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PREPARATION AND BIOLOGICAL ACTIVITY OF NOVEL TWIN-DRUG TYPE *C*$_2$-SYMMETRICAL CYCLIC PHENYLBORONIC ACID DERIVATIVES

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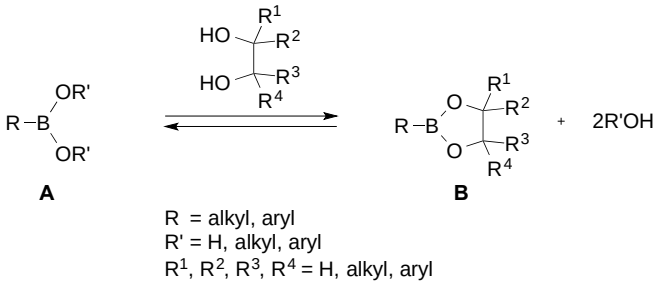
Abstract – We here report the results of evaluation of antibacterial and anti-herpes simplex virus-1 (HSV-1) activities of a novel twin-drug type *C*$_2$-symmetrical boronic acid and its pinacol ester derivatives. By using a primitive amide bond formation reaction, various targeted *C*$_2$-symmetrical cyclic phenylboronic acid derivatives were obtained from the reactions of commercially available amino-substituted phenylboronic acid derivatives and diacid dichlorides. The *C*$_2$-symmetrical bivalent molecule **3bd** containing two cyclic phenylboronic acid pinacol ester moieties and a flexible hexamethylene linker showed both antibacterial activity (*S. aureus*) and anti-HSV-1 activity. The corresponding boronic acid derivative **3dd** showed neither antibacterial nor anti-HSV-1 activity, indicating the importance of two pinacol ester functionalities.

Many synthetic bioactive *C*$_2$-symmetrical bivalent molecules have been studied for the development of new agents to treat various infectious diseases or new valuable ligands for treatment of diseases caused by dysfunction of various receptors.[1] On the other hand, regarding molecules for recognition of saccharides (sugar chains), much attention has been paid to the design of synthetic molecules. From the viewpoint of molecular geometry, we have already investigated a few symmetrical molecules for the purpose of finding new bioactive leads.[2-7] In terms of the chemical properties of functional groups, we have been

interested in boronic acids and related derivatives because many boronic acid derivatives (**A**) have a property to react with various 1,2-diol moieties such as sugars and generate cyclic boronic acid ester derivatives (**B**) formed with reversible covalent bonds (see Scheme 1).[8]



Scheme 1

We have therefore incorporated such characteristic cyclic boronic acid ester functional groups in newly targeted bivalent C_2-symmetrical mid-size molecules.[9] We have recently reported new twin-drug type C_2-symmetrical non-peptide bivalent molecules (**3**) for biological evaluation of these molecules in order to find new bioactive leads.[10]

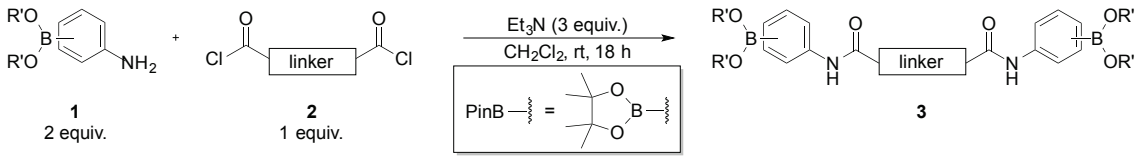
In this article, we describe the results of evaluation of the antibacterial and anti-HSV-1 activities of these newly designed bivalent twin-drug type C_2-symmetrical cyclic phenylboronic acid esters and additionally prepared new C_2-symmetrical analogues.

