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## NOVEL TRIVALENT $C_3$ -SYMMETRICAL PHENYLBORONIC ACID PINACOL ESTERS AND THEIR BIOLOGICAL EVALUATION

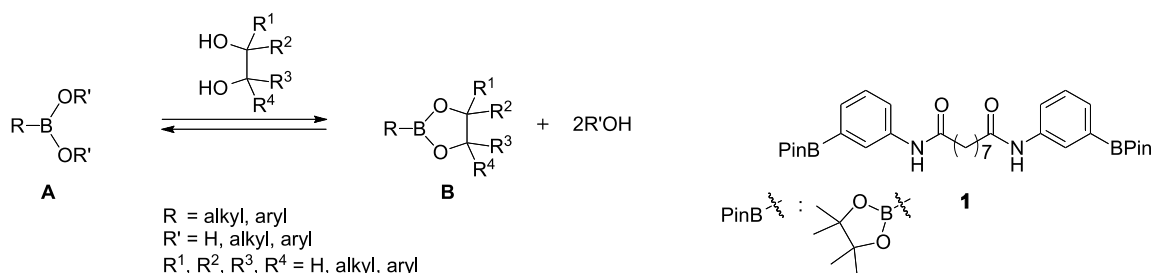
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**Abstract** – We report the preparation of newly designed trivalent  $C_3$ -symmetrical cyclic phenylboronic acid derivatives constructed on a symmetrical benzene or a cyclohexane ring. The synthesis of these  $C_3$ -symmetrical molecules **4** was accomplished by an amide bond formation reaction using amino-substituted phenylboronic acid pinacol esters **2** and  $C_3$ -symmetrical benzene-1,3,5-tricarboxylic acid trichloride **3a** or cyclohexane-1,3,5-tricarboxylic acid trichloride **3b** in the presence of Et<sub>3</sub>N. We confirmed that this procedure is conventionally applicable to the preparation of targeted  $C_3$ -symmetrical cyclic boronic acid derivatives **4** in good to excellent yields. We also report the results of biological evaluation of the prepared compounds.

Many host receptors that consist of homo-oligometric units (homo-multiligands) often construct symmetric macromolecule architectures such as  $C_2$ - or  $C_3$ -symmetrical geometry receptor systems. Molecular recognition of two-fold ( $C_2$ ) or three-fold ( $C_3$ ) geometric symmetrical macromolecules is one of the common features in several important biological processes.<sup>1,2</sup> With reference to the molecular symmetry, small oligovalent molecules having  $C_2$ - or  $C_3$ -symmetrical geometry have frequently appeared in various biologically active substances.<sup>2-4</sup> An oligovalent molecule is generally expected to show enhanced biological potential compared to that of the corresponding monovalent molecule.<sup>4</sup> On the other hand, regarding lectin-like carbohydrate recognition molecules, much attention has recently been paid to the design of synthetic receptors for carbohydrates.<sup>5</sup> We have been interested in small molecules that

interfere with such carbohydrate recognition stages in order to find new bioactive leads.<sup>6-8</sup> Regarding carbohydrate (sugar chain) recognition molecules, we have been particularly interested in boronic acid derivatives because many boronic acid functionalities (**A**) have a property to react with various 1,2-diol functionalities included in carbohydrates and generate cyclic derivatives (**B**) formed with reversible covalent bonds (see Figure 1).<sup>9,10</sup> From this point of view, we have recently synthesized a few  $C_2$ -symmetrical cyclic phenylboronic acid esters as new targeted bivalent molecules.<sup>11,12</sup> Among previously targeted  $C_2$ -symmetrical bivalent phenylboronic acid ester derivatives in this series, we have found an interesting bivalent seed molecule **1** (Figure 1) possessing significant antibacterial and anti-herpes simplex virus type 1 (anti-HSV-1) activities. The identified bivalent  $C_2$ -symmetrical molecule **1** has a C7-methylene linker and two *meta*-oriented boronic acid pinacol ester functionalities in the molecule. Compound **1** showed a high level of antibacterial activity (MIC=27.1  $\mu$ M) against a Gram-positive strain [*Staphylococcus aureus* (*S. aureus*)] and anti-HSV-1 activity [50% effective concentration (EC<sub>50</sub>)=8.0  $\mu$ M].<sup>11</sup>



