HETEROCYCLES, Vol. 102, No. 12, 2021, pp. 2379 - 2390. © 2021 The Japan Institute of Heterocyclic Chemistry
Received, 3rd September, 2021, Accepted, 4th October, 2021, Published online, 12th October, 2021
DOI: 10.3987/COM-21-14549

HYBRID LINKER MODE C_2-SYMMETRICAL 1,3,5-TRIAZINE DERIVATIVES AND THEIR BIOLOGICAL EVALUATION

Shunsuke Shimomura,[1] Kazumi Yokomizo,[2] Jian-Rong Zhou,[2] Kaori Ota,[1] Nobuko Mibu,[1] Makoto Furutachi,[1] and Kunihiro Sumoto[1]*

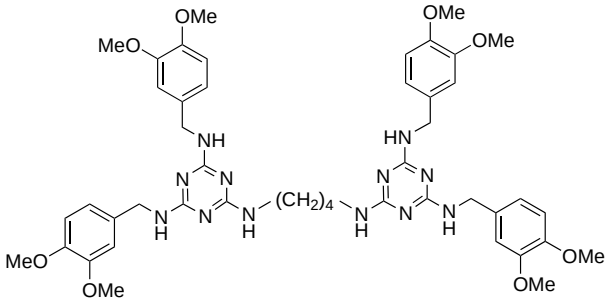
[1]Faculty of Pharmaceutical Sciences, Fukuoka University, 8-19-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan. [2]Faculty of Pharmaceutical Sciences, Sojo University, 4-22-1 Ikeda, Nishi-ku, Kumamoto 860-0082, Japan. E-mail: kunihiro@fukuoka-u.ac.jp

Abstract – We report the preparation of some new multivalent hybrid-type C_2-symmetrical molecules having a methylene linker group and 1,3,5-triazine (TAZ) moieties in the molecule and the results of biological evaluation of their anti-herpes simplex virus type 1 (anti-HSV-1) activity and cytotoxic activity against Vero cells. Some of the mid-sized C_2-symmetrical multivalent hybrid-type molecules (**3a**) showed considerably high levels of anti-HSV-1 activity (EC_{50} = 28.8 ~ 32.0 μM) with low levels of cytotoxicity (CC_{50} = > 200 μM) against Vero cells. Among the tested hybrid-type TAZ derivatives, we reconfirmed that the hybrid-type C_2-symmetrical multivalent molecule (**3a-4**) is an interesting candidate in the search for new hybrid-type multivalent mid-sized antiviral compounds.

Faced with the possibility of pandemics of viral infections such as COVID-19, the development of new antiviral drugs is needed. Carbohydrate-containing glycoproteins, proteoglycans and glycolipids on the cell surface interact with various factors for virus invasion and propagation to control cell activity for the processes of viral infection.[1-3] Moreover, supramolecular interaction by macromolecules with two-fold (C_2) or three-fold (C_3) geometry is one of the common stages of progression in many crucial biological responses.[4] To develop new oligovalent symmetrical bioactive molecules, we have designed and synthesized a few new compounds with such molecular geometry and evaluated their bioactivities in order to find new types of bioactive leads.[6-17] Application of the isosterism concept for the development of new compounds with enhanced biological activity led to significant advances in medicinal chemistry. The symmetrical 1,3,5-triazine scaffold may increase the level of molecular diversity and allow covering of the chemical space in important areas of medicinal chemistry.[18] In connection with these projects, we have

recently reported the preparation of a few new hybrid-type C_2-symmetrical trivalent 1,3,5-triazine (TAZ) derivatives and the results of biological evaluation of the synthesized symmetrical TAZ derivatives.[13,17,19] Among previously tested symmetrical TAZ molecules, we found that a hybrid-type C_2-symmetrical tri-substituted TAZ derivative A (**3a-4**) showed a considerably high level of anti-HSV-1 activity (EC_{50} = 7.6 μM) and a low level of cytotoxic activity (CC_{50} = > 200 μM) against Vero cells.[19] Considering TAZ as a promising scaffold[5,18] for its biological behavior, this non-peptide synthetic multivalent TAZ derivative is considered to be a potential new lead in the search for hybrid-type antiviral active molecules (Figure 1). The carbohydrate recognition property of a few C_3-symmetrical TAZ derivatives[7,14] with high levels of anti-herpes simplex virus type 1 (anti-HSV-1) activity also prompted us to investigate this new C_2-symmetrical multivalent TAZ derivative **A** and related compounds to find a more promising new antiviral candidate.

As a further extension of modification of this hybrid linker mode TAZ derivative **A**,[19] we synthesized such multivalent hybrid-type C_2-symmetrical TAZ derivatives having longer methylene linker groups. In this paper, we describe the results of evaluation of their anti-HSV-1 activities and the structure-activity relationships (SARs) of these unique multivalent symmetrical TAZ-related derivatives.