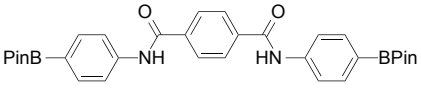
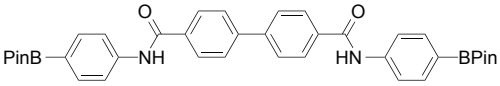
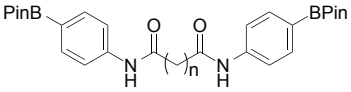
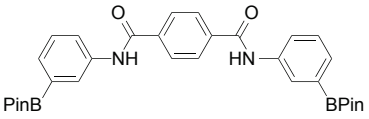
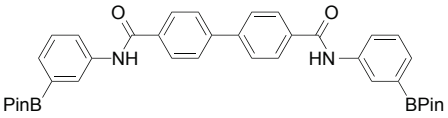
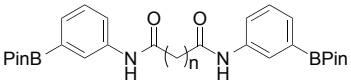
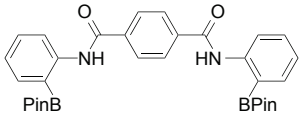
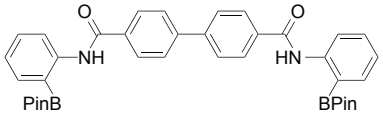
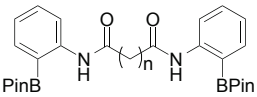
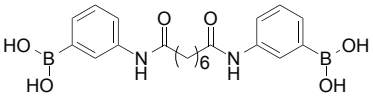
The structures of the prepared compounds and the results of biological evaluation by antibacterial and antiviral assays are shown in Table 1. *Staphylococcus aureus* (*S. aureus*; a Gram-positive strain) and *Escherichia coli* (*E. coli*; a Gram-negative strain) were used for the antibacterial assay, and antiviral activities were evaluated by using HSV-1 virus. We also evaluated cytotoxic activity to Vero cells. MIC values are expressed as molar concentrations (mM) for discussion of structure-activity relationships.

Preparation of target bivalent C_2-symmetrical cyclic phenylboronic acid derivatives has already been reported.[10] Details of the preparation and spectroscopic data of a few new additional C_2-symmetrical phenylboronic acid derivatives are given in the EXPERIMENTAL section.

The structures of target C_2-symmetrical molecules and the results of bioassays are shown in Table 1. Among the compounds shown in Table 1, most of the compounds that have aromatic groups as linkers in the molecules showed no significant bioactivities; however, three cyclic phenylboronic acid derivatives (**3ad**, **3ba** and **3bd**) showed antibacterial activity against a Gram-positive *S. aureus* strain or a Gram-negative *E. coli* strain. The obtained MIC values were in the range of 0.111-0.113 mM. Compounds **3ad** and **3ba** showed antibacterial activities against both Gram-positive *S. aureus* and Gram-negative *E. coli* strains. (MIC=0.111-0.113 mM). On the other hand, two compounds (**3bd** and **3be)** showed anti-HSV-1 activity (EC_{50}=38.6-41.1 μM). It is noteworthy that compound **3bd** showed both antibacterial activity (only against a Gram-positive *S. aureus* strain; MIC= 0.111 mM) and anti-HSV-1

Table 1. Structures of the Prepared Compounds and the Results of Biological Evaluation by Antibacterial and Antiviral Assays



Entry	Product **3**			Yield (%)[b]	MIC (mM) *S. aureus*	MIC (mM) *E. coli*	EC_{50} (μM) Anti-HSV-1 activity	IC_{50} (μM) Cytotoxic activity
1			**3aa**	47[c]	≧0.225	≧0.225	>100	>200
2			**3ab**	88[c]	≧0.199	≧0.199	>100	>200
3		n = 4	**3ac**	76[c]	≧0.233	≧0.233	>100	>200
4		6	**3ad**	60[c]	0.111	0.111	>100	>200
5		8	**3ae**	89	≧0.212	≧0.212	>100	>200
6			**3ba**	98[c]	0.113	0.113	>100	>200
7			**3bb**	51[c]	≧0.199	≧0.199	>100	>200
8		n = 4	**3bc**	82[c]	≧0.233	≧0.233	>100	>200
9		6	**3bd**	98[c]	0.111	≧0.222	38.6	>200
10		8	**3be**	85	≧0.212	≧0.212	41.1	>200
11			**3ca**	90[c]	ND[d]	ND[d]	>100	>200
12			**3cb**	55[c]	ND[d]	ND[d]	>100	>200
13								
14		n = 4	**3cc**	43[c]	>0.233	>0.233	>100	>200
15		6	**3cd**	68[c]	>0.222	>0.222	>100	>200
		8	**3ce**	59	≧0.212	≧0.212	>100	>200
16[a]			**3dd**	35	>0.212	>0.212	>100	>200

[a] 4 Equiv. of Et_3N were used and reaction time was 1 h. [b] Isolated yield. [c] Data were taken from ref 10. [d] Not determined due to low solubility.

activity (EC_{50}=38.6 μM), though the levels of activity were not so high. None of these cyclic phenylboronic acid derivatives showed cytotoxic activity against Vero cells, and none of the *ortho*-substituted phenylboronic acid derivatives were active.

