a** where the *trans* conformation is observed. The linking C7–N1 bond is elongated in **2a** by 0.045 Å in comparison to the relevant bond in **1a**. The piperazine fragment is similar in **1a** and **2a**. Also the close to perpendicular orientation of the piperazine ring and the phenyl moiety is observed (the relevant dihedral angle equals to 87.0387(3)º). Although one OH group is involved in intramolecular H-bond formation, the second one forms typical dimeric $R^2_2(8)$ O-H…O hydrogen bond motif. However, the molecule of **2a** is centrosymmetric and therefore the creation of an infinite supramolecular chain propagating along crystallographic *a* axis is observed (Fig. 3). An analogous chain motif was also observed in case of *ortho* substituted diboronic acid derivative with 4,4'-bipyridinium linker,[51] while in structures with bis(*N*-(1-phenylethyl)aminomethylanthracene)[19] and ethynylene[52] *ortho* bridges supramolecular dimers and layers are formed, respectively. The H-bonded chains in **2a** are further joined by weaker C-H…O and C-H…π interactions. The molecules of **3** (Fig. 4) crystallize in $P2_1/c$ space group symmetry of the monoclinic system (Table 1 in ESI), and as in **1a** and **2a** they are generated by an inversion center. The diboronic acid molecule is in this case protonated on nitrogen atom and therefore the intramolecular O-H…N hydrogen bond is not formed. Instead, N-H…O intramolecular interaction is observed, with the *syn* oriented OH group acting as an acceptor (N…O, H…O distances equal to 2.812(1) and 2.13 Å, respectively, while N-H…O angle equals to 136º). The poorer geometry of this intramolecular interaction may result for the bigger twist on B1-C1 bond comparing to **2a**, which amounts to 35.1(1)º in **3**. Nevertheless this interaction also forces the *synplanar* orientation of $B(OH)_2$ moiety towards nitrogen lone pair (protonated in **3**) as in **2a**. The protonation of nitrogen atom causes also the elongation of C7-N1 bond length to 1.522 Å. The comparison of other geometrical parameters of **2a** and **3** revealed no significant differences. In turn, the dramatic change is observed in supramolecular architecture. Even though two OH donors are capable of extending the structure *via* hydrogen bonds, the observed motif is a finite one. Both the chloride anion and solvent water molecule serve as acceptors for boronic OH donors (Fig. 4). Further, numerous hydrogen bonds join molecules of **3** into 3-D structure. The hydrophilic zigzag channels along [010] direction are observed.

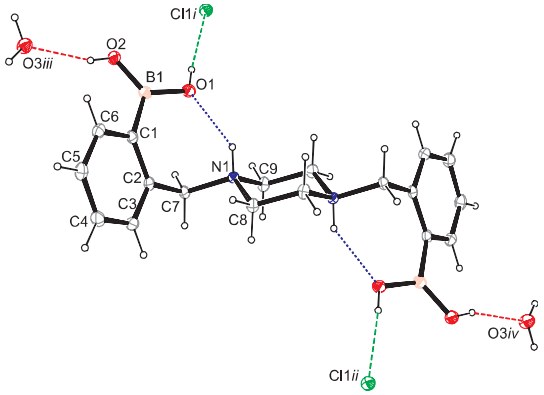


Fig. 4. The molecule of **3** with 50% probability thermal ellipsoids and atom numbering scheme are shown. The intra- and intermolecular hydrogen bonds involving boronic moieties are denoted as dotted and dashed lines, respectively.

Crystallization of the pure product from methanol resulted in a species in which one of the OH group in each boronic unit was esterified with methanol (**4**). Not many examples of phenylboronic acids methanol hemiesters have been reported so far.[53-55] The molecules of hemiester **4** (Fig. 5) are also centrosymmetric and crystallize in monoclinic system in $P2_1/c$ space group symmetry (Table 1, ESI). Similarly to **3**, the diboronic moiety is cationic with protonated nitrogen atoms. Also the change from OH in **3** to OCH_3 group in **4** does not change their conformation towards B1-C1 bond, i.e. the ester moiety is in *syn* conformation while OH in the *anti* one. Hence, in contrast to **3** no intramolecular hydrogen bond is formed in **4**. The absence of this H-bond leads to the twist of the piperazine moiety and thus the relevant orientation of the phenyl ring and the N-H group is like in benzoxaborole **1a**, i.e. *trans*. Similarly to **3**, the C7-N1 bond is elongated comparing to the value of unprotonated amines. No substantial differences are found in the geometry of piperazine unit, while in boronic moiety the dihedral angle between planes comprising B(OH)(OCH_3) group or phenyl ring is much smaller than in **3** and equals to 22.3(9)º. Besides, the B1-C1 bond slightly elongates upon esterification and amounts to 1.590(1) Å. Lack of intramolecular hydrogen bond results also in different supramolecular structure. In the case of **4** both OH and NH donors interact with chloride anion resulting in infinite chain structure. The detected solvent accessible voids are propagating along *a* axis. No reliable solvent model was applied during refinement.