**Figure 1**

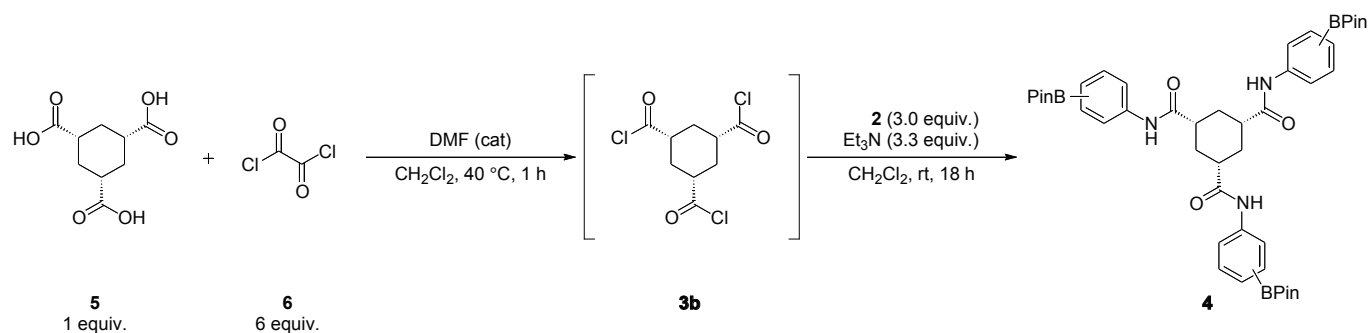
As an extension of this study, we carried out further investigations of these symmetrical classes of compounds. In this paper, we report the synthesis of new trivalent  $C_3$ -symmetrical phenylboronic acid derivatives incorporating a benzene or cyclohexane ring as a symmetrical template in the molecules and we report results of biological evaluations of the obtained  $C_3$ -symmetrical phenylboronic acid derivatives. The results for synthesis of new  $C_3$ -symmetrical cyclic boronic acid derivatives constructed on a benzene ring or a cyclohexane ring having three amide bonds are summarized in Tables 1 and 2. The synthesis of these target trivalent  $C_3$ -symmetrical molecules **4aa~4ca** constructed on a benzene ring was accomplished by an amide bond formation reaction using amino-substituted phenylboronic acid pinacol esters **2** and benzene-1,3,5-tricarboxylic acid trichloride **3a** in the presence of a base such as Et<sub>3</sub>N. The preparation and physical and spectroscopic data of compounds **4aa~4ca** have been reported in detail as a separated paper.<sup>13</sup> New  $C_3$ -symmetrical compounds **4ab** and **4bb** constructed on a cyclohexane ring were also prepared by a procedure similar to that for compounds **4aa~4ca** with cyclohexane-1,3,5-tricarboxylic acid trichloride in good yields (see EXPERIMENTAL). The structures of targeted trivalent  $C_3$ -symmetrical products **4ab** and **4bb** were confirmed by both spectroscopic data and elemental analysis.<sup>14,15</sup> The

**Table 1.** Preparation of Trivalent  $C_3$ -Symmetrical Phenylboronic Acid Pinacol Esters

Entry	Product <b>4</b>	Yield (%) <sup>a</sup>	MIC [ $\mu\text{M}$ ( $\mu\text{g/mL}$ )]		EC <sub>50</sub> ( $\mu\text{M}$ ) Anti-HSV-1 activity	CC <sub>50</sub> ( $\mu\text{M}$ ) Cytotoxic activity
			<i>S. aureus</i>	<i>E. coli</i>		
1		<b>4aa</b> 91 <sup>b</sup>	>157.4 (>128)	157.4 (128)	>100	101.0
2		<b>4ba</b> 81 <sup>b</sup>	157.4 (128)	>157.4 (>128)	>100	>200
3		<b>4ca</b> 36 <sup>b</sup> (76 <sup>b,c</sup> )	157.4 (128)	>157.4 (>128)	>100	>200

<sup>a</sup> Isolated yield. <sup>b</sup> Data were taken from ref. 13. <sup>c</sup> Estimated crude yield.

$C_3$ -symmetrical structures of synthesized boronic acid derivatives **4ab** and **4bb** were confirmed by <sup>13</sup>C-NMR spectroscopic analysis. All  $C_3$ -symmetrical cyclic phenylboronic acid pinacol esters **4** showed magnetically equivalent carbon signals assignable to a third of the molecules that indicated  $C_3$ -symmetrical molecular structures in solution, except for the carbon in a phenyl ring connected to a substituent (boronic acid esters).<sup>14</sup> The structures of the  $C_3$ -symmetrical phenylboronic acid derivatives **4** and the results of evaluation of biological activities (antibacterial and anti-HSV-1 activities) are summarized in Tables 1 and 2. All  $C_3$ -symmetrical molecules **4aa~4ca** constructed on a benzene ring were inactive by assays for antibacterial activities [against *S. aureus* and *Escherichia coli* (*E. coli*)] and anti-HSV-1 activities. Only *para*-substituted compound **4aa** showed a low level of cytotoxic activity [50%