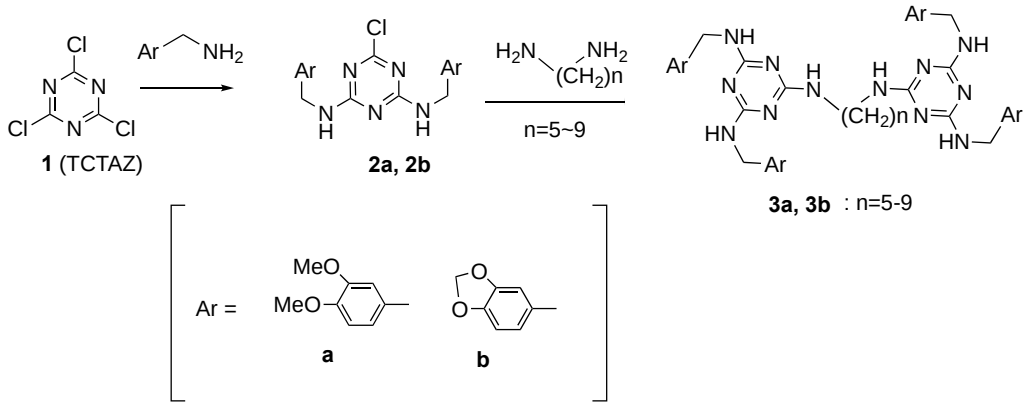
A

Figure 1. Anti-HSV-1 active hybrid-type C_2-symmetrrical TAZ derivative (**A**)

RESULTS AND DISCUSSION

For the preparation of various new target mid-sized multivalent hybrid-type TAZ molecules (**3a** and **3b**), we used a conventional synthetic route consisting of stepwise coupling of intermediate TAZ derivatives (**2a** and **2b**)[13] with various diaminoalkanes (**1** → **2** → **3**, see Scheme 1). The structures of the obtained new hybrid-type C_2-symmetrical multivalent TAZ derivatives (**3a** and **3b**) were established by spectroscopic methods and elemental analysis. Correct molecular ion peaks were observed in high-resolution positive FAB-MS spectra of all TAZ derivatives (**3**). All ^{13}C-NMR spectra of the target C_2-symmetrical TAZ derivatives showed magnetically equivalent spectroscopic signal patterns, indicating a symmetrical molecular feature in solution. The details of the stepwise preparation of these new C_2-symmetrical TAZ derivatives (**3a** and **3b**) are given in EXPERIMENTAL.

The structures of target hybrid-type C_2-symmetrical multivalent TAZ derivatives obtained in this study are shown in Table 1. As can be seen in EXPERIMENTAL, the yields obtained by this procedure with the starting TCTAZ (**1**) to target new hybrid-type C_2-symmetrical trivalent 1,3,5-triazine (TAZ) derivatives (**3a-n**) were good, and this method for synthesis of hybrid-type TAZ derivatives was reproducible and was reconfirmed to be useful as a general procedure for synthesis of hybrid-type C_2-symmetrical multivalent TAZ derivatives.[19] The results of biological evaluation of these hybrid-type derivatives [anti-HSV-1 activity (EC_{50}) and cytotoxicity (CC_{50})] together with a previously reported lead compound (**A**: **n=4**) and the data for aciclovir[21] are also shown in Table 1.



Scheme 1. Synthesis of C_2-symmetrical multivalent hybrid-type TAZ derivatives (**3a** and **3b**)

Some of the new linear methylene linker mode multivalent C_2-symmetrical TAZ derivatives **3a-6** and **3a-8** in the **3a** series showed considerably high levels of anti-HSV-1 activity (EC_{50} = 28.8 ~ 32.0 μM) with low levels of cytotoxicity (CC_{50} = > 200 μM) (see Table 1). In contrast, all of the hybrid-type multivalent TAZ derivatives **3b-5** ~ **3b-9** (**3b** series) having methylenedioxy groups on the phenyl ring in benzyl groups had low levels of cytotoxicity (CC_{50} = > 200 μM) but did not show anti-HSV-1 activity (EC_{50} = > 100 μM). It is noteworthy that both of the single-drug type of C_3-symmetrical trivalent TAZ derivatives (**4a** and **4b**) corresponding to the fragment structures of **3a** and **3b** showed considerably high levels of anti-HSV-1 activity (EC_{50} = 0.98 and 5.4 μM, respectively).[13,15]

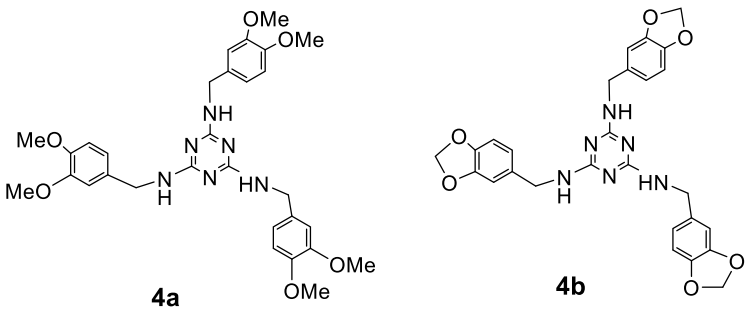
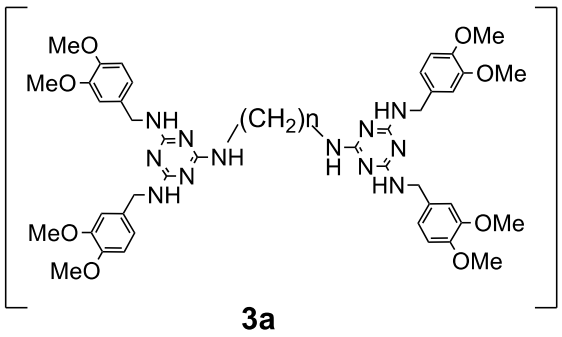
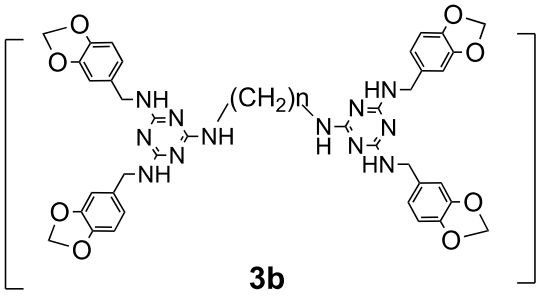