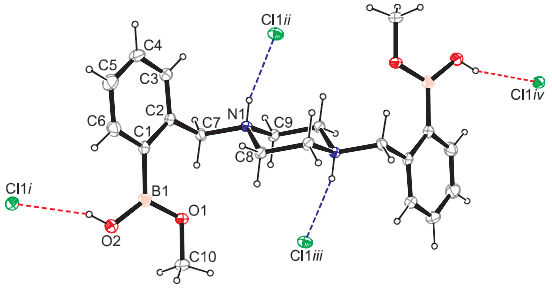


Fig. 5. The molecule of **4** with 50% probability thermal ellipsoids and atom numbering scheme are shown. Intermolecular hydrogen bonds with chloride anions are given as dashed lines.

3. Conclusions

A straightforward synthesis of a highly biologically active 3-piperazine-bisbenzoxaborole (**1a**) and its fluorine analog (**1b**) has been described. The obtained bisbenzoxaboroles have been used in the synthesis of their boronic acids analogs (**2a**, **2b**). Compound **2a** has been also isolated in the form of the hydrochloride (**3**) as well as its methoxy hemiester (**4**). The obtained products display unique molecular architectures, which have been determined by X-Ray measurements. The crystal structure analysis of compounds **1a**-**4** revealed the presence of centrosymmetric molecules in the crystalline state. The relevant orientation of piperazine nitrogen lone pair or NH group towards boronic BO_2 group was found to be labile and dependent on intramolecular hydrogen bond formation. The influence of the intermolecular hydrogen bonds on boronic hydroxyl groups' conformation was detected.

4. Experimental section

4.1. General information

All reactions were set up under air and using undistilled solvents. The reagents were purchased from commercial sources and used without further purification. The reported yields refer to pure isolated products. NMR spectra were recorded on a Varian Inova 500 MHz spectrometer in deuterated solvents. Elemental analyses were obtained by means of a Perkin Elmer 2400 apparatus. All melting points (m.p.) are given uncorrected. The IR spectra were recorded on a Perkin Elmer 2000 with a diamond Gladi ATR optics.

4.2. Experimental procedures and characterization data

4.2.1. 3,3'-(Piperazine-1,4-diyl)bis(benzo[c][1,2]oxaborol-1(3*H*)-ol) (1a)

The solution 2-formylphenylboronic acid (4.80 g, 32 mmol) in diethyl ether (200 mL) was prepared in a 500 mL round-bottomed flask equipped with magnetic stirrer and dropping funnel. A solution of piperazine (1.345 g, 15.6 mmol) in diethyl ether (180 mL) was dropped slowly (about 1 drop per second) into the 2-formylphenylboronic acid solution while stirring. After addition of about 10% of the piperazine solution, a fine white solid precipitated. The whole piperazine solution was then dropped-in to the suspension and the reaction mixture was left for 24 hours at room temperature. The solid was filtered off and dried on air resulting in 5.27 g (94% yield) of **1a** as white solid, m.p. 220 °C (dec.); [Found: C, 61.64; H, 5.69, N: 7.93. $C_{18}H_{20}B_2N_2O_4$ requires C, 61.77; H, 5.76; N, 8.00%]; ν_{max} = 3295 (br), 1611, 1443, 1343, 1171, 1137, 1010, 818, 754, 726, 631 cm^{-1}; δ_H (500 MHz, CD_3OD) 7.53-7.25 (8 H, m, Ph); 5.90 (2 H, s, C<u>H</u>); 3.01-2.90 (8 H, m, C<u>H</u>$_2$); δ_C (126 MHz, CD_3OD) 149.7, 130.2, 128.8, 128.6, 123.5, 104.9, 45.1; δ_B (64 MHz CD_3OD) 13.6; δ_H (500 MHz, DMSO-d_6) 9.14 (0.5 H, s, BO<u>H</u>), 9.11 (0.5 H, s, BO<u>H</u>), 7.71-7.30 (8 H, m, Ph), 5.84 (0.5 H, s, C<u>H</u>), 5.79 (0.5 H, s, C<u>H</u>), 2.13 (4 H, m, br, C<u>H</u>$_2$C<u>H</u>$_2$), 1.96 (4 H, m, br, C<u>H</u>$_2$C<u>H</u>$_2$); δ_C (126 MHz, DMSO-d_6) 152.6, 152.5, 132.3, 130.9, 130.8, 130.2, 130.1, 128.1, 128.0, 122.5, 122.4, 95.7, 95.6, 46.4. Crystallization of an analytical sample from DMSO resulted in crystals of **1a** suitable for X-Ray measurements.

