HETEROCYCLES, Vol. 92, No. 5, 2016, pp. 925 - 935. © 2016 The Japan Institute of Heterocyclic Chemistry
Received, 25th January, 2016, Accepted, 10th March, 2016, Published online, 15th March, 2016
DOI: 10.3987/COM-16-13418

NOVEL TWIN-DRUG TYPE C_2-SYMMETRICAL PHENYLBORONIC ACID PINACOL ESTERS

Makoto Furutachi,[a] Ayumi Ejima,[a] Reika Tsuru,[a] Saho Goto,[a] Toshiaki Gondo,[a] Kenta Ako,[a] Saya Fujii,[a] Arisa Okumura,[a] Ayumi Tozuka,[a] Kazumi Yokomizo,[b] Jian-Rong Zhou,[b] Hiroshi Inao,[b] Yutaro Ono,[b] Nobuhiro Kashige,[a] Fumio Miake,[a] and Kunihiro Sumoto[a,*]

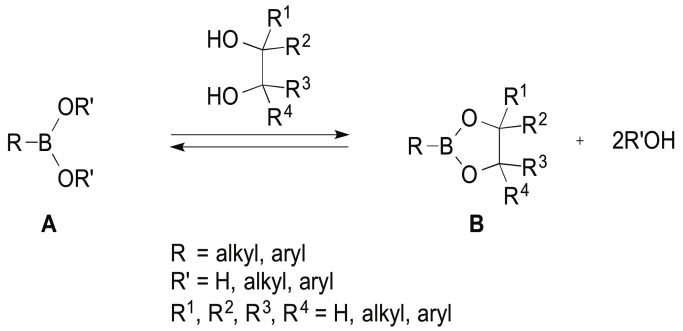
[a]Faculty of Pharmaceutical Sciences, Fukuoka University, 8-19-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan, [b]Faculty of Pharmaceutical Sciences, Sojo University, 4-22-1 Ikeda, Nishi-ku, Kumamoto 860-0082, Japan; E-mail: kunihiro@adm.fukuoka-u.ac.jp

Abstract – We here report the preparation of newly designed bivalent twin-drug type C_2-symmetrical cyclic phenylboronic acid derivatives. The synthesis of these C_2-symmetrical mid-size molecules **3** was accomplished by an amide bond formation reaction using amino-substituted phenylboronic acid pinacol esters **1** and dicarboxylic acid dichlorides **2** in the presence of Et_3N. We confirmed that this procedure is conventionally applicable to the preparation of various C_2-symmetrical cyclic boronic acid derivatives **3** in good to excellent yields.

The design of C_2-symmetrical bivalent molecules in the search for bioactive compounds has attracted much attention because of the promising clinical or pharmacological value in treatment for many types of disease.[1,2] 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.[3] A bivalent molecule is generally expected to show enhanced affinity (or biological potential) compared to that of the corresponding monovalent molecule. Therefore, many scientists studying bioactive molecules have an interest in developing such new symmetrical bivalent molecules.[4]

On the other hand, regarding lectin-like molecules for recognition of saccharides (sugar chains), much attention has been paid to the design of synthetic receptors and detectors for carbohydrates.[5] We have been interested in molecules that interfere with such carbohydrate recognition stages in order to find new bioactive leads.[6-8] In terms of the chemical properties of functional groups, we have been particularly

interested in boronic acids and related derivatives because many boronic acid derivatives (**A**) have a property to react with various 1,2-diol functionalities such as sugars and generate cyclic derivatives (**B**) formed with reversible covalent bonds (see Scheme 1).[9]