Figure 2. Structures of single drug types of C_3-symmetrical trivalent TAZ derivatives (**4a** and **4b**)

Through these molecular modification studies, we confirmed that hybrid-type C_2-symmetrical multivalent TAZ derivative **3a-4** showed the highest anti-HSV-1 activity, which was slightly less potent than that of aciclovir (see Table 1). We are considering to continue studies for further structural modifications including changes in other new types of linkers and partial structures in the hybrid-type C_2-symmetrical multivalent TAZ structure **3a-4**.

Table 1. Anti-HSV-1 activity (EC_{50}) and cytotoxicity (CC_{50}) against Vero cells of target hybrid-type TAZ derivatives (**3**)

Compound	n	Structure	EC_{50} (μM)	CC_{50} (μM)
3a-4 [a] (A)	4	 **3a**	7.6	>200
3a-5 [b]	5		>100	>200
3a-6	6		28.8	>200
3a-7	7		>100	>200
3a-8	8		32.0	>200
3a-9	9		>100	>200
3b-5	5	 **3b**	>100	>200
3b-6	6		>100	>200
3b-7	7		>100	>200
3b-8	8		>100	>200
3b-9	9		>100	>200
aciclovir [c]			1.1	> 444

a) Data were taken from reference 19. b) Data were taken from reference 17.
c) Data were taken from reference 21.

EXPERIMENTAL

Melting points were determined using a micro melting point apparatus (Yanaco MP-S3) without correction. IR spectra were measured by a Shimadzu FTIR-8100 IR spectrophotometer. Low- and high-resolution mass spectra (LR-MS and HR-MS) were obtained by a JEOL JMS HX-110 double-focusing model equipped with an FAB ion source interfaced with a JEOL JMA-DA 7000 data system. ^{1}H- and ^{13}C-NMR spectra were obtained by ECG600R. Chemical shifts are expressed in δ ppm relative to the solvent peaks for ^{l}H-NMR [$CDCl_3$ (7.26 ppm), DMSO-d_6 (2.50 ppm)] and ^{13}C-NMR [$CDCl_3$ (77.16 ppm), DMSO-d_6 (39.52 ppm)]. The signal assignments were confirmed by two-dimensional (2D)-NMR analyses: ^{1}H-^{1}H 2D correlation spectroscopy (COSY), ^{1}H-^{13}C heteronuclear multiple-quantum coherence (HMQC), and ^{1}H-^{13}C heteronuclear multiple-bond connectivity (HMBC). Microanalysis was performed with a Yanaco MT-6 CHN corder. Routine monitoring of reactions was carried out using precoated Kieselgel 60F_{254} plates (E. Merck). Detection of products was accomplished with UV light and iodine. Flash column chromatography separations of the reaction products were performed on silica gel with a Biotage Select Two Channel Extended Collection Bed UV Detector. Commercially available starting materials were used without further purification, and dry solvents were used in all reactions. Intermediate di-benzylamino-substituted TAZ derivatives (**2a** and **2b**)[13] were prepared from TCTAZ (**1**) and an appropriate benzylamine by a previously reported procedure.[13] The hybrid-type C_2-symmetrical multivalent TAZ derivatives **3a-4** (**A**) and **3a-5** were prepared by previously reported procedures.[17,19]

Procedure for C_2-Symmetrical Multivalent Hybrid-type TAZ Derivatives (Table 1)

Synthesis of N^2,$N^{2'}$-(Hexane-1,6-diyl)bis(N^4,N^6-bis(3,4-dimethoxybenzyl)-1,3,5-triazine-2,4,6-triamine) (3a-6).