4.2.2. 3,3'-(Piperazine-1,4-diyl)bis(5-fluorobenzo[c][1,2]oxaborol-1(3*H*)-ol) (1b)

To a stirred solution of 4-fluoro-2-formylphenylboronic acid (500 mg, 2.98 mmol) in diethyl ether (15 mL) and tetrahydrofuran (5 mL), a solution of piperazine (125 mg, 1.45 mmol) in diethyl ether (17 mL) was added dropwise. After addition of ca. 1/2 of the piperazine solution, a white fine precipitate started to form. When the addition was finished, stirring was turned off and the reaction mixture was left at room temperature for 24 hours. The precipitate was filtered and dried in air for 4 days. The product was obtained (481 mg, 1.25 mmol, 86%) as a white powder, m.p. 222 °C (dec.); [Found: C, 56.20; H, 4.88; N, 7.13. $C_{18}H_{18}B_2F_2N_2O_4$ requires C, 56.01; H, 4.70; N, 7.26%]; ν_{max} = 3312 (br), 1614, 1434, 1421, 1344, 1181, 1015, 839, 824, 806, 701, 629 cm^{-1}; δ_H (500 MHz, CD_3OD) 7.55-6.94 (6 H, m, Ph), 5.87 (2 H, s, C<u>H</u>), 3.09-2.91 (8 H, m, C<u>H</u>$_2$C<u>H</u>$_2$); δ_F (470 MHz, CD_3OD) –109.44, –109.55; δ_B (160 MHz, CD_3OD) 14.9; δ_H (500 MHz, DMSO-d_6) 9.22 (1 H, s, B-O<u>H</u>), 9.20 (1 H, s, B-O<u>H</u>), 7.75-7.72 (1 H, m, Ph), 7.70-7.68 (1 H, m, Ph), 7.25-7.16 (2 H, m, Ph), 7.12-7.06 (2 H, m, Ph), 5.83 (1 H, s, C<u>H</u>), 5.79 (1 H, s, C<u>H</u>), 2.60 (4 H, s, br, C<u>H</u>$_2$C<u>H</u>$_2$), 2.43 (4 H, s, br, C<u>H</u>$_2$C<u>H</u>$_2$); δ_c (126 MHz, DMSO-d_6) 166.4, 166.4, 164.5, 164.3, 156.5, 156.5, 156.3, 156.3, 133.4, 133.3, 133.4, 133.2, 116.9, 116.7, 116.6, 116.7, 110.5, 110.3, 110.2, 110.2, 95.7, 95.7, 95.8, 47.2.

4.2.3. Piperazine-1,4-diylbis(methylene))bis(2,1-phenylene))diboronic acid (2a)

*4.2.3.1. Synthesis of **2a** via reduction of benzoxaborole (**1a**)*

Solution of **1a** (0.25 g, 0.71 mmol) in methanol (20 mL) was placed in a 50 mL round-bottomed flask. $NaBH_4$ (0.09 g, 2.4 mmol) was added portionwise while stirring. The mixture was stirred for 1 h at room temperature. After that time, distilled water (15 mL) was added resulting in white solid. The solid was filtered off and dried on air resulting in 0.221 g (87% yield) of **2a**. δ_H (500 MHz, CD_3OD) 7.53-7.51 (2 H, m, Ph), 7.25-7.15 (6 H, m, Ph), 3.89 (4 H, s, 2*C$\underline{H_2}$), 2.85 (8 H, s, 2*C$\underline{H_2}$C$\underline{H_2}$). Crystallization of the analytical sample from DMSO resulted in **2a** crystals suitable for X-Ray measurements.