Considering the structures of the bioactive molecules, derivatives that have aliphatic methylene-chain structures [such as -$(CH_2)_n$-; n=6] as a linker moiety were thought to be derivatives with the most

preferable structure for the C_2-symmetrical bivalent cyclic phenylboronic acid esters among the derivatives that were tested.

On the other hand, an additionally prepared free phenylboronic acid (**3dd**) that corresponded to the biologically active *meta*-substituted **3bd** showed no antibacterial or anti-HSV-1 activity, indicating that the presence of a cyclic boronic acid ester functionality is important for the expression of bioactivities of this series.

The application of new phenylboronic acid derivative-decorated lectin in order to form boronate ester linkages with a sugar moiety in glycoproteins has recently been reported. In the reported modification, a *meta*-acylamino-substituted phenylboronic acid with a size similar to that of the methylene linker is used as a functional part for carbohydrate recognition.[11]

Although further detailed investigation is required for elucidation of these biological phenomena together with the formation of reversible covalent bonds between these C_2-symmetrical molecules and 1,2-diol moieties in sugars, we consider that the biological activities of a few compounds obtained in this study arose from the carbohydrate recognition property of a cyclic phenylboronic acid ester functionality. We are investigating further modifications and conducting an SAR study in order to find new biologically active C_2-symmetrical leads as well as conducting additional calorimetric experiments on new active compounds. The results of modification and SAR studies including C_3-type geometric molecules of these related cyclic phenylboronic acid derivatives will be described in the following paper.

EXPERIMENTAL

IR spectra were measured by a Shimadzu FT/IR-8100 spectrometer. ^{1}H- and ^{13}C-NMR spectra were obtained by a JEOL JNM A-500 at 35 °C. Chemical shifts are expressed in δ ppm downfield from an internal tetramethylsilane (TMS) signal for ^{1}H-NMR and the carbon signal of the corresponding solvent [DMSO-d_6 (39.50 ppm)] for ^{13}C-NMR. The signal assignments were confirmed by ^{1}H-^{1}H two-dimensional (2D) correlation spectroscopy (COSY), ^{1}H-^{13}C heteronuclear multiple quantum coherence (HMQC), and ^{1}H-^{13}C heteronuclear multiple-bond connectivity (HMBC) spectra. High-resolution FAB-MS spectra [HRMS (FAB)] were obtained by a JEOL JMS-HX110 mass spectrometer. Some of the C_2-symmetrical compounds (**3aa**-**3ad**, **3ba**-**3bd** and **3ca**-**3cd**) listed in Table 1 were prepared by reactions of amino-substituted phenylboronic acid derivatives and diacid dichlorides using the reported procedure. Physical and spectroscopic data of these compounds were presented in our previous paper.[10]

Preparation of C_2-Symmetrical Cyclic Phenylboronic Acid Derivatives.

***N*^{1},*N*^{10}-Bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)decanediamide (3ae).** After cooling a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**1a**) (438.2 mg, 2.00 mmol) and CH_2Cl_2 (4.348 mL) at 4.0 °C with stirring under atmospheric conditions, Et_3N (415.9 μL, 3.00 mmol) and