To a solution of intermediate (**2a**)[13] (1.110 g, 2.50 mmol) in DMF (2 mL) were added 1,6-diaminohexane (116.2 mg, 1.00 mmol) and K_2CO_3 (691.0 mg, 5.00 mmol) at room temperature with stirring. The reaction mixture was refluxed in an oil bath for 8 h with stirring. After addition of water (20 mL), the resulting mixture was extracted with CH_2Cl_2 (20 mL×3). The combined organic layer was washed with brine (20 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residual oil was purified by silica gel column chromatography with CH_2Cl_2/MeOH as an eluent to give the desired product (**3a-6**) (742.0 mg, 79% yield) as a yellow solid. Mp 68-73 ℃; FAB-MS (positive) *m*/*z* 935 $(M+H)^+$. HR-FAB-MS *m*/*z* 935.4886 (Calcd for $C_{48}H_{63}N_{12}O_8^+$: 935.4886). ^{1}H-NMR ($CDCl_3$) *δ*: 1.34 [4H, bs, (Ar-NH-CH_2-C$\underline{H}_2$-CH_2-)$_2$ or (Ar-NH-CH_2-CH_2-C$\underline{H}_2$-)$_2$], 1.50 [4H, bs, (Ar-NH-CH_2-C$\underline{H}_2$-CH_2-)$_2$ or (Ar-NH-CH_2-CH_2-C$\underline{H}_2$-)$_2$], 3.33 [4H, s, (Ar-NH-C$\underline{H}_2$-CH_2-CH_2-)$_2$], 3.73-3.98 [24H, m, C_6H_3(OC$\underline{H}_3$)$_2$], 4.48 (8H, s, Ar-C$\underline{H}_2$-NH), 6.67-7.08 (12H, m, Ar $\underline{H}$-2, Ar $\underline{H}$-5, Ar $\underline{H}$-6 in C_6H_3). ^{13}C-NMR ($CDCl_3$) *δ*: 26.6 [(Ar-NH-CH_2-$\underline{C}H_2$-CH_2-)$_2$ or (Ar-NH-CH_2-CH_2-$\underline{C}H_2$-)$_2$], 29.7 [(Ar-NH-CH_2-$\underline{C}H_2$-CH_2-)$_2$ or (Ar-NH-CH_2-CH_2-$\underline{C}H_2$-)$_2$], 40.5 [(Ar-NH-$\underline{C}H_2$-CH_2-CH_2-)$_2$], 44.7 (Ar-$\underline{C}H_2$-NH), 56.0, 56.1 [C_6H_3(O$\underline{C}H_3$)$_2$], 111.0 (Ar $\underline{C}$-2 or Ar $\underline{C}$-5 or Ar $\underline{C}$-6 in

C_6H_3), 111.2 (Ar C-2 or Ar C-5 Ar C-6 in C_6H_3), 119.9 (Ar C-2 or Ar C-5 or Ar C-6 in C_6H_3), 132.3 (Ar C-1 or Ar C-3 or Ar C-4 in C_6H_3), 148.3 (Ar C-3 or Ar C-4 in C_6H_3), 149.2 (Ar C-1 or Ar C-3 or Ar C-4 in C_6H_3), 166.2 (C-2, C-4, and C-6 in triazine). *Anal.* Calcd for $C_{48}H_{62}N_{12}O_8 \cdot 3H_2O$: C, 58.29; H, 6.93; N, 16.99. Found: C, 58.26; H, 6.85; N, 17.06.

Synthesis of $N^2,N^{2'}$-(Heptane-1,7-diyl)bis(N^4,N^6-bis(3,4-dimethoxybenzyl)-1,3,5-triazine-2,4,6-triamine) (3a-7).

To a solution of intermediate (**2a**)[13] (1.110 g, 2.50 mmol) and 1,7-diaminoheptane (130.2 mg, 1.00 mmol) in DMF (2 mL) was added K_2CO_3 (691.0 mg, 5.00 mmol) at room temperature with stirring. The reaction mixture was refluxed in an oil bath for 8 h with stirring. After addition of water (20 mL), the resulting mixture was extracted with CH_2Cl_2 (20 mL×3). The combined organic layer was washed with brine (20 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residual oil was purified by silica gel column chromatography with CH_2Cl_2/MeOH as an eluent to give the desired product (**3a-7**) (589.7 mg, 62% yield) as a white solid. Mp 74-82 ℃; FAB-MS (positive) *m/z* 949 $(M+H)^+$. HR-FAB-MS *m/z* 949.5035 (Calcd for $C_{49}H_{65}N_{12}O_8^+$: 949.5043. ^{1}H-NMR ($CDCl_3$) δ: 1.31 [6H, bs, (Ar-NH-CH_2-CH_2)CH_2, (Ar-NH-CH_2-CH_2-CH_2)$_2$$CH_2$], 1.50 [4H, bs, (Ar-NH-$CH_2$-C$H_2$-$CH_2$)$_2$$CH_2$], 3.34 [4H, s, (Ar-NH-C$H_2$-$CH_2$-$CH_2$)$_2$$CH_2$], 3.77-3.90 [24H, m, C_6H_3(OCH_3)$_2$], 4.49 (8H, s, Ar-CH_2-NH), 6.67-6.95 (12H, m, Ar H-2, Ar H-5, Ar H-6 in C_6H_3). ^{13}C-NMR ($CDCl_3$) δ: 26.9 [(Ar-NH-CH_2-CH_2-CH_2)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-CH_2)$_2$CH_2], 29.1 [(Ar-NH-CH_2-CH_2-CH_2)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-CH_2)$_2$CH_2], 29.8 [(Ar-NH-CH_2-CH_2-CH_2)$_2$$CH_2$], 40.8 [(Ar-NH-C$H_2$-$CH_2$-$CH_2$)$_2$$CH_2$], 44.7 (Ar-C$H_2$-NH), 56.0, 56.1 [$C_6H_3$(OC$H_3$)$_2$], 111.1 (Ar C-2 or Ar C-5 or Ar C-6 in C_6H_3), 111.3 (Ar C-2 or Ar C-5 or Ar C-6 in C_6H_3), 120.0 (Ar C-2 or Ar C-5 or Ar C-6 in C_6H_3), 132.0 (Ar C-1 or Ar C-3 or Ar C-4 in C_6H_3), 148.4 (Ar C-1 or Ar C-3 or Ar C-4 in C_6H_3), 149.2 (Ar C-1 or Ar C-3 or Ar C-4 in C_6H_3), 166.0 (C-2, C-4, and C-6 in triazine). *Anal.* Calcd for $C_{49}H_{64}N_{12}O_8 \cdot 1.7H_2O$: C, 60.07; H, 6.93; N, 17.16. Found: C, 60.08; H, 6.74; N, 17.06.