*4.2.3.2. Synthesis of **2a** via one-pot amination-reduction*

Piperazine (1.17 g, 13.6 mmol) was dissolved in methanol (375 mL) in a 1000 mL round-bottomed flask equipped with magnetic stirrer and a cooling bath (ice/NaCl). 2-Formylphenylboronic acid (4.03 g, 26.9 mmol) was added resulting in clear solution. The reaction mixture was cooled down to -10 °C. While intense stirring, $NaBH_4$ (4.70 g, 0.12 mol) was added portionwise. The stirring was continued for another 20 min at -10 °C. Distilled water (280 mL) was added dropwise to the resulting post-reaction mixture at room temperature. After addition of about 70 mL of water, white precipitate appeared. The suspension was left for 24 h at room temperature. The solid was filtered off after that time and dried under vacuum to give **2a** (3.52 g, 74%) as a white powder, m.p. 226 °C; [Found: C, 60.28; H, 6.92; N, 7.92. 3*$C_{18}H_{24}B_2N_2O_4$*H_2O requires C, 60.05; H, 6.91; N, 7.78%]; ν_{max} = 3262 (br), 1318, 1345, 1318, 1144, 1031, 990, 826, 768, 750, 658, 425 cm^{-1}; δ_H (500 MHz, CD_3OD) 7.54-7.51 (2 H, m, Ph), 7.25-7.21 (4 H, m, Ph), 7.18-7.15 (2 H, m, Ph) 3.89 (4 H, 2*CH_2); 2.88 (8 H, s, br, 2*C$\underline{H_2}$C$\underline{H_2}$); δ_c (126 MHz, CD_3OD) 140.4, 130.0, 128.9, 128.7, 128.2, 62.4, 50.9; δ_B (64MHz, CD_3OD) 19.0.

4.2.4. ((Piperazine-1,4-diylbis(methylene))bis(4-fluoro-2,1-phenylene))diboronic acid (2b)

*4.2.4.1. Synthesis of **2b** via reduction of benzoxaborole **1b**.*

To a stirred solution of **1b** (72 mg, 0.187 mmol) in methanol (8.0 mL), sodium borohydride (24 mg, 0.636 mmol) was added portionwise at room temperature. The mixture was stirred for 1.5 h at room temperature. Distilled water (12 mL) was added resulting in the formation of a white fine precipitate after ca. 2 minutes. The solid was filtered off and dried in air for 2 days at ca. 35 °C. The product was obtained as a white solid (33 mg, 0.085 mmol, 45%).

δ_H (500 MHz, CD_3OD) 7.50-7.47 (2 H, m, Ph), 6.98-6.94 (4 H, m, Ph), 3.90 (4 H, s, 2*CH_2), 2.87 (8 H, s, 2*CH_2CH_2); δ_F (470 MHz, CD_3OD) –116.72.

*4.2.4.2. Synthesis of **2b** via one-pot amination-reduction.*

To a stirred solution of piperazine (126 mg, 1.462 mmol, 1.00 eq) in methanol (40 mL), 4-fluoro-2-formylphenylboronic acid (491 mg, 2.924 mmol, 2.00 eq) was added in one portion at room temperature. The resulting mixture was cooled to –10 °C with sodium chloride/ice bath. Sodium borohydride (489 mg, 12.866 mmol, 8.80 eq) was added portionwise over 10 minutes, maintaining the temperature of –10 °C, and the reaction mixture was stirred for the next 35 minutes at –10 °C. The cooling bath was removed and distilled water (30 mL) was added to the mixture, resulting in the formation a white fine precipitate after ca. 5 minutes. The solid was filtered and dried: firstly for 2 hours at ca. 35 °C, then at room temperature for 2 days. The product **2b** was afforded as a white solid (386 mg, 0.944 mmol, 65%), m.p. 226 °C; [Found: C, 55.35; H, 5.74; N, 7.23. $C_{18}H_{22}B_2F_2N_2O_4$ requires C, 55.43; H, 5.69; N, 7.18%]; ν_{max} = 3297 (br), 1739 (br), 1368, 1228, 1146, 1033, 999, 823, 640, 544 cm^{-1}; δ_H (500 MHz, CD_3OD) 7.50-7.47 (2 H, m, Ph), 6.98-6.95 (4 H, m, Ph), 3.89 (4 H, s, 2*C<u>H</u>$_2$), 2.87 (8 H, s, 2*C<u>H</u>$_2$C<u>H</u>$_2$); δ_C (126 MHz, DMSO-d_6) 165.1, 163.1, 143.5, 135.6, 115.1, 114.6, 114.6, 61.5, 50.1; δ_F (470 MHz, CD_3OD) –116.56; δ_B (160 MHz, CD_3OD) 19.3.