**Table 2.** Preparation of Trivalent  $C_3$ -Symmetrical Phenylboronic Acid Pinacol Esters<sup>15</sup>

Entry	Product <b>4</b>	Yield (%) <sup>a</sup>	MIC [ $\mu\text{M}$ ( $\mu\text{g/mL}$ )]		EC <sub>50</sub> ( $\mu\text{M}$ ) Anti-HSV-1 activity	CC <sub>50</sub> ( $\mu\text{M}$ ) Cytotoxic activity
			<i>S. aureus</i>	<i>E. coli</i>		
1		<b>4ab</b> 46	156.2 (128)	>156.2 (>128)	>100	>200
2		<b>4bb</b> 77	156.2 (128)	>156.2 (>128)	65.2	>200

<sup>a</sup> Isolated yield.

cytotoxic concentration (CC<sub>50</sub>)=101.0  $\mu\text{M}$ ].

On the other hand, among the  $C_3$ -symmetrical compounds constructed on a cyclohexane ring, *meta*-substituted compound **4bb** showed a moderate level of anti-HSV-1 activity (EC<sub>50</sub>=65.2  $\mu\text{M}$ ) with a low level of cytotoxic activity (CC<sub>50</sub>=>200  $\mu\text{M}$ ). The results of biological evaluation of previously prepared compounds **1** with a flexible methylene linker indicated that the length of a linker is important for the expression of biological activities.<sup>11</sup> Regarding the  $C_3$ -type molecules described in this paper, a saturated flexible cyclohexane core (compound **4bb**) seems to be a preferable structure rather than a rigid unsaturated benzene core for the expression of anti-HSV-1 activity. Trivalent  $C_3$ -symmetrical phenylboronic acid pinacol esters **4bb** in this study also had an *meta*-substituted cyclic boronic acid ester group on the phenyl rings. Regarding  $C_3$ -type molecules in this study, it is noteworthy that *meta*-substituted cyclic boronic acid ester (**4bb**) was again biologically active compound and that compound **4bb** with a flexible cyclohexane ring as the  $C_3$ -template showed remarkable anti-HSV-1 activity (EC<sub>50</sub>=65.2  $\mu\text{M}$ ) compared to that of compound **4ba** with a rigid benzene ring as the  $C_3$ -template.

On the basis of the structural information obtained by the above-described modifications for biological activities in the  $C_2$ - and  $C_3$ -symmetrical phenylboronic acid ester series together with recent information on other receptor-type molecule series, further molecular modifications to other new types of molecules are now under investigation in order to develop new promising bioactive leads.

## EXPERIMENTAL

IR spectra were measured on a Shimadzu FT/IR-8100 spectrometer.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra were obtained on a JEOL JNM ECZ600R at 25 °C. Chemical shifts are expressed in  $\delta$  ppm relative to the solvent peaks for  $^1\text{H}$ -NMR [dimethyl sulfoxide- $d_6$  (DMSO- $d_6$ ) (2.50 ppm)] and  $^{13}\text{C}$ -NMR [DMSO- $d_6$  (39.50 ppm)]. The signal assignments were confirmed by  $^1\text{H}$ - $^1\text{H}$  two-dimensional (2D) correlation spectroscopy (COSY),  $^1\text{H}$ - $^{13}\text{C}$  heteronuclear multiple-quantum coherence (HMQC), and  $^1\text{H}$ - $^{13}\text{C}$  heteronuclear multiple-bond connectivity (HMBC) spectra. High-resolution FAB-MS spectra [HRMS (FAB)] were obtained by a JEOL JMS-700T mass spectrometer.

### Preparation of $C_3$ -Symmetrical Cyclic Phenylboronic Acid Pinacol Esters.

The preparation of and spectroscopic data for the three compounds **4aa~4ca** in Table 1 have already been reported.<sup>13</sup> New  $C_3$ -symmetrical compounds **4ab** and **4bb** constructed on a cyclohexane ring were also prepared by a procedure similar to that for compounds **4aa~4ca** with (1s,3s,5s)-cyclohexane-1,3,5-tricarboxylic acid **5** in good yields (46-77%).