Synthesis of $N^2,N^{2'}$-(Octane-1,8-diyl)bis(N^4,N^6-bis(3,4-dimethoxybenzyl)-1,3,5-triazine-2,4,6-triamine) (3a-8).

To a solution of intermediate (**2a**)[13] (1.110 g, 2.50 mmol) in DMF (2 mL) were added 1,8-diaminooctane (144.3 mg, 1.00 mmol) and K_2CO_3 (691.0 mg, 5.00 mmol) at room temperature with stirring. The reaction mixture was refluxed in an oil bath for 8 h with stirring. After addition of water (20 mL), the resulting mixture was extracted with CH_2Cl_2 (20 mL×3). The combined organic layer was washed with brine (20 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residual oil was purified by silica gel column chromatography with CH_2Cl_2/MeOH as an eluent to give the desired product (**3a-8**) (716.4 mg, 74% yield) as a yellow solid. Mp 68-83 ℃; FAB-MS (positive) *m/z* 963 $(M+H)^+$. HR-FAB-MS *m/z* 963.5197 (Calcd for $C_{50}H_{67}N_{12}O_8^+$: 963.5199). ^{1}H-NMR ($CDCl_3$) δ: 1.28 [8H, bs, (Ar-NH-CH_2-CH_2-CH_2-)$_2$ and/or (Ar-NH-CH_2-CH_2-CH_2-CH_2-)$_2$ and/or (Ar-NH-CH_2-CH_2-CH_2-CH_2-)$_2$], 1.50 [4H, s, (Ar-NH-

CH_2-C<u>H</u>$_2$-CH_2-CH_2-)$_2$ or (Ar-NH-CH_2-CH_2-C<u>H</u>$_2$-CH_2-)$_2$ or (Ar-NH-CH_2-CH_2-CH_2-C<u>H</u>$_2$-)$_2$], 3.34 [4H, bs, (Ar-NH-C<u>H</u>$_2$-CH_2-CH_2-CH_2-)$_2$], 3.63-4.02 [24H, m, C_6H_3(OC<u>H</u>$_3$)$_2$], 4.50 (8H, s, Ar-C<u>H</u>$_2$-NH), 6.62-7.11 (12H, m, Ar <u>H</u>-2, Ar <u>H</u>-5, Ar <u>H</u>-6 in C_6H_3). ^{13}C-NMR ($CDCl_3$) δ: 26.8 [(Ar-NH-CH_2-<u>C</u>H_2-CH_2-CH_2-)$_2$ or (Ar-NH-CH_2-CH_2-<u>C</u>H_2-CH_2-)$_2$ or (Ar-NH-CH_2-CH_2-CH_2-<u>C</u>H_2-)$_2$], 29.3 [(Ar-NH-CH_2-<u>C</u>H_2-CH_2-CH_2-)$_2$ or (Ar-NH-CH_2-CH_2-<u>C</u>H_2-CH_2-)$_2$ or (Ar-NH-CH_2-CH_2-CH_2-<u>C</u>H_2-)$_2$], 29.9 [(Ar-NH-CH_2-<u>C</u>H_2-CH_2-CH_2-)$_2$ or (Ar-NH-CH_2-CH_2-<u>C</u>H_2-CH_2-)$_2$ or (Ar-NH-CH_2-CH_2-CH_2-<u>C</u>H_2-)$_2$], 40.7 [(Ar-NH-<u>C</u>H_2-CH_2-CH_2-CH_2-)$_2$], 44.7 (Ar-<u>C</u>H_2-NH), 56.0, 56.1 [C_6H_3(O<u>C</u>H_3)$_2$], 111.1 (Ar <u>C</u>-2 or Ar <u>C</u>-5 or Ar <u>C</u>-6 in C_6H_3), 111.2 (Ar <u>C</u>-2 or Ar <u>C</u>-5 or Ar <u>C</u>-6 in C_6H_3), 120.0 (Ar <u>C</u>-2 or Ar <u>C</u>-5 or Ar <u>C</u>-6 in C_6H_3), 132.1 (Ar <u>C</u>-1 in C_6H_3), 148.3 (Ar <u>C</u>-3 or Ar <u>C</u>-4 in C_6H_3), 149.2 (Ar <u>C</u>-3 or Ar <u>C</u>-4 in C_6H_3), 166.3 (<u>C</u>-2, <u>C</u>-4, and <u>C</u>-6 in triazine). *Anal.* Calcd for $C_{50}H_{66}N_{12}O_8$•1.7H_2O: C, 60.43; H, 7.04; N, 16.91. Found: C, 60.39; H, 7.11; N, 17.15.