4.2.5. ((Piperazine-1,4-diylbis(methylene))bis(4-fluoro-2,1-phenylene))diboronic acid hydrochloride (3)

*4.2.5.1 Synthesis of **3** in an amination-reduction reaction*

Piperazine (1.15 g, 13.4 mmol) was dissolved in MeOH (70 mL) and stirred at -10ºC. 2-Formylphenylboronic acid (4.00 g, 26.7 mmol) was added resulting in clear solution. $NaBH_4$ (4.70 g, 13.4 mmol) was added and intense stirring was continued for 20 minutes. HCl aq (3 M, 25 mL) was added (pH~1) and the mixture was stirred for 10 minutes. Diethyl ether (40 mL) was poured into the solution resulting in precipitation of a white solid that was left for 18 hours at room temperature, filtered off and dried on air giving 4.24 g (73%) of the diboronic product hydrochloride (**3**). Crystallization of the analytical sample of the product from a water:acetonitrile mixture resulted in monocrystals of **3** suitable for X-Ray analysis. Crystallization from MeOH resulted in monocrystals of **4** suitable for X-Ray analysis.

*4.2.5.2 Synthesis of **3** starting from the acid **2a***

Diboronic acid **2a** (0.300 g) and distilled water (4 mL) were placed in a 15 mL beaker. Hydrochloric acid (3 M, 4 mL) was added to the white suspension while intense stirring. In few seconds, the solid dissolved and considerable amount of a white solid of the hydrochloride appeared. The mixture was left for two hours on stirring at room temperature

and than the solid was filtered off. The solid was washed with distilled water till the pH of the rinse solution was not acidic. The resulting solid was dried on air to give **3** hexahydrate (0.170 g, 47%) as a white solid, m.p. 252 °C (dec.); [Found C, 40.42; H, 7.10; N, 5.24. $C_{18}H_{38}B_2Cl_2N_2O_{10}$ requires C, 40.41; H, 7.16; N, 5.24%]; ν_{max} = 3442 (br), 3246 (br), 3106, 3015, 1738, 1365, 1202, 1155, 1100, 938, 641, 527 cm^{-1}; δ_H (500 MHz, CD_3OD) 7.89 (2 H, d, *J* 5.9 Hz, Ph), 7.58-7.48 (6 H, m, Ph), 4.65 (4 H, s, br., 2*Ph-C$\underline{H_2}$-N), 3.68 (8 H, s, br., 2*N-C$\underline{H_2}$-C$\underline{H_2}$-N), δ_B (160 MHz, CD_3OD) 30.0; δ_H (500 MHz, $(CD_3)_2SO$) 7.81 (2 H, d, *J* 7.0 Hz, Ph); 7.63 (2 H, d, *J* 7.5 Hz, Ph), 7.48-7.40 (4 H, m, Ph), 4.50 (4 H, s, br., 2*Ph-C$\underline{H_2}$-N), 3.44 (8 H, s, br., 2*N-C$\underline{H_2}$-C$\underline{H_2}$-N); δ_C (125.7 MHz, $(CD_3)_2SO$) 136.5, 135.3, 134.4, 131.7, 129.9, 128.6, 59.0, 47.9.

4.3. X-ray diffraction measurements

Single crystal data for **1a**-**4** (Table 1) were collected on Gemini A Ultra Diffractometer (Agilent Technologies) with mirror monochromated Cu/Kα radiation (λ = 1.5418 Å). The CrysAlisPro[56] program was used for data collection, cell refinement, data reduction and the empirical absorption corrections using spherical harmonics, implemented in multi-scan scaling algorithm. The structures were solved using direct methods, and refined with the full-matrix least-squares technique using the SHELXS97 and SHELXL97 programs, respectively,[57] both implemented in OLEX2 program.[58] All non-hydrogen atoms were refined with anisotropic temperature factors. The positions of hydrogen atoms bonded to oxygen or nitrogen atoms were refined freely with fixed isotropic thermal parameters equal to 1.2 ×U_{eq} of appropriate atom. The hydrogen atoms bonded to carbon atoms were introduced in geometrically idealized positions and refined with a riding model with U_{iso}(H) values of 1.2 ×U_{eq}(C) or 1.5 ×U_{eq}(C) for methyl groups in **1a**. In case of **4**, all atoms of the phenylboronic acid moiety can be located and refined satisfactorily to give R_1 ca. 11% and wR_2 ca. 30%. Residual electron density remains, distributed throughout the channels (along the *a* direction) and calculated total solvent accesible volume per unit cell amounted to 234.5 $Å^3$ (~18%). This cannot be resolved into any meaningful atomic positions and was treated, therefore, using the MASK procedure[59] implemented in OLEX2 program.[58] The electron density was estimated to be 51 electrons per unit cell, and correction of the F_{obs} data to remove its contribution resulted in R_1 and wR_2 falling to 3.05% and 7.91%, respectively, and the residual electron density below 0.4 e/$Å^3$. Figures presenting molecular structures with basic H-bonded motives were generated using ORTEP-3 for Windows.[34] The geometric calculations were done by

PLATON package.[60] Values involving hydrogen atoms in the calculated positions are given without estimated standard deviations.