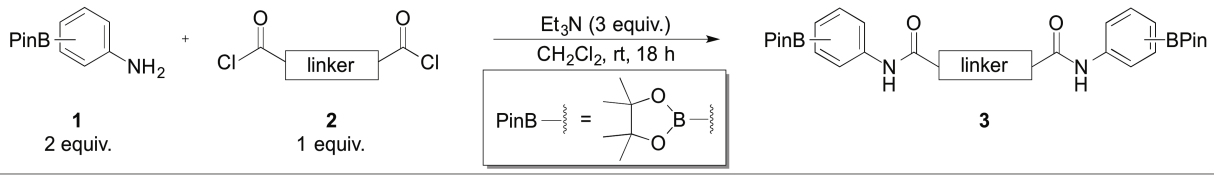
Scheme 1

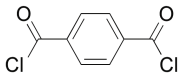
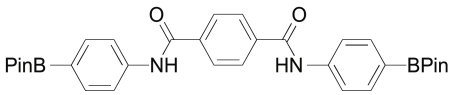
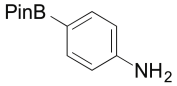
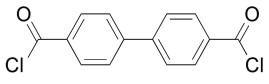
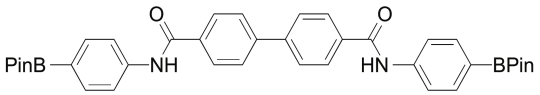
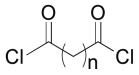
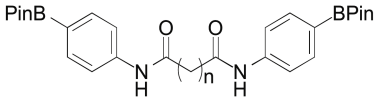
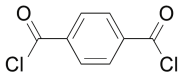
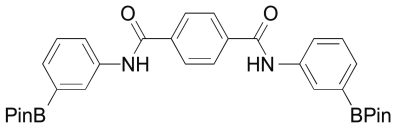
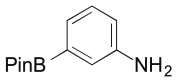
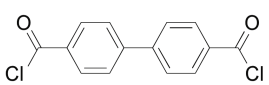
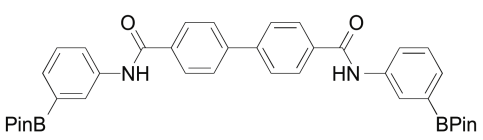
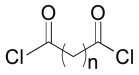
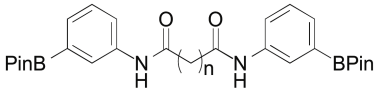
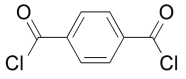
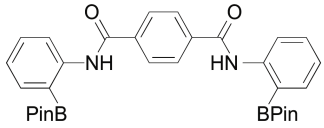
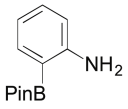
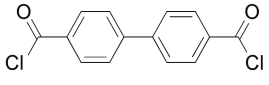
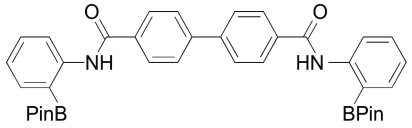
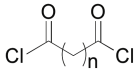
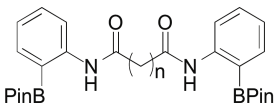
We have therefore incorporated such characteristic cyclic boronic acid ester functional groups in newly targeted bivalent C_2-symmetrical molecules.[10] In the field of peptide biomedicine, much attention is being paid to interesting substances known as middle-size molecules (mid-size molecules) having molecular weights of over ca. 500. New bivalent C_2-symmetrical derivatives of targeted phenylboronic acid pinacol esters have considerably large molecular weights over ca. 550, however, the target C_2-symmetrical mid-size molecules (**3**) belong to a new class of non-peptide compounds. Mid-size molecules that show lectin-like carbohydrate recognition properties might have interesting functions as new ligands or drug candidates. Considering the formation of strong drug-host interaction for host sugar recognition by multivalent molecules, attempts to synthesize such non-peptide mid-size molecules are thought to be valid in the search for new bioactive leads.

In this article, we describe the preparation of newly designed bivalent twin-drug type C_2-symmetrical cyclic phenylboronic acid pinacol esters.

The results for synthesis of twin-drug type C_2-symmetrical cyclic boronic acid pinacol esters having a linker consisting of two amide bonds are summarized in Table 1. The synthesis of these target bivalent symmetrical molecules was accomplished by a primitive amide bond formation reaction using amino-substituted phenylboronic acid pinacol esters **1** and dicarboxylic acid dichlorides **2a**~**2d** in the presence of a base such as Et_3N.[11] In entries 1~4, 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **1a** that has a *para*-amino group on cyclic phenylboronic acid pinacol ester was employed for the preparation of targeted symmetrical molecules **3aa**~**3ad**. Thus, terephthaloyl chloride **2a** easily reacted with 2 equivalents of phenylboronic acid pinacol ester **1a** in the presence of Et_3N (3 equivalents) in CH_2Cl_2 at room temperature to give the targeted twin-drug type C_2-symmetrical cyclic boronic acid pinacol ester **3aa** in 47% yield (Entry 1). We further carried out the preparation of some C_2-symmetrical

Table 1. Preparation of Twin-drug Type C_2-Symmetrical Phenylboronic Acid Pinacol Esters



Entry	Compound **1**	Dicarboxylic Acid Dichloride **2**			Product **3**			Yield (%)[a]
1				**2a**			**3aa**	47
2	 **1a** *para*			**2b**			**3ab**	88
3			n = 4	**2c**		n = 4	**3ac**	76
4			6	**2d**		6	**3ad**	60
5				**2a**			**3ba**	98
6	 **1b** *meta*			**2b**			**3bb**	51
7			n = 4	**2c**		n = 4	**3bc**	82
8			6	**2d**		6	**3bd**	98
9				**2a**			**3ca**	90
10	 **1c** *ortho*			**2b**			**3cb**	55
11			n = 4	**2c**		n = 4	**3cc**	43
12			6	**2d**		6	**3cd**	68

[a] Isolated yield.

analogues (see Entries 2~4), the results of which are shown in Table 1. Most of the targeted C_2-symmetrical boronic acid ester derivatives were obtained in good to excellent yields (60~88%) (see Entries 2~4). We confirmed that this synthetic procedure is conventionally applicable to the preparation of twin-drug type C_2-symmetrical cyclic boronic acid pinacol esters **3**.

Regarding the reactions of a *meta*-amino-substituted phenylboronic acid derivative, i.e., an aniline derivative **1b**, the use of terephthaloyl chloride **2a** resulted in the formation of the desired *meta*-oriented twin-drug type C_2-symmetrical cyclic boronic acid pinacol ester **3ba** in excellent yield (98%) (see Entry 5 shown in Table 1). In other trials for the target molecules **3bb**~**3bd**, the reactions of compound **1b** with