**(1s,3s,5s)- $N^1,N^3,N^5$ -Tris(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclohexane-1,3,5-tricarboxamide (4ab).** To a solution of (1s,3s,5s)-cyclohexane-1,3,5-tricarboxylic acid (**5**) (216.2 mg, 1.00 mmol) in  $\text{CH}_2\text{Cl}_2$  (6.000 mL) were added oxalyl chloride (**6**) (514.1  $\mu\text{L}$ , 6.00 mmol) and DMF (2 drops). The resulting mixture was stirred at reflux for 1 h. After evaporation,  $\text{CH}_2\text{Cl}_2$  (16.00 mL), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**2a**) (657.3 mg, 3.00 mmol), and  $\text{Et}_3\text{N}$  (457.5  $\mu\text{L}$ , 3.30 mmol) were successively added to the mixture. The resulting solution was stirred for 18 h at room temperature and then water (ca. 100 mL) was added. The mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (x3) and the combined organic extract was dried over  $\text{Na}_2\text{SO}_4$ . After filtration, the solvents that were used were evaporated under reduced pressure. The obtained crude material was washed with  $\text{CH}_2\text{Cl}_2/n$ -hexane to give the desired product (**4ab**) (377.1 mg, 46% yield) as a white solid. Mp >250 °C; IR (KBr) 3450 (NH), 1655  $\text{cm}^{-1}$  (C=O); FAB-MS (positive)  $m/z$  820 ( $\text{M}+\text{H}$ )<sup>+</sup>. HRMS (FAB) Calcd for  $\text{C}_{45}\text{H}_{61}\text{B}_3\text{N}_3\text{O}_9$ <sup>+</sup>:  $m/z$  820.4681 ( $\text{M}+\text{H}$ )<sup>+</sup>. Found: 820.4696;  $^1\text{H}$ -NMR (DMSO- $d_6$ )  $\delta$  1.27 (36H, s,  $\text{CH}_3$ ), 1.66 [3H, dd,  $J = 13.2, 25.8$  Hz, C(=O)-CH- $\text{CH}_2$ ], 1.97-2.05 [3H, m, C(=O)-CH- $\text{CH}_2$ ], 2.51-2.60 [3H, m, C(=O)- $\text{CH}-\text{CH}_2$ ], 7.60 (6H, d,  $J = 8.4$  Hz, Ar H-3, H-5 in B- $\text{C}_6\text{H}_4\text{-N}$ ), 7.63 (6H, d,  $J = 8.4$  Hz, Ar H-2, H-6 in B- $\text{C}_6\text{H}_4\text{-N}$ ), 10.01 (3H, s, NH);  $^{13}\text{C}$ -NMR (DMSO- $d_6$ )  $\delta$  24.7 ( $\text{CH}_3$ ), 31.1 [C(=O)-CH- $\text{CH}_2$ ], 43.5 [C(=O)- $\text{CH}-\text{CH}_2$ ], 83.4 (B-O- $\text{C}-\text{O}-\text{B}$ ), 118.3 (Ar C-2, C-6 in B- $\text{C}_6\text{H}_4\text{-N}$ ), 135.2 (Ar C-3, C-5 in B- $\text{C}_6\text{H}_4\text{-N}$ ), 142.0 (Ar C-1 in

B-C<sub>6</sub>H<sub>4</sub>-N), 173.2 (C=O). Anal. Calcd for C<sub>45</sub>H<sub>60</sub>B<sub>3</sub>N<sub>3</sub>O<sub>9</sub>•1.7H<sub>2</sub>O: C, 63.58; H, 7.52; N, 4.94. Found: C, 63.55; H, 7.25; N, 4.85.

**(1s,3s,5s)-N<sup>1</sup>,N<sup>3</sup>,N<sup>5</sup>-Tris(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclohexane-1,3,5-tricarboxamide (4bb).** To a solution of (1s,3s,5s)-cyclohexane-1,3,5-tricarboxylic acid (**5**) (216.2 mg, 1.00 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6.000 mL) were added oxalyl chloride (**6**) (514.1 μL, 6.00 mmol) and DMF (2 drops). The resulting mixture was stirred at reflux for 1 h. After evaporation, CH<sub>2</sub>Cl<sub>2</sub> (16.00 mL), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**2b**) (657.3 mg, 3.00 mmol), and Et<sub>3</sub>N (457.5 μL, 3.30 mmol) were successively added to the mixture. The resulting solution was stirred for 18 h at room temperature and then water (ca. 100 mL) was added. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (x3) and the combined organic extract was dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, the solvents that were used were evaporated under reduced pressure. The obtained crude material was washed with CH<sub>2</sub>Cl<sub>2</sub>/*n*-hexane to give the desired product (**4bb**) (629.2 mg, 77% yield) as a white solid.