Table 1. Crystal data.

Parameters	**1a**	**2a**	**3**	**4**
Empirical formula	$C_{22}H_{32}B_2N_2O_6S_2$	$C_{18}H_{24}B_2N_2O_4$	$C_{18}H_{38}B_2Cl_2N_2O_{10}$	$C_{20}H_{30}B_2Cl_2N_2O_4$
Formula moiety	$C_{18}H_{20}B_2N_2O_4$, 2 (C_2H_6SO)	$C_{18}H_{24}B_2N_2O_4$	$C_{18}H_{26}B_2N_2O_4^+$, $2Cl^-$, $6H_2O$	$C_{20}H_{30}B_2N_2O_4^+$, $2Cl^-$
Formula weight	506.24	354.01	535.02	454.98
Temperature/K	100.0	100.0	100.0	100.0
Crystal system	Triclinic	monoclinic	monoclinic	Monoclinic
Space group	*P*–1	$P2_1/c$	$P2_1/c$	$P2_1/c$
a /Å, *b* /Å, *c* /Å	5.7946(8), 8.1940(12), 13.093(2)	6.03695(17) 7.74920(18) 19.9827(4)	11.57123(16) 16.19904(18) 7.14661(11)	7.11214(7) 17.23967(12) 11.10757(10)
α /°, β /°, γ /°	89.403(13) 87.300(13) 88.998(12)	90 92.895(2) 90	90 107.9826(15) 90	90 107.9866(10) 90
Volume /Å^3	620.85(16)	933.63(4)	1274.14(3)	1295.35(2)
Z	1	2	2	2
ρ_{calc} /mg mm^{-3}	1.354	1.259	1.395	1.166
μ /mm^{-1}	2.286	0.702	2.761	2.462
F(000)	268	376	568	480
Index ranges	$-6 \le h \le 6$, $-9 \le k \le 9$, $-15 \le l \le 15$	$-7 \le h \le 6$, $-9 \le k \le 9$, $-23 \le l \le 23$	$-13 \le h \le 13$, $-19 \le k \le 19$, $-8 \le l \le 8$	$-8 \le h \le 7$, $-20 \le k \le 20$, $-13 \le l \le 13$
Reflections collected	30583	5577	32254	46051
Independent reflections	2198[$R_{(int)}$ = 0.078]	1662[$R_{(int)}$ = 0.016]	2282[$R_{(int)}$ = 0.039]	2318[$R_{(int)}$ = 0.0345]
Data/restraints/parameters	2198/0/159	1662/0/124	2282/0/181	2318/0/143
Goodness-of-fit on F^2	1.063	1.051	1.063	1.077
Final *R* indexes [$I > 2\sigma(I)$]	R_1 = 0.0405, wR_2 = 0.0973	R_1 = 0.0356, wR_2 = 0.0930	R_1 = 0.0271, wR_2 = 0.0708	R_1 = 0.0305, wR_2 = 0.0787
Final *R* indexes [all data]	R_1 = 0.0476, wR_2 = 0.1015	R_1 = 0.0370, wR_2 = 0.0941	R_1 = 0.0288, wR_2 = 0.0721	R_1 = 0.0312, wR_2 = 0.0793

Largest diff. peak/hole/e Å^{-3}	0.41/–0.29	0.28/–0.21	0.30/–0.19	0.26/–0.22

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Supplementary data

Supplementary data related to this article can be found online at [link]. Crystallographic data (excluding structure factors) for the structure reported in this paper has been deposited with the Cambridge Crystallographic Data Centre as deposit numbers CCDC 940237-940240. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Rd, Cambridge CB2IEZ UK (fax: +44 (1223) 336 033; e-mail: deposit@ccdc.cam.ac.uk.

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Supplementary data

Straightforward synthesis and crystal structures of the 3-piperazine-bisbenzoxaboroles and their boronic acid analogs

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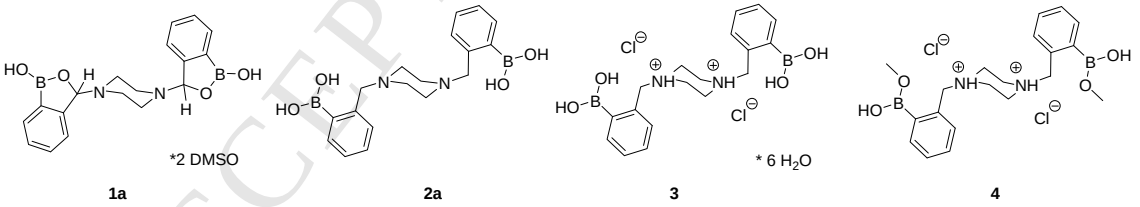

Figure. Structures determined by X-Ray.