dicarboxylic acid dichlorides **2b**~**2d** also gave good to excellent results (51~98% yields) (see Entries 6~8). Our protocol was further extended to the reactions of *ortho*-amino-substituted phenylboronic acid pinacol ester **1c** with dicarboxylic acid dichlorides **2a**~**2d**. *Ortho*-amino-substituted twin-drug type C_2-symmetrical boronic acid pinacol esters **3ca**~**3cd** were also obtained in moderate to excellent yields (43~90%) (see Entries 9~12 in Table 1). The structures of these twin-drug type symmetrical products were confirmed by both spectroscopic data and elemental analysis.[12] IR (KBr) spectra of cyclic phenylboronic acid pinacol esters **3** showed typical absorption bands at 1631~1681 cm^{-1} and 3266~3382 cm^{-1} attributable to the amide C=O and NH groups, respectively. In all ^{1}H-NMR spectra, four methyl group protons on a phenylboronic acid pinacol ester ring were observed at δ 1.17~1.44 ppm as a magnetically equivalent sharp singlet, and NH protons of two amide groups at 9.80~11.70 ppm were also observed as a singlet-like signal. Other signals for aromatic protons in the linker moiety were also in good agreement with the represented structures **3** shown in Table 1 (see EXPERIMENTAL for detail). The C_2-symmetrical structures of synthesized boronic acid derivatives were confirmed by ^{13}C-NMR spectroscopic analysis. All twin-drug type cyclic phenylboronic acid pinacol esters **3** showed magnetically equivalent carbon signals assignable to half of the molecules that indicated C_2-symmetrical molecular structures in solution, except for the carbon in a phenyl ring connected to a substituent (boronic acid esters). We consider that this characteristic behavior (difficulty in observing the corresponding signal over the background noise)[13] of this quaternary aromatic carbon linked with boronic acid functionality is attributable to the quadrupolar relaxation of ^{11}B.[14] The evidence obtained from FAB-MS spectroscopic (molecular ion) measurement and elemental analysis is consistent with the above assumption of the characteristic ^{13}C-NMR behavior (see EXPERIMENTAL for details).

In this article, we described the preparation of novel C_2-symmetrical bivalent cyclic boronic acid pinacol esters **3**. All of the synthesized C_2-symmetrical boronic acid derivatives are now under biological evaluation. The results of evaluation of biological activities (antibacterial and antiviral activities) and details of a structure-activity relationship study will be described separately.

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 [$CDCl_3$ (77.00 ppm), DMSO-d_6 (39.50 ppm), and DMF-d_7 (163.15 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.

Preparation of C_2-Symmetrical Cyclic Phenylboronic Acid Pinacol Esters.

***N*^{1},*N*^{4}-Bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)terephthalamide (3aa).** 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 terephthaloyl chloride (**2a**) (203.0 mg, 1.00 mmol) were added. The resulting solution was stirred for 18 h at room temperature and then water (ca. 100 mL) was added. The mixture was extracted with AcOEt (x3) and the combined organic extract containing a white solid material was filtered. The obtained solid material was washed with AcOEt to give the desired product (**3aa**) (264.7 mg, 47% yield) as a white solid. The structure of the product was easily established by spectroscopic data shown below.

Mp >250 °C; IR (KBr) 3266 (NH), 1652 cm^{-1} (C=O); FAB-MS (positive) *m*/*z* 569 $(M+H)^+$; ^{1}H-NMR (DMSO-d_6) δ 1.30 (24H, s, C$\underline{H}_3$), 7.68 (4H, d, J = 8.7 Hz, Ar H-3, H-5 in B-C$_6\underline{H}_4$-N), 7.84 (4H, d, J = 8.7 Hz, Ar H-2, H-6 in B-C$_6\underline{H}_4$-N), 8.10 [4H, s, C(=O)-C$_6\underline{H}_4$-C(=O)], 10.50 (2H, s, N$\underline{H}$); ^{13}C-NMR (DMSO-d_6) δ 24.6 (C$\underline{H}_3$), 83.4 (B-O-$\underline{C}$-$\underline{C}$-O-B), 119.4 (Ar C-2, C-6 in B-C$_6\underline{H}_4$-N), 127.7 [Ar C-2, C-6 in C(=O)-C$_6\underline{H}_4$-C(=O)], 135.0 (Ar C-3, C-5 in B-C$_6\underline{H}_4$-N), 137.3 [Ar C-1 in C(=O)-$\underline{C}_6$H$_4$-C(=O)], 141.8 (Ar C-1 in B-$\underline{C}_6$H$_4$-N), 164.9 ($\underline{C}$=O). HRMS (FAB) Calcd for $C_{32}H_{39}B_2N_2O_6^+$: *m*/*z* 569.2989 $(M+H)^+$. Found: 569.2997.