Synthesis of *N*^{2},*N*$^{2'}$-(Nonane-1,9-diyl)bis(*N*^{4},*N*^{6}-bis(3,4-dimethoxybenzyl)-1,3,5-triazine-2,4,6-triamine) (3a-9).

To a solution of intermediate (**2a**)[13] (1.110 g, 2.50 mmol) and 1,9-diaminononane (158.3 mg, 1.00 mmol) in DMF (2 mL) was added K_2CO_3 (691.0 mg, 5.00 mmol) at room temperature with stirring. The reaction mixture was refluxed in an oil bath for 8 h with stirring. After addition of water (20 mL), the resulting mixture was extracted with CH_2Cl_2 (20 mL×3). The combined organic layer was washed with brine (20 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residual oil was purified by silica gel column chromatography with CH_2Cl_2/MeOH as an eluent to give the desired product (**3a-9**) (410.4 mg, 42% yield) as a yellow solid. Mp 89-100 ℃; FAB-MS (positive) *m*/*z* 977 $(M+H)^+$. HR-FAB-MS *m*/*z* 977.5353 (Calcd for $C_{51}H_{69}N_{12}O_8^+$: 977.5356). ^{1}H-NMR ($CDCl_3$) δ: 1.26 [(10H, bs, (Ar-NH-CH_2-CH_2-C<u>H</u>$_2$-CH_2)$_2$$CH_2$, (Ar-NH-$CH_2$-$CH_2$-$CH_2$-C<u>H</u>$_2$)$_2$$CH_2$, (Ar-NH-$CH_2$-$CH_2$-$CH_2$-$CH_2$)$_2$C<u>H</u>$_2$], 1.51 [4H, s, (Ar-NH-$CH_2$-C<u>H</u>$_2$-$CH_2$-$CH_2$)$_2$$CH_2$], 3.35 [4H, bs, (Ar-NH-C<u>H</u>$_2$-CH_2-CH_2-CH_2)$_2$$CH_2$], 3.62-4.00 [24H, m, C_6H_3(OC<u>H</u>$_3$)$_2$], 4.50 (8H, s, Ar-C<u>H</u>$_2$-NH), 6.61-7.03 (12H, m, Ar <u>H</u>-2, Ar <u>H</u>-5, Ar <u>H</u>-6 in C_6H_3). ^{13}C-NMR ($CDCl_3$) δ: 26.9 [(Ar-NH-CH_2-CH_2-<u>C</u>H_2-CH_2)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-CH_2-<u>C</u>H_2)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-CH_2-CH_2)$_2$<u>C</u>H_2], 29.2 [(Ar-NH-CH_2-CH_2-<u>C</u>H_2-CH_2)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-CH_2-<u>C</u>H_2)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-CH_2-CH_2)$_2$<u>C</u>H_2], 29.4 [(Ar-NH-CH_2-CH_2-<u>C</u>H_2-CH_2)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-CH_2-<u>C</u>H_2)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-CH_2-CH_2)$_2$<u>C</u>H_2], 29.8 [(Ar-NH-CH_2-<u>C</u>H_2-CH_2-CH_2)$_2$$CH_2$], 40.8 [(Ar-NH-<u>C</u>$H_2$-$CH_2$-$CH_2$-$CH_2$)$_2$$CH_2$], 44.7 (Ar-<u>C</u>$H_2$-NH), 56.0, 56.1 [$C_6H_3$(O<u>C</u>$H_3$)$_2$], 111.1 (Ar <u>C</u>-2 or Ar <u>C</u>-5 or Ar <u>C</u>-6 in C_6H_3), 111.3 (Ar <u>C</u>-2 or Ar <u>C</u>-5 or Ar <u>C</u>-6 in C_6H_3), 120.0 (Ar <u>C</u>-2 or Ar <u>C</u>-5 Ar <u>C</u>-6 in C_6H_3), 131.8 (Ar <u>C</u>-1 or Ar <u>C</u>-3 or Ar <u>C</u>-4 in C_6H_3), 148.4 (Ar <u>C</u>-1 or Ar <u>C</u>-3 or Ar <u>C</u>-4 in C_6H_3), 149.2 (Ar <u>C</u>-1 or Ar <u>C</u>-3 or Ar <u>C</u>-4 in C_6H_3), 165.8 (<u>C</u>-2, <u>C</u>-4, and <u>C</u>-6 in triazine). *Anal.* Calcd for $C_{51}H_{68}N_{12}O_8$: C, 62.69; H, 7.01; N, 17.20. Found: C, 62.67; H, 6.92; N, 17.11.

Synthesis of *N*^{2},*N*$^{2'}$-(Pentane-1,5-diyl)bis(*N*^{4},*N*^{6}-bis(benzo[*d*][1,3]dioxol-5-ylmethyl)-1,3,5-triazine-2,4,6-triamine) (3b-5).