The structure of the product was easily established by spectroscopic data shown below.

Mp >250 °C; IR (KBr) 3444 (NH), 1658 cm<sup>-1</sup> (C=O); FAB-MS (positive) *m/z* 820 (M+H)<sup>+</sup>. HRMS (FAB) Calcd for C<sub>45</sub>H<sub>61</sub>B<sub>3</sub>N<sub>3</sub>O<sub>9</sub><sup>+</sup>: *m/z* 820.4681 (M+H)<sup>+</sup>. Found: 820.4682; <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ 1.27 (36H, s, CH<sub>3</sub>), 1.65 [3H, dd, *J* = 12.6, 25.8 Hz, C(=O)-CH-CH<sub>2</sub>], 1.91-2.03 [3H, m, C(=O)-CH-CH<sub>2</sub>], 2.43-2.56 [3H, m, C(=O)-CH-CH<sub>2</sub>], 7.26-7.35 (6H, m, Ar H-4, H-5 in B-C<sub>6</sub>H<sub>4</sub>-N), 7.75 (3H, d, *J* = 6.6 Hz, Ar H-6 in B-C<sub>6</sub>H<sub>4</sub>-N), 7.91 (3H, s, Ar H-2 in B-C<sub>6</sub>H<sub>4</sub>-N), 9.87 (3H, s, NH); <sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>) δ 24.7 (CH<sub>3</sub>), 31.2 [C(=O)-CH-CH<sub>2</sub>], 43.6 [C(=O)-CH-CH<sub>2</sub>], 83.6 (B-O-C-C-O-B), 122.3 (Ar C-6 in B-C<sub>6</sub>H<sub>4</sub>-N), 125.4 (Ar C-2 in B-C<sub>6</sub>H<sub>4</sub>-N), 128.3 (Ar C-5 in B-C<sub>6</sub>H<sub>4</sub>-N), 129.1 (Ar C-4 in B-C<sub>6</sub>H<sub>4</sub>-N), 138.8 (Ar C-1 in B-C<sub>6</sub>H<sub>4</sub>-N), 173.0 (C=O).

### Assays for Antibacterial Activity

We used *S. aureus* ATCC6538P and *E. coli* NBRC14237 (NIHJ) (Gram-positive and Gram-negative bacteria, respectively) as target organisms. Synthesized compounds were dissolved in DMSO or dimethylformamide (DMF) to a concentration of 1.280 μg/mL. The MIC of a standard strain was measured by the authentic microdilution method to monitor bacterial growth turbidity in Müller-Hinton broth according to the Japanese Society of Chemotherapy.<sup>17,18</sup> The values of MIC are expressed as molar concentrations (μM) for discussion of structure-activity relations.

### Antiviral Activity Assay and Cytotoxicity

The anti-HSV-1 activities (EC<sub>50</sub>) of the synthesized symmetrical cyclic phenylboronic acid ester derivatives were measured by using a plaque reduction assay,<sup>19</sup> and their cytotoxicity against Vero cells (CC<sub>50</sub>) was also evaluated.

## ACKNOWLEDGEMENTS

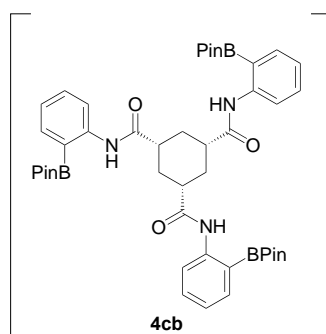
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14. In <sup>13</sup>C-NMR spectra of compounds **4**, we consider that the difficulty in observing the corresponding signal of this quaternary aromatic carbon linked with a boronic acid ester functionality is attributable

to the quadrupolar relaxation of  $^{11}\text{B}$ .<sup>16</sup>

15. In the reaction in which *ortho*-amino-substituted phenylboronic acid pinacol ester was used, the target *ortho*-substituted  $C_3$ -type compound **4cb** could not be isolated and the reaction provided a complex mixture including a few unknown compounds. Our attempts to isolate the target  $C_3$ -type *ortho*-substituted **4cb** were unsuccessful. However, the observation of a product showing an amide absorption [3444 (NH) and 1633  $\text{cm}^{-1}$  (C=O)] and an ion peak [ $m/z$  820 ( $\text{M}+\text{H}^+$ )] indicate formation of the  $C_3$ -type target compound **4cb**.



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