***N*^{4},*N*$^{4'}$-Bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-[1,1'-biphenyl]-4,4'-dicarboxamide (3ab).** 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 4,4'-biphenyldicarbonyl chloride (**2b**) (279.1 mg, 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 (**3ab**) (567.1 mg, 88% yield) as a white solid. Mp >250 °C; IR (KBr) 3318 (NH), 1654 cm^{-1} (C=O); FAB-MS (positive) *m*/*z* 645 $(M+H)^+$. HRMS (FAB) Calcd for $C_{38}H_{43}B_2N_2O_6^+$: *m*/*z* 645.3302 $(M+H)^+$. Found: 645.3324; ^{1}H-NMR (DMSO-d_6) δ 1.30 (24H, s, C$\underline{H}_3$), 7.68 (4H, d, J = 8.7 Hz, Ar H-3, H-5 in B-C$_6\underline{H}_4$-N), 7.85 (4H, d, J = 8.7 Hz, Ar H-2, H-6 in B-C$_6\underline{H}_4$-N), 7.94 [4H, d, J = 8.4 Hz, Ar H-2, H-6 in C(=O)-C$_6\underline{H}_4$-C$_6\underline{H}_4$-C(=O)], 8.11 [4H, d, J = 8.4 Hz, Ar H-3, H-5 in C(=O)-C$_6\underline{H}_4$-C$_6\underline{H}_4$-C(=O)], 10.40 (2H, s, N$\underline{H}$); ^{13}C-NMR (DMSO-d_6) δ 24.6 (C$\underline{H}_3$), 83.4 (B-O-$\underline{C}$-$\underline{C}$-O-B), 119.3 (Ar C-2, C-6 in B-C$_6\underline{H}_4$-N), 126.8 [Ar C-2, C-6 in C(=O)-C$_6\underline{H}_4$-C$_6$H$_4$-C(=O)], 128.4 [Ar C-3, C-5 in C(=O)-C$_6\underline{H}_4$-C$_6\underline{H}_4$-C(=O)], 134.1, 141.9, 142.0 [Ar C-1 in B-C$_6\underline{H}_4$-N or Ar C-1 or C-4 in C(=O)-C$_6\underline{H}_4$-C$_6\underline{H}_4$-C(=O)], 135.0 (Ar C-3, C-5 in B-C$_6\underline{H}_4$-N), 165.1 ($\underline{C}$=O). Anal. Calcd for $C_{38}H_{42}B_2N_2O_6 \cdot 1.2H_2O$: C, 68.53; H, 6.72; N, 4.21. Found: C, 68.56; H, 6.59; N, 4.14.

***N*^{1},*N*^{6}-Bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)adipamide (3ac).** From the reaction of adipoyl chloride (**2c**) (145.2 μL, 1.00 mmol) instead of 4,4'-biphenyldicarbonyl chloride (**2b**) with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**1a**) by using the same procedure as that shown above for compound **3ab**, the compound (**3ac**) (414.7 mg, 76% yield) was obtained as a white solid. Mp >250 °C; IR (KBr) 3304 (NH), 1667 cm^{-1} (C=O); FAB-MS (positive) *m*/*z* 549 $(M+H)^+$. HRMS (FAB) Calcd for $C_{30}H_{43}B_2N_2O_6^+$: *m*/*z* 549.3302 $(M+H)^+$. Found: 549.3285; ^{1}H-NMR (DMSO-d_6) δ 1.28 (24H, s, C$\underline{H}_3$), 1.59-1.67 [4H, m, C(=O)-CH$_2$-C$\underline{H}_2$-C$\underline{H}_2$-CH$_2$-C(=O)], 2.31-2.38 [4H, m, C(=O)-C$\underline{H}_2$-CH$_2$-CH$_2$-C$\underline{H}_2$-C(=O)], 7.55-7.65 (8H, m, Ar), 9.95 (2H, s, N$\underline{H}$); ^{13}C-NMR (DMSO-d_6) δ 24.6 (C$\underline{H}_3$), 24.7 [C(=O)-CH$_2$-C$\underline{H}_2$], 36.2 [C(=O)-C$\underline{H}_2$-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), 171.2 (C=O). Anal. Calcd for $C_{30}H_{42}B_2N_2O_6$: C, 65.72; H, 7.72; N, 5.11. Found: C, 65.65; H, 7.71; N, 5.16.

***N*^{1},*N*^{8}-Bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)octanediamide (3ad).** From the reaction of suberoyl chloride (**2d**) (178.9 μL, 1.00 mmol) instead of terephthaloyl chloride (**2a**) with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**1a**) by the same procedure as that shown above for the preparation of compound **3aa**, the targeted product (**3ad**) (344.3 mg, 60% yield) was obtained as a white solid. Mp >250 °C; IR (KBr) 3309 (NH), 1671 cm^{-1} (C=O); FAB-MS (positive) *m*/*z* 577 $(M+H)^+$. HRMS (FAB) Calcd for $C_{32}H_{47}B_2N_2O_6^+$: *m*/*z* 577.3615 $(M+H)^+$. Found: 577.3627; ^{1}H-NMR (DMF-d_7) δ 1.32 (24H, s, C$\underline{H}_3$), 1.36-1.42 [4H, m, C(=O)-CH$_2$-CH$_2$-C$\underline{H}_2$-C$\underline{H}_2$-CH$_2$-CH$_2$-C(=O)], 1.62-1.72 [4H, m, C(=O)-CH$_2$-C$\underline{H}_2$-CH$_2$-CH$_2$-C$\underline{H}_2$-CH$_2$-C(=O)], 2.40 [4H, t, *J* = 7.5, Hz, C(=O)-C$\underline{H}_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-C$\underline{H}_2$-C(=O)], 7.66 (4H, d, *J* = 8.5 Hz, Ar H-3, H-5) ,7.74 (4H, d, *J* = 8.5 Hz, Ar H-2, H-6), 10.02 (2H, s, N$\underline{H}$); ^{13}C-NMR (DMF-d_7) δ 25.5 (C$\underline{H}_3$), 26.4 [C(=O)-CH$_2$-C$\underline{H}_2$-CH$_2$], 30.1 [C(=O)-CH$_2$-CH$_2$-C$\underline{H}_2$], 37.9 [C(=O)-C$\underline{H}_2$-CH$_2$-CH$_2$], 84.6 (B-O-C-C-O-B), 119.3 (Ar C-2, C-6), 136.4 (Ar C-3, C-5), 143.9 (Ar C-1), 172.9 (C=O). Anal. Calcd for $C_{32}H_{46}B_2N_2O_6 \cdot 0.8\ H_2O$: C, 65.06; H, 8.12; N, 4.74. Found: C, 65.03; H, 7.95; N, 4.81.