sebacoyl chloride (**2e**) (213.5 μL, 1.00 mmol) were added. The resulting mixture was stirred at room temperature for 18 h and then water (ca. 100 mL) was added. The mixture was extracted with AcOEt (x3) and the combined organic extract was dried over Na_2SO_4. After filtration, the solvents were evaporated under reduced pressure, and then the obtained crude material was washed with CH_2Cl_2/*n*-hexane to afford the desired product (**3ae**) (540.9 mg, 89% yield) as a white solid. Mp 228-234 °C. IR (KBr) 3312 (NH), 1666 cm^{-1} (C=O); FAB-MS (positive) *m*/*z* 605 $(M+H)^+$. HRMS (FAB) Calcd for $C_{34}H_{51}B_2N_2O_6^+$: *m*/*z* 605.3928 $(M+H)^+$. Found: 605.3948; ^{1}H-NMR (DMSO-d_6) δ 1.28 (24H, s, C$\underline{H}_3$), 1.22-1.35 [8H, m, C(=O)-CH_2-CH_2-C$\underline{H}_2$-C$\underline{H}_2$-C$\underline{H}_2$-C$\underline{H}_2$-CH_2-CH_2-C(=O)], 1.52-1.63 [4H, m, C(=O)-CH_2-C$\underline{H}_2$-CH_2-CH_2-CH_2-CH_2-C$\underline{H}_2$-CH_2-C(=O)], 2.30 [4H, t, *J* = 7.5 Hz, C(=O)-C$\underline{H}_2$-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-C$\underline{H}_2$-C(=O)], 7.56-7.62 (8H, m, Ar), 9.91 (2H, s, N$\underline{H}$); ^{13}C-NMR (DMSO-d_6) δ 24.6 (C$\underline{H}_3$), 24.9 [C(=O)-CH_2-C$\underline{H}_2$-CH_2-CH_2], 28.5, 28.6 [C(=O)-CH_2-CH_2-C$\underline{H}_2$-CH_2 or C(=O)-CH_2-CH_2-CH_2-C$\underline{H}_2$], 36.4 [C(=O)-C$\underline{H}_2$-CH_2-CH_2-CH_2], 83.3 (B-O-C-C-O-B), 118.0 (Ar C-2, C-6), 135.1 (Ar C-3, C-5), 142.0 (Ar C-1), 171.4 (C=O). Anal. Calcd for $C_{34}H_{50}B_2N_2O_6 \cdot 0.25H_2O$: C, 67.07; H, 8.36; N, 4.60. Found: C, 67.12; H, 8.47; N, 4.61.

***N*^{1},*N*^{10}-Bis(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)decanediamide (3be).** A solution of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**1b**) (438.2 mg, 2.00 mmol) and CH_2Cl_2 (4.348 mL) was cooled to 4.0 °C, and then Et_3N (415.9 μL, 3.00 mmol) and sebacoyl chloride (**2e**) (213.5 μL, 1.00 mmol) were added to the resulting solution. The resulting mixture was stirred for 18 h at room temperature and then water (ca. 100 mL) was added. The obtained solution was extracted with AcOEt (x3) and the combined organic extract was dried over Na_2SO_4. After filtration, the solvents that were used were evaporated under reduced pressure. The obtained crude material was washed with CH_2Cl_2/*n*-hexane to give the desired product (**3be**) (512.1 mg, 85% yield) as a white solid. Mp 195-196 °C. IR (KBr) 3299 (NH), 1662 cm^{-1} (C=O); FAB-MS (positive) *m*/*z* 605 $(M+H)^+$. HRMS (FAB) Calcd for $C_{34}H_{51}B_2N_2O_6^+$: *m*/*z* 605.3928 $(M+H)^+$. Found 605.3928; ^{1}H-NMR (DMSO-d_6) δ 1.29 (24H, s, C$\underline{H}_3$), 1.20-1.38 [8H, m, C(=O)-CH_2-CH_2-C$\underline{H}_2$-C$\underline{H}_2$-C$\underline{H}_2$-C$\underline{H}_2$-CH_2-CH_2-C(=O)], 1.50-1.70 [4H, m, C(=O)-CH_2-C$\underline{H}_2$-CH_2-CH_2-CH_2-CH_2-C$\underline{H}_2$-CH_2-C(=O)], 2.28 [4H, t, *J* = 7.5 Hz, C(=O)-C$\underline{H}_2$-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-C$\underline{H}_2$-C(=O)], 7.28 (2H, dd, *J* = 7.6, 7.6 Hz, Ar H-5), 7.31-7.38 (2H, m, Ar H-4), 7.65-7.78 (2H, m, Ar H-6), 7.91 (2H, s, Ar H-2), 9.80 (2H, s, N$\underline{H}$); ^{13}C-NMR (DMSO-d_6) δ 24.6 (C$\underline{H}_3$), 25.0 [C(=O)-CH_2-C$\underline{H}_2$-CH_2-CH_2], 28.5, 28.6 [C(=O)-CH_2-CH_2-C$\underline{H}_2$-CH_2 or C(=O)-CH_2-CH_2-CH_2-C$\underline{H}_2$], 36.3 [C(=O)-C$\underline{H}_2$-CH_2-CH_2-CH_2], 83.5 (B-O-C-C-O-B), 121.9 (Ar C-6), 125.0 (Ar C-2), 128.1 (Ar C-5), 128.8 (Ar C-4), 138.8 (Ar C-1), 171.2 (C=O). Anal. Calcd for $C_{34}H_{50}B_2N_2O_6 \cdot 0.25H_2O$: C, 67.07; H, 8.36; N, 4.60. Found: C, 67.03; H, 8.35; N, 4.62.