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Table S1. Bond lengths for compounds **1a**, **2a**, **3** and **4**, Å

	1a	**2a**	**3**	**4**
O1–B1	1.379(3)	1.365(2)	1.367(2)	1.366(2)
O2–B1	1.350(3)	1.354(2)	1.356(2)	1.352(2)
O1–C7	1.465(2)			
O1–C10				1.436(2)
C1–B1	1.565(3)	1.586(2)	1.579(2)	1.590(2)
N1–C7	1.435(3)	1.480(1)	1.522(2)	1.514(2)
N1–C8	1.467(2)	1.468(2)	1.498(2)	1.500(2)
N1–C9	1.467(3)	1.471(1)	1.497(2)	1.499(2)
C8–C9^{x}	1.520(3)	1.516(2)	1.511(2)	1.516(2)
C1–C2	1.400(3)	1.414(2)	1.409(2)	1.409(2)
C1–C6	1.401(3)	1.400(2)	1.399(2)	1.402(2)
C2–C3	1.381(3)	1.394(2)	1.392(2)	1.396(2)
C2–C7	1.508(3)	1.517(2)	1.512(2)	1.511(2)
C3–C4	1.388(3)	1.386(2)	1.390(2)	1.383(2)
C4–C5	1.396(3)	1.385(2)	1.384(2)	1.381(2)
C5–C6	1.381(3)	1.388(2)	1.385(2)	1.391(2)
S1–O3	1.516(2)			
S1–C10	1.786(2)			
S1–C11	1.786(2)			

Symmetry operation (x) for (**1a**) 1–*x*, 1–*y*, 2–*z;* (**2a**, **4**) 2–*x*, 1–*y*, 1–*z*; (**3**) 2–*x*, 1–*y*, –*z*.

Table S2. Bond angles for compounds **1a**, **2a**, **3** and **4**, °

	1a	**2a**	**3**	**4**
O2–B1–O1	119.5(2)	119.6(1)	119.5(1)	118.1(1)
O1–B1–C1	108.4(2)	122.8(1)	118.1(1)	118.9(1)
O2–B1–C1	132.0(2)	117.6(1)	122.5(1)	123.0(1)
B1–O1–C7	110.7(2)			
B1–O1–C10				119.3(1)
C7–N1–C8	113.5(2)	112.3(1)	109.8(1)	110.3(1)
C7–N1–C9	112.5(2)	110.5(1)	111.7(1)	111.9(1)
C8–N1–C9	110.1(2)	109.7(1)	108.9(1)	110.0(1)
O1–C7–C2	105.0(2)			
N1–C7–O1	113.3(2)			
N1–C7–C2	113.7(2)	113.6(1)	111.9(1)	111.2(1)
N1–C8–C9^{x}	109.8(2)	110.1(1)	111.3(1)	110.8(1)
N1–C9–C8^{x}	110.3(2)	110.4(1)	111.8(1)	110.8(1)
C2–C1–C6	118.6(2)	117.5(1)	117.7(1)	117.1(1)
C2–C1–B1	104.8(2)	126.1(1)	123.4(1)	125.6(1)
C6–C1–B1	136.5(2)	116.4(1)	118.9(1)	117.3(1)
C1–C2–C7	110.9(2)	122.5(1)	122.0(1)	123.2(1)
C3–C2–C1	122.2(2)	119.8(1)	120.2(1)	120.3(1)
C3–C2–C7	126.8(2)	117.6(1)	117.8(1)	116.5(1)
C2–C3–C4	118.3(2)	121.1(1)	120.7(1)	121.1(1)
C3–C4–C5	120.5(2)	119.9(1)	119.7(1)	119.6(1)
C4–C5–C6	120.8(2)	119.2(1)	119.6(1)	119.6(1)
C5–C6–C1	119.5(2)	122.4(1)	122.0(1)	122.3(1)
O3–S1–C10	105.9(1)			
O3–S1–C11	105.6(1)			
C10–S1–C11	97.7(1)			

Symmetry operation (x) for (**1a**) 1–*x*, 1–*y*, 2–*z;* (**2a**, **4**) 2–*x*, 1–*y*, 1–*z*; (**3**) 2–*x*, 1–*y*, –*z*.