***N*^{1},*N*^{4}-Bis(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)terephthalamide (3ba).** 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 terephthaloyl chloride (**2a**) (203.0 mg, 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 (**3ba**) (554.7 mg, 98% yield) as a white solid. Mp >250 °C; IR (KBr) 3315 (NH), 1651 cm^{-1} (C=O); FAB-MS (positive) *m*/*z* 569 $(M+H)^+$. HRMS (FAB) Calcd for $C_{32}H_{39}B_2N_2O_6^+$: *m*/*z* 569.2989 $(M+H)^+$. Found: 569.3004; ^{1}H-NMR (DMF-d_7) δ 1.36 (24H, s, C$\underline{H}_3$), 7.44 (2H, dd, *J* = 7.8,

7.8 Hz, Ar H-5 in B-C_6H_4-N), 7.48-7.53 (2H, m, Ar H-4 in B-C_6H_4-N), 8.08-8.12 (2H, m, Ar H-6 in B-C_6H_4-N), 8.22 [4H, s, C(=O)-C_6H_4-C(=O)], 8.28-8.32 (2H, m, Ar H-2 in B-C_6H_4-N), 10.42 (2H, s, NH); ^{13}C-NMR (DMF-d_7) δ 25.6 (CH_3), 85.0 (B-O-C-C-O-B), 124.4 (Ar C-6 in B-C_6H_4-N), 127.6 (Ar C-2, in B-C_6H_4-N), 128.8 [Ar C-2, C-6 in C(=O)-C_6H_4-C(=O)], 129.3 (Ar C-5 in B-C_6H_4-N), 131.1 (Ar C-4 in B-C_6H_4-N), 139.0 [Ar C-1 in C(=O)-C_6H_4-C(=O)], 140.3 (Ar C-1 in B-C_6H_4-N), 166.2 (C=O). Anal. Calcd for $C_{32}H_{38}B_2N_2O_6 \cdot 0.85H_2O$: C, 65.86; H, 6.86; N, 4.80. Found: C, 65.88; H, 6.73; N, 4.74.

***N*^{4},*N*$^{4'}$-Bis(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-[1,1'-biphenyl]-4,4'-dicarboxamide (3bb).** To a mixture 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) were added Et_3N (415.9 μL, 3.00 mmol) and 4,4'-biphenyldicarbonyl chloride (**2b**) (279.1 mg, 1.00 mmol) under cooling at 4.0 °C. 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 containing white solid material was filtered and washed with AcOEt to give the targeted product (**3bb**) (331.7 mg, 51% yield) as a white solid. The structure of the product was easily established by spectroscopic data shown below.

Mp >250 °C; IR (KBr) 3306 (NH), 1650 cm^{-1} (C=O); FAB-MS (positive) *m*/*z* 645 $(M+H)^+$; ^{1}H-NMR (DMSO-d_6) δ 1.32 (24H, s, CH_3), 7.39 (2H, dd, J = 7.6, 7.6 Hz, Ar H-5 in B-C_6H_4-N), 7.41-7.45 (2H, m, Ar H-4 in B-C_6H_4-N), 7.94 [4H, d, J = 8.5 Hz, H-2, H-6 in C(=O)-C_6H_4-C_6H_4-C(=O)], 7.97-8.04 (2H, m, Ar H-6 in B-C_6H_4-N), 8.09-8.18 [6H, m, Ar H-2 in B-C_6H_4-N, Ar H-3, H-5 in C(=O)-C_6H_4-C_6H_4-C(=O)], 10.30 (2H, s, NH); ^{13}C-NMR (DMSO-d_6) δ 24.6 (CH_3), 83.6 (B-O-C-C-O-B), 123.3 (Ar C-6 in B-C_6H_4-N), 126.4 (Ar C-2 in B-C_6H_4-N), 126.7 [Ar C-2, C-6 in C(=O)-C_6H_4-C_6H_4-C(=O)], 128.1 (Ar C-5 in B-C_6H_4-N), 128.3 [Ar C-3, C-5, in C(=O)-C_6H_4-C_6H_4-C(=O)], 129.6 (Ar C-4, in B-C_6H_4-N), 134.0, 141.9 [Ar C-1 or C-4 in C(=O)-C_6H_4-C_6H_4-C(=O)], 138.7 (Ar C-1 in B-C_6H_4-N), 164.8 (C=O). HRMS (FAB) Calcd for $C_{38}H_{43}B_2N_2O_6^+$: *m*/*z* 645.3302 $(M+H)^+$. Found: 645.3309.