***N*^{1},*N*^{10}-Bis(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)decanediamide (3ce).** After cooling a solution of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**1c**) (438.2 mg, 2.00 mmol) and

CH_2Cl_2 (4.348 mL) at 4.0 °C, Et_3N (415.9 μL, 3.00 mmol) and sebacoyl chloride (**2e**) (213.5 μL, 1.00 mmol) were added. The mixture was stirred at room temperature for 18 h and then water (ca. 100 mL) was added. The resulting mixture was extracted with AcOEt (x3) and the combined organic extract containing white solid material was filtered. The isolated material was washed with AcOEt to give the desired product (**3ce**) (355.1 mg, 59% yield) as a white solid. Mp 183-193 °C. IR (KBr) 3379 (NH), 1632 cm^{-1} (C=O); FAB-MS (positive) *m*/*z* 605 $(M+H)^+$. HRMS (FAB) Calcd for $C_{34}H_{51}B_2N_2O_6^+$: *m*/*z* 605.3928 $(M+H)^+$. Found: 605.3948; ^{1}H-NMR (DMSO-d_6) δ 1.16 (24H, s, C$\underline{H}_3$), 1.23-1.39 [8H, m, C(=O)-CH_2-CH_2-C$\underline{H}_2$-C$\underline{H}_2$-C$\underline{H}_2$-C$\underline{H}_2$-CH_2-CH_2-C(=O)], 1.60-1.70 [4H, m, C(=O)-CH_2-C$\underline{H}_2$-CH_2-CH_2-CH_2-CH_2-C$\underline{H}_2$-CH_2-C(=O)], 2.53 [4H, t, *J* = 6.6 Hz, C(=O)-C$\underline{H}_2$-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-C$\underline{H}_2$-C(=O)], 7.02 (2H, d, *J* = 8.4 Hz, Ar H-6), 7.13 (2H, dd, *J* = 7.2, 7.8 Hz, Ar H-4), 7.20-7.26 (2H, m, Ar H-5), 7.40 (2H, d, *J* = 7.8 Hz, Ar H-3), 11.82 (2H, s, N$\underline{H}$); ^{13}C-NMR (DMSO-d_6) δ 25.2 (C(=O)-CH_2-$\underline{C}H_2$-CH_2-CH_2), 26.6 ($\underline{C}H_3$), 28.7, 29.1 [C(=O)-CH_2-CH_2-$\underline{C}H_2$-CH_2 or C(=O)-CH_2-CH_2-CH_2-$\underline{C}H_2$], 80.0 (B-O-$\underline{C}$-$\underline{C}$-O-B), 116.1 (Ar C-6 in B-$\underline{C}_6H_4$-N), 125.8 (Ar C-4 in B-$\underline{C}_6H_4$-N), 128.0 (Ar C-5 in B-$\underline{C}_6H_4$-N), 133.1 (Ar C-3 in B-$\underline{C}_6H_4$-N), 138.6 (Ar C-1 in B-$\underline{C}_6H_4$-N), 172.9 ($\underline{C}$=O). Anal. Calcd for $C_{34}H_{50}B_2N_2O_6 \cdot 1.5H_2O$: C, 64.68; H, 8.46; N, 4.44. Found: C, 64.60; H, 8.19; N, 4.46.