Table S3. Torsion angles for compounds **1a**, **2a**, **3** and **4**, º

	1a	**2a**	**3**	**4**
C2–C1–B1–O1	–2.4(2)	–25.6(2)	36.5(2)	23.2(2)
C2–C1–B1–O2	176.7(2)	156.9(1)	–143.6(1)	–159.8(1)
C6–C1–B1–O1	174.9(2)	153.0(1)	–147.1(1)	–157.0(1)
C6–C1–B1–O2	–6.0(4)	–24.5(2)	32.8(2)	20.1(2)
C7–O1–B1–O2	–174.9(2)			
C7–O1–B1–C1	4.3(2)			
C10–O1–B1–O2				5.1(2)
C10–O1–B1–C1				–177.7(1)
B1–O1–C7–N1	–129.0(2)			
B1–O1–C7–C2	–4.4(2)			
C1–C2–C7–O1	2.8(2)			
C3–C2–C7–O1	–175.8(2)			
C8–N1–C7–O1	59.6(2)			
C9–N1–C7–O1	–66.3(2)			
C8–N1–C7–C2	–60.2(2)	63.3(1)	177.1(1)	–171.3(1)
C9–N1–C7–C2	174.0(2)	–173.9(1)	–62.0(1)	65.9(1)
C7–N1–C8–C9^{x}	174.4(2)	–178.3(1)	178.9(1)	179.0(1)
C9–N1–C8–C9^{x}	–58.4(2)	58.4(1)	56.3(2)	–57.1(2)
C7–N1–C9–C8^{x}	–173.6(2)	177.2(1)	–178.0(1)	–179.9(1)
C8–N1–C9–C8^{x}	58.7(2)	–58.5(1)	–56.6(1)	57.1(2)
B1–C1–C2–C3	178.3(2)	179.5(1)	172.8(1)	179.5(1)
B1–C1–C2–C7	–0.4(2)	–3.0(2)	–6.0(2)	1.6(2)
C6–C1–C2–C7	–178.3(2)	178.5(1)	177.5(1)	–178.3(1)
B1–C1–C6–C5	–176.3(2)	–178.7(1)	–174.5(1)	179.0(1)
C3–C1–C2–C6	0.4(3)	1.0(2)	–3.6(2)	–0.4(2)
C2–C1–C6–C5	0.7(3)	0.0(2)	2.1(2)	–1.1(2)
C1–C2–C3–C4	–1.4(3)	–1.1(2)	2.0(2)	1.5(2)
C4–C2–C3–C7	177.1(2)	–178.7(1)	–179.1(1)	179.5(1)
C2–C3–C4–C5	1.3(3)	0.3(2)	1.3(2)	–1.1(2)
C3–C4–C5–C6	–0.2(3)	0.7(2)	–2.8(2)	–0.3(2)
C4–C5–C6–C1	–0.8(3)	–0.8(2)	1.1(2)	1.5(2)
C1–C2–C7–N1	127.2(2)	60.9(2)	–75.5(2)	–111.4(1)
C3–C2–C7–N1	–51.5(3)	–121.5(1)	105.7(1)	70.6(2)

Symmetry operation (x) for (1) 1–x, 1–y, 2–z; (2,4) 2–x, 1–y, 1–z; (3) 2–x, 1–y, –z.

Table S4. Hydrogen bonds geometry for compounds **1a**, **2a**, **3** and **4**, Å,º.

	D–H	**H…A**	**D–H…A**	**D…A**
1a				
O2–H2…O3[–*x*+2,–*y*+1,–*z*+1]	0.815	1.897	178.73	2.712
2a				
O1–H1…N1	0.921	1.696	167.59	2.603
O2–H2…O1[–*x*+1,–*y*,–*z*+1]	0.827	1.894	176.83	2.720
3				
N1–H1A…O1	0.880	2.125	135.58	2.821
O1–H1…Cl1[*x*+1,–*y*+3/2,*z*–1/2]	0.785	2.358	175.23	3.142
O2–H2…O3[*x*,–*y*+3/2,*z*–1/2]	0.765	1.978	161.58	2.714
O3–H3A…O4[–*x*+1,–*y*+1,–*z*+1]	0.826	1.990	169.73	2.806
O3–H3B…O4	0.845	2.004	164.08	2.826
O4–H4A…O5	0.808	1.947	170.04	2.746
O4–H4B…Cl1	0.835	2.375	164.95	3.188
O5–H5A…Cl1[*x*,*y*,*z*–1]	0.819	2.394	170.52	3.205
O5–H5B…Cl1[*x*,–*y*+3/2,*z*–1/2]	0.810	2.348	177.50	3.157
4				
O2–H2…Cl1[–*x*+1,*y*–1/2,–*z*+1/2]	0.782	2.349	160.89	3.099
N1–H1…Cl1[–*x*+1,–*y*+1,–*z*+1]	0.851	2.298	164.09	3.125