***N*^{1},*N*^{6}-Bis(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)adipamide (3bc).** By the same procedure as that for the preparation of compound **3ba**, the reaction of adipoyl chloride (**2c**) (145.2 μL, 1.00 mmol) instead of terephthaloyl chloride (**2a**) gave the desired product (**3bc**) (449.2 mg, 82% yield) as a white solid. Mp 226-231 °C; IR (KBr) 3291 (NH), 1658 cm^{-1} (C=O); FAB-MS (positive) *m*/*z* 549 $(M+H)^+$. HRMS (FAB) Calcd for $C_{30}H_{43}B_2N_2O_6^+$: *m*/*z* 549.3302 $(M+H)^+$. Found: 549.3328; ^{1}H-NMR (DMSO-d_6) δ 1.28 (24H, s, CH_3), 1.57-1.66 [4H, m, C(=O)-CH_2-CH_2-CH_2-CH_2-C(=O)], 2.25-2.36 [4H, m, C(=O)-CH_2-CH_2-CH_2-CH_2-C(=O)], 7.27 (2H, dd, J = 7.5, 7.5 Hz, Ar H-5), 7.29-7.33 (2H, m, Ar H-4), 7.66-7.74 (2H, m, Ar H-6), 7.90 (2H, s, Ar H-2), 9.82 (2H, s, NH); ^{13}C-NMR (DMSO-d_6) δ 24.6 (CH_3), 24.8 [C(=O)-CH_2-CH_2], 36.2 [C(=O)-CH_2-CH_2], 83.6 (B-O-C-C-O-B), 122.0 (Ar C-6), 125.0 (Ar C-2), 128.1(Ar C-5), 128.9 (Ar C-4), 138.8 (Ar C-1), 171.0 (C=O). Anal. Calcd for $C_{30}H_{42}B_2N_2O_6 \cdot 0.3H_2O$: C, 65.08; H, 7.76; N, 5.06. Found: C, 65.01; H, 7.82; N, 5.14.

***N*^{1},*N*^{8}-Bis(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)octanediamide (3bd).** The reaction of suberoyl chloride (**2d**) (178.9 μL, 1.00 mmol) instead of 4,4'-biphenyldicarbonyl chloride (**2b**) in the same manner as that shown for the preparation of compound **3ba** afforded the targeted product (**3bd**) (563.8 mg, 98% yield) as a white solid. Mp 174-179 °C; IR (KBr) 3307 (NH), 1656 cm^{-1} (C=O); FAB-MS (positive) *m*/*z* 577 $(M+H)^+$. HRMS (FAB) Calcd for $C_{32}H_{47}B_2N_2O_6^+$: *m*/*z* 577.3615 $(M+H)^+$. Found: 577.3627; ^{1}H-NMR (DMSO-d_6) δ 1.29 (24H, s, C$\underline{H}_3$), 1.31-1.37 [4H, m, C(=O)-CH_2-CH_2-C$\underline{H}_2$-C$\underline{H}_2$-CH_2-CH_2-C(=O)], 1.53-1.65 [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* = 7.5, Hz, C(=O)-C$\underline{H}_2$-CH_2-CH_2-CH_2-CH_2-C$\underline{H}_2$-C(=O)], 7.28 (2H, dd, *J* = 7.5, 7.5 Hz, Ar H-5), 7.30-7.36 (2H, m, Ar H-4), 7.68-7.76 (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$\underline{H}_3$), 24.9 [C(=O)-CH_2-C$\underline{H}_2$-CH_2], 28.4 [C(=O)-CH_2-CH_2-C$\underline{H}_2$], 36.3 [C(=O)-C$\underline{H}_2$-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), 171.1 (C=O). Anal. Calcd for $C_{32}H_{46}B_2N_2O_6$: C, 66.69; H, 8.05; N, 4.86. Found: C, 66.43; H, 8.16; N, 4.88.

***N*^{1},*N*^{4}-Bis(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)terephthalamide (3ca).** 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 terephthaloyl chloride (**2a**) (203.0 mg, 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 combined organic extract containing yellow solid material was filtered. The separated insoluble material was washed with AcOEt to give the desired product (**3ca**) (511.9 mg, 90% yield) as a pale yellow solid. The structure of the product was easily established by spectroscopic data shown below.

Mp >250 °C; IR (KBr) 3382 (NH), 1631 cm^{-1} (C=O); FAB-MS (positive) *m*/*z* 569 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$) δ 1.43 (24H, s, C$\underline{H}_3$), 7.10-7.17 (2H, m, Ar H-4 in B-$C_6\underline{H}_4$-N), 7.51-7.58 (2H, m, Ar H-5 in B-$C_6\underline{H}_4$-N), 7.82-7.87 (2H, m, Ar H-3 in B-$C_6\underline{H}_4$-N), 8.17 [4H, s, C(=O)-$C_6\underline{H}_4$-C(=O)], 8.75 (2H, d, *J* = 8.2 Hz, Ar H-6 in B-$C_6\underline{H}_4$-N), 10.38 (2H, s, N$\underline{H}$); ^{13}C-NMR ($CDCl_3$) δ 25.0 (C$\underline{H}_3$), 84.7 (B-O-C-C-O-B), 119.3 (Ar C-6 in B-$\underline{C}_6H_4$-N), 123.4 (Ar C-4 in B-$\underline{C}_6H_4$-N) 127.5 [Ar C-2, C-6 in C(=O)-$\underline{C}_6H_4$-C(=O)], 133.2 (Ar C-5 in B-$\underline{C}_6H_4$-N), 136.5 (Ar C-3 in B-$\underline{C}_6H_4$-N), 138.2 [Ar C-1 in C(=O)-$\underline{C}_6H_4$-C(=O)], 144.8 (Ar C-1 in B-$\underline{C}_6H_4$-N), 164.2 (C=O). HRMS (FAB) Calcd for $C_{32}H_{39}B_2N_2O_6^+$: *m*/*z* 569.2989 $(M+H)^+$. Found: 569.3004.