To a solution of intermediate (**2b**)[13] (1.030 g, 2.50 mmol) in DMF (2 mL) were added 1,5-diaminopentane (117.1 μL, 1.00 mmol) and K_2CO_3 (691.0 mg, 5.00 mmol) at room temperature with stirring. The reaction mixture was refluxed in an oil bath for 8 h with stirring. After addition of water (20 mL), the resulting mixture was extracted with CH_2Cl_2 (20 mL×3). The combined organic layer was washed with brine (20 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residual oil was purified by silica gel column chromatography with CH_2Cl_2/MeOH as an eluent to give the desired product (**3b-5**) (420.5 mg, 49% yield) as a brown solid. Mp 79-90 ℃; FAB-MS (positive) *m*/*z* 857 $(M+H)^+$. HR-FAB-MS *m*/*z* 857.3482 (Calcd for $C_{43}H_{45}N_{12}O_8^+$: 857.3478). ^{1}H-NMR ($CDCl_3$) δ: 1.32 [2H, bs, (Ar-NH-CH_2-CH_2)$_2$C$\underline{H}_2$], 1.49 [4H, bs, (Ar-NH-CH_2-C$\underline{H}_2$)$_2$$CH_2$], 3.30 [4H, bs, (Ar-NH-C$\underline{H}_2$-CH_2)$_2$$CH_2$], 4.42 (8H, s, Ar-C$\underline{H}_2$-NH), 5.89 (8H, s, O-C$\underline{H}_2$-O), 6.41-6.98 (12H, m, Ar $\underline{H}$-4, Ar $\underline{H}$-6, Ar $\underline{H}$-7 in C_6H_3). ^{13}C-NMR ($CDCl_3$) δ: 24.2 [(Ar-NH-CH_2-CH_2)$_2$C$\underline{H}_2$], 29.6 [(Ar-NH-CH_2-C$\underline{H}_2$)$_2$$CH_2$], 40.7 [(Ar-NH-C$\underline{H}_2$-$CH_2$)$_2$$CH_2$], 44.5 (Ar-C$\underline{H}_2$-NH), 101.0 (O-C$\underline{H}_2$-O), 108.2 (Ar $\underline{C}$-4 or Ar $\underline{C}$-6 or Ar $\underline{C}$-7 in C_6H_3), 108.3 (Ar $\underline{C}$-4 or Ar $\underline{C}$-6 or Ar $\underline{C}$-7 in C_6H_3), 120.7 (Ar $\underline{C}$-4 or Ar $\underline{C}$-6 or Ar $\underline{C}$-7 in C_6H_3), 133.6 (Ar $\underline{C}$-5 in C_6H_3), 146.7 (Ar $\underline{C}$-3a or Ar $\underline{C}$-7a in C_6H_3), 147.8 (Ar $\underline{C}$-3a or Ar $\underline{C}$-7a in C_6H_3), 166.2 ($\underline{C}$-2, $\underline{C}$-4, and $\underline{C}$-6 in triazine). *Anal.* Calcd for $C_{43}H_{44}N_{12}O_8$•1.5H_2O: C, 58.43; H, 5.36; N, 19.02. Found: C, 58.44; H, 5.44; N, 19.24.

Synthesis of *N*^{2},*N*$^{2'}$-(Hexane-1,6-diyl)bis(*N*^{4},*N*^{6}-bis(benzo[*d*][1,3]dioxol-5-ylmethyl)-1,3,5-triazine-2,4,6-triamine) (3b-6).

To a solution of intermediate (**2b**)[13] (1.030 g, 2.50 mmol) in DMF (2 mL) were added 1,6-diaminohexane (116.2 mg, 1.00 mmol) and K_2CO_3 (691.0 mg, 5.00 mmol) at room temperature with stirring. The reaction mixture was refluxed in an oil bath for 8 h with stirring. After addition of water (20 mL), the resulting mixture was extracted with CH_2Cl_2 (20 mL×3). The combined organic layer was washed with brine (20 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residual oil was purified by silica gel column chromatography with CH_2Cl_2/MeOH as an eluent to give the desired product (**3b-6**) (775.0 mg, 89% yield) as a pale yellow solid. Mp 69-79 ℃; FAB-MS (positive) *m*/*z* 871 $(M+H)^+$. HR-FAB-MS *m*/*z* 871.3654 (Calcd for $C_{44}H_{47}N_{12}O_8^+$: 871.3634). ^{1}H-NMR ($CDCl_3$) δ: 1.36 [4H, bs, (Ar-NH-CH_2-CH_2-C$\underline{H}_2$-)$_2$], 1.54 [4H, s, (Ar-NH-CH_2-C$\underline{H}_2$-CH_2-)$_2$], 3.36 [4H, s, (Ar-NH-C$\underline{H}_2$-CH_2-CH_2-)$_2$], 4.47 (8H, bs, Ar-C$\underline{H}_2$-NH), 5.92 (8H, s, O-C$\underline{H}_2$-O), 6.54-6.98 (12H, m, Ar $\underline{H}$-4, Ar $\underline{H}$-6, Ar $\underline{H}$-7 in C_6H_3). ^{13}C-NMR ($CDCl_3$) δ: 26.6 [(Ar-NH-CH_2-CH_2-C$\underline{H}_2$-)$_2$], 29.5 [(Ar-NH-CH_2-C$\underline{H}_2$-CH_2-)$_2$], 40.6 [(Ar-NH-C$\underline{H}_2$-CH_2-CH_2-)$_2$], 44.6 (Ar-C$\underline{H}_2$-NH), 101.1 (O-C$\underline{H}_2$-O), 108.3 (Ar $\underline{C}$-4 or Ar $\underline{C}$-6 or Ar $\underline{C}$-7 in C_6H_3), 108.4 (Ar $\underline{C}$-4 or Ar $\underline{C}$-6 or Ar $\underline{C}$-7 in C_6H_3), 120.8 (Ar $\underline{C}$-4 or Ar $\underline{C}$-6 or Ar $\underline{C}$-7 in C_6H_3), 133.5 (Ar $\underline{C}$-5 in C_6H_3), 146.8 (Ar $\underline{C}$-3a or Ar $\underline{C}$-7a in C_6H_3), 147.9 (Ar $\underline{C}$-3a or Ar $\underline{C}$-7a in C_6H_3), 166.2 ($\underline{C}$-2, $\underline{C}$-4, and $\underline{C}$-6 in triazine). *Anal.* Calcd for $C_{44}H_{46}N_{12}O_8$•1.7H_2O: C, 58.62; H, 5.52; N, 18.64. Found: C, 58.64; H, 5.41; N, 18.60.