((Octanedioylbis(azanediyl))bis(3,1-phenylene))diboronic acid (3dd). After cooling a solution of *meta*-aminophenylboronic acid (**1d**) (273.8 mg, 2.00 mmol) and CH_2Cl_2 (5.000 mL) at 4.0 °C with stirring under atmospheric conditions, Et_3N (554.5 μL, 4.00 mmol) and suberoyl chloride (**2d**) (178.9 μL, 1.00 mmol) were added.[12] The resulting solution was stirred for 1 h at room temperature and then water (ca. 100 mL) was added. The mixture was extracted with AcOEt (x3) and the combined organic extract was dried over Na_2SO_4. After filtration, the solvents were evaporated under reduced pressure, and the obtained crude material was washed with MeOH/CH_2Cl_2/*n*-hexane to afford the desired product (**3dd**) (142.6 mg, 35% yield) as a white solid. Mp 212-223 °C. IR (KBr) 3317 (NH), 1661 cm^{-1} (C=O); HRMS (FAB) (positive)[13] Calcd for $C_{26}H_{35}B_2N_2O_8^+$: *m*/*z* 525.2574 (**C**+H)$^+$. Found: 525.2596; ^{1}H-NMR (DMSO-d_6) δ 1.28-1.40 [4H, m, C(=O)-CH_2-CH_2-C$\underline{H}_2$-C$\underline{H}_2$-CH_2-CH_2-C(=O)], 1.54-1.66 [4H, m, C(=O)-CH_2-C$\underline{H}_2$-CH_2-CH_2-C$\underline{H}_2$-CH_2-C(=O)], 2.29 [4H, t, *J* = 7.3, Hz, C(=O)-C$\underline{H}_2$-CH_2-CH_2-CH_2-CH_2-C$\underline{H}_2$-C(=O)], 7.23 (2H, dd, *J* = 7.8, 7.8 Hz, Ar H-5), 7.44 (2H, d, *J* = 7.8 Hz, Ar H-4), 7.70 (2H, d, *J* = 7.8 Hz, Ar H-6), 7.82 (2H, s, Ar H-2), 7.91 [4H, s, B(O$\underline{H}$)$_2$], 9.72 (2H, s, N$\underline{H}$); ^{13}C-NMR (DMSO-d_6) δ 25.0 [C(=O)-CH_2-$\underline{C}H_2$-CH_2], 28.4 [C(=O)-CH_2-CH_2-$\underline{C}H_2$], 36.3 [C(=O)-$\underline{C}H_2$-CH_2-CH_2], 121.1 (Ar C-6), 125.1 (Ar C-2), 127.4 (Ar C-5), 128.7 (Ar C-4), 138.4 (Ar C-1), 171.0 ($\underline{C}$=O).

Assays for Antibacterial Activity

We used *Staphylococcus aureus* ATCC6538P and *Escherichia coli* NBRC14237 (NIHJ) (Gram-positive and Gram-negative bacteria, respectively) as target organisms. Synthesized compounds were dissolved in

dimethyl sulfoxide (DMSO) or dimethylformamide (DMF) to a concentration of 1.280 μg/mL. The minimum inhibitory concentration (MIC) of a standard strain was measured by the authentic microdilution method to monitor bacterial growth turbidity in Muller-Hinton broth according to the Japanese Society of Chemotherapy.[14,15] The values of MIC are expressed as molar concentrations (mM) for discussion of structure-activity relations.

Antiviral Activity Assay and Cytotoxicity

The anti-HSV-1 activities (EC_{50}) of the synthesized boronic acid derivatives were measured by using a plaque reduction assay,[16] and their cytotoxicity against Vero cells (IC_{50}) was also evaluated.

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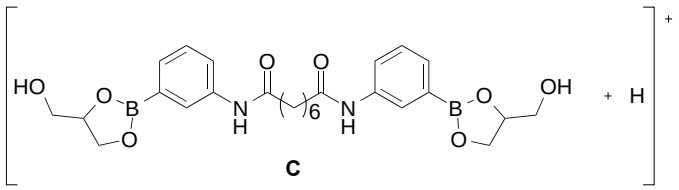
13. In a high-resolution positive FAB-MS spectrum of C_2-symmetrical phenylboronic acid (**3dd**), the observed molecular ion peak had *m*/*z* of 525.2596, and this ion may be directly derived from the reaction of compound **3dd** with two molar amounts of the matrix used (1,2,3-propanetriol). In negative FAB-MS, we also observed the negative molecular ion (*m*/*z* of 523.2426) of compound **3dd** combined with two molar amounts of the matrix (1,2,3-propanetriol). The appearance of these positive and negative characteristic ions in FAB-MS may be due to the formation of 5-membered dioxaborborane **C** by reaction of two boronic acid functionalities in molecule **3dd** with 1,2-diol functionality of glycerin. Both values of elemental analysis of these positive and negative ions were identical with the composition derived from represented phenylboronic acid cyclic ester derivative **C** shown below.



C

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