***N*^{4},*N*$^{4'}$-Bis(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-[1,1'-biphenyl]-4,4'-dicarboxamide (3cb).** From the reaction of 4,4'-biphenyldicarbonyl chloride (**2b**) (279.1 mg, 1.00 mmol) instead of terephthaloyl chloride (**2a**) by the same procedure as that for the preparation of compound **3ca**, the desired compound (**3cb**) (354.3 mg, 55% yield) was obtained as a white solid. The structure of the product was established by spectroscopic data shown below.

Mp >250 °C; IR (KBr) 3378 (NH), 1681 cm^{-1} (C=O); FAB-MS (positive) *m*/*z* 645 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$) δ 1.44 (24H, s, C<u>H</u>$_3$), 7.07-7.18 (2H, m, Ar H-4 in B-C$_6$<u>H</u>$_4$-N), 7.50-7.58 (2H, m, Ar H-5 in B-C$_6$<u>H</u>$_4$-N), 7.78 [4H, d, *J* = 8.5 Hz, Ar H-2, H-6 in C(=O)-C$_6$<u>H</u>$_4$-C$_6$<u>H</u>$_4$-C(=O)], 7.81-7.88 (2H, m, Ar H-3 in B-C$_6$<u>H</u>$_4$-N), 8.16 [4H, d, *J* = 8.5 Hz, Ar H-3, H-5 in C(=O)-C$_6$<u>H</u>$_4$-C$_6$<u>H</u>$_4$-C(=O)], 8.76 (2H, d, *J* = 8.2 Hz, Ar H-6 in B-C$_6$<u>H</u>$_4$-N), 10.33 (2H, s, N<u>H</u>). Owing to the very poor solubility of this compound against many solvents such as $CDCl_3$, DMSO-d_6, and DMF-d_7, no satisfactory ^{13}C-NMR data were available for unambiguous assignment of the molecular structure. HRMS (FAB) Calcd for $C_{38}H_{43}B_2N_2O_6^+$: *m*/*z* 645.3302 $(M+H)^+$. Found: 645.3309.

***N*^{1},*N*^{6}-Bis(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)adipamide (3cc).** From the reaction of adipoyl chloride (**2c**) (145.2 μL, 1.00 mmol) instead of terephthaloyl chloride (**2a**) in the same manner as that for the preparation of compound **3ca**, the targeted product (**3cc**) (238.0 mg, 43% yield) was obtained as a white solid. The structure of the product was easily established by spectroscopic data shown below.

Mp 206-213 °C; IR (KBr) 3307 (NH), 1645 cm^{-1} (C=O); FAB-MS (positive) *m*/*z* 549 $(M+H)^+$; ^{1}H-NMR (DMSO-d_6) δ 1.18 (24H, s, C<u>H</u>$_3$), 1.71-1.80 [4H, m, C(=O)-CH$_2$-C<u>H</u>$_2$-C<u>H</u>$_2$-CH$_2$-C(=O)], 2.55-2.63 [4H, m, C(=O)-C<u>H</u>$_2$-CH$_2$-CH$_2$-C<u>H</u>$_2$-C(=O)], 7.04 (2H, d, *J* = 7.6 Hz, Ar H-3 or H-6), 7.09-7.15 (2H, m, Ar H-4 or H-5), 7.19-7.26 (2H, m, Ar H-4 or H-5), 7.38-7.44 (2H, m, Ar H-3 or H-6), 11.68 (2H, s, N<u>H</u>); ^{13}C-NMR (DMSO-d_6) δ 23.9 [C(=O)-CH$_2$-<u>C</u>H$_2$], 26.0 (<u>C</u>H$_3$), 33.7 [C(=O)-<u>C</u>H$_2$-CH$_2$], 79.6 (B-O-<u>C</u>-<u>C</u>-O-B), 115.8, 132.5 (Ar C-3 or C-6 in B-<u>C</u>$_6$H$_4$-N), 125.1, 127.4 (Ar C-4 or C-5 in B-<u>C</u>$_6$H$_4$-N), 138.2 (Ar C-1 in B-<u>C</u>$_6$H$_4$-N), 172.0 (<u>C</u>=O). HRMS (FAB) Calcd for $C_{30}H_{43}B_2N_2O_6^+$: *m*/*z* 549.3302 $(M+H)^+$. Found: 549.3315.

***N*^{1},*N*^{8}-Bis(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)octanediamide (3cd).** From the reaction of suberoyl chloride (**2d**) (178.9 μL, 1.00 mmol) instead of terephthaloyl chloride (**2a**) in the same manner as that described for the preparation of compound **3ca**, the targeted compound (**3cd**) (389.2 mg, 68% yield) was obtained as a white solid. The structure of the product was easily established by spectroscopic data shown below.

Mp 186-196 °C; IR (KBr) 3379 (NH), 1634 cm^{-1} (C=O); FAB-MS (positive) *m*/*z* 577 $(M+H)^+$; ^{1}H-NMR (DMSO-d_6) δ 1.17 (24H, s, C<u>H</u>$_3$), 1.35-1.43 [4H, m, C(=O)-CH$_2$-CH$_2$-C<u>H</u>$_2$-C<u>H</u>$_2$-CH$_2$-CH$_2$-C(=O)], 1.62-1.73 [4H, m, C(=O)-CH$_2$-C<u>H</u>$_2$-CH$_2$-CH$_2$-C<u>H</u>$_2$-CH$_2$-C(=O)], 2.54 [4H, t, *J* = 7.2 Hz, C(=O)-C<u>H</u>$_2$-CH$_2$-CH$_2$- CH$_2$-CH$_2$-C<u>H</u>$_2$-C(=O)], 7.02 (2H, d, *J* = 7.9 Hz, Ar H-3 or H-6), 7.09-7.15 (2H, m, Ar H-4 or H-5), 7.18-7.25 (2H, m, Ar H-4 or H-5), 7.38-7.44 (2H, m, Ar H-3 or H-6), 11.70 (2H, s, N<u>H</u>); ^{13}C-NMR (DMSO-d_6) δ 24.4 [C(=O)-CH$_2$-<u>C</u>H$_2$-CH$_2$], 26.0 (<u>C</u>H$_3$), 27.7 [C(=O)-CH$_2$-CH$_2$-<u>C</u>H$_2$], 34.0 [C(=O)-<u>C</u>H$_2$-CH$_2$-CH$_2$], 79.5 (B-O-<u>C</u>-<u>C</u>-O-B), 115.6, 132.5 (Ar C-3 or C-6 in B-<u>C</u>$_6$H$_4$-N), 125.1, 127.4

(Ar C-4 or C-5 in B-$\underline{C}_6H_4$-N), 138.1 (Ar C-1 in B-$\underline{C}_6H_4$-N), 172.2 ($\underline{C}$=O). HRMS (FAB) Calcd for $C_{32}H_{47}B_2N_2O_6^+$: *m*/*z* 577.3615 $(M+H)^+$. Found: 577.3627.

REFERENCES AND NOTES

1. G. V. Oshovsky, D. N. Reinhoudt, and W. Verboom, *Angew. Chem. Int. Ed.*, 2007, **46**, 2366.
2. S. E. Gibson and M. P. Castaldi, *Angew. Chem. Int. Ed.*, 2006, **45**, 4718.
3. G. Berube, *Curr. Med. Chem.*, 2006, **13**, 131 and related references cited therein.
4. C. G. Wermuth, 'The Practice of Medicinal Chemistry', 3rd ed., Academic Press, San Diego, 2008 and related references cited therein.
5. A. Varki, R. D. Cummings, J. D. Esko, H. H. Freeze, P. Stanley, C. R. Bertozzi, G. W. Hart, and M. E. Etzler, 'Essentials of Glycobiology', 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N. Y, 2009 and related references cited therein.
6. F. Fujisaki, M. Furutachi, R. Fujiwara, M. Okabe, H. Aki, N. Kashige, F. Miake, and K. Sumoto, *Heterocycles*, 2015, **91**, 1668.
7. F. Fujisaki, H. Aki, A. Naito, E. Fukami, N. Kashige, F. Miake, and K. Sumoto, *Chem. Pharm. Bull.*, 2014, **62**, 429 and related references cited therein.
8. N. Mibu, H. Aki, H. Ikeda, A. Saito, W. Uchida, K. Yokomizo, J. Zhou, T. Miyata, and K. Sumoto, *J. Therm. Anal. Calorim.*, 2013, **113**, 1015.
9. S. D. Bull, M. G. Davidson, J. M. H. van den Elsen, J. S. Fossey, A. T. A. Jenkins, Y.-B. Jiang, Y. Kubo, F. Marken, K. Sakurai, J. Zhao, and T. D. James, *Acc. Chem. Res.*, 2013, **46**, 312.
10. Regarding C_2-symmetrical boronic acid derivatives, a few molecules have been reported as an effective fluorescent probe for some sugars. For example, see the following reference: A. Resendez, M. A. Halim, C. M. Landhage, P. M. Hellström, B. Singaram, and D.-L. Webb, *Clin. Chim. Acta*, 2015, **439**, 115 and related references cited therein.
11. Y. Dai, K. Hartandi, Z. Ji, A. A. Ahmed, D. H. Albert, J. L. Bauch, J. J. Bouska, P. F. Bousquet, G. A. Cunha, K. B. Glaser, C. M. Harris, D. Hickman, J. Guo, J. Li, P. A. Marcotte, K. C. Marsh, M. D. Moskey, R. L. Martin, A. M. Olson, D. J. Osterling, L. J. Pease, N. B. Soni, K. D. Stewart, V. S. Stoll, P. Tapang, D. R. Reuter, S. K. Davidsen, and M. R. Michaelides, *J. Med. Chem.*, 2007, **50**, 1584.
12. Although the observed whole signals in NMR spectroscopic data indicated that all of the purified products have almost no organic contaminant, it was difficult to obtain adequate elemental analysis data (within ±0.3%) for some compounds. Elemental analysis for some compounds (**3aa**, **3bb**, **3ca**, **3cb**, **3cc**, and **3cd**) was carried out by using high-resolution FAB-MS spectra (see EXPERIMENTAL).

13. Only in ^{13}C-NMR spectra of the compound **3aa**, we detected a weak broad signal (δ 123.5 ppm) over the background noise attributable to this quaternary aromatic carbon by an operation with a very large number of scans (6400 times). The assignment of the signal was supported by a ^{1}H- ^{13}C heteronuclear multiple-bond connectivity (HMBC) spectrum of compound **3aa**.
14. D. G. Hall, 'Boronic Acids', 2nd ed., Vol. 1, Wiley-VCH, 2011.