Synthesis of *N*^{2},*N*$^{2'}$-(Heptane-1,7-diyl)bis(*N*^{4},*N*^{6}-bis(benzo[*d*][1,3]dioxol-5-ylmethyl)-1,3,5-triazine-2,4,6-triamine) (3b-7).

To a solution of intermediate (**2b**)[13] (1.030 g, 2.50 mmol) in DMF (2 mL) were added 1,7-diaminoheptane (130.2 mg, 1.00 mmol) and K_2CO_3 (691.0 mg, 5.00 mmol) at room temperature with stirring. The reaction mixture was refluxed in an oil bath for 8 h with stirring. After addition of water (20 mL), the resulting mixture was extracted with CH_2Cl_2 (20 mL×3). The combined organic layer was washed with brine (20 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residual oil was purified by silica gel column chromatography with CH_2Cl_2/MeOH as an eluent to give the desired product (**3b-7**) (668.1 mg, 75% yield) as a pale yellow solid. Mp 59-68 ℃; FAB-MS (positive) *m*/*z* 885 $(M+H)^+$. HR-FAB-MS *m*/*z* 885.3791 (Calcd for $C_{45}H_{49}N_{12}O_8^+$: 885.3791). ^{1}H-NMR ($CDCl_3$) δ: 1.29 [6H, bs, (Ar-NH-CH_2-C$\underline{H}_2$-CH_2)$_2$$CH_2$ and (Ar-NH-CH_2-CH_2-C$\underline{H}_2$)$_2$$CH_2$ and (Ar-NH-CH_2-CH_2-CH_2)$_2$C$\underline{H}_2$], 1.49 [4H, bs,–(Ar-NH-CH_2-C$\underline{H}_2$-CH_2)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-C$\underline{H}_2$)$_2$$CH_2$], 3.32 [4H, s, (Ar-NH-C$\underline{H}_2$-$CH_2$-$CH_2$)$_2$$CH_2$], 4.45 (8H, s, Ar-C$\underline{H}_2$-NH), 5.91 (8H, s, O-C$\underline{H}_2$-O), 6.63-6.92 (12H, m, Ar $\underline{H}$-4, Ar $\underline{H}$-6, Ar $\underline{H}$-7 in C_6H_3). ^{13}C-NMR ($CDCl_3$) δ: 26.8 [(Ar-NH-CH_2-$\underline{C}H_2$-CH_2)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-$\underline{C}H_2$)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-CH_2)$_2$$\underline{C}H_2$] 29.1 [(Ar-NH-$CH_2$-$\underline{C}H_2$-$CH_2$)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-$\underline{C}H_2$)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-CH_2)$_2$$\underline{C}H_2$], 29.7[(Ar-NH-$CH_2$-$\underline{C}H_2$-$CH_2$)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-$\underline{C}H_2$)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-CH_2)$_2$$\underline{C}H_2$], 40.7 [(Ar-NH-$\underline{C}H_2$-$CH_2$-$CH_2$)$_2$$CH_2$], 44.6 (Ar-$\underline{C}H_2$-NH), 101.1 (O-$\underline{C}H_2$-O), 108.3 (Ar $\underline{C}$-4 or Ar $\underline{C}$-6 or Ar $\underline{C}$-7 in C_6H_3), 108.4 (Ar $\underline{C}$-4 or Ar $\underline{C}$-6 or Ar $\underline{C}$-7 in C_6H_3), 120.9 (Ar $\underline{C}$-4 or Ar $\underline{C}$-6 or Ar $\underline{C}$-7 in C_6H_3), 133.3 (Ar $\underline{C}$-5 in C_6H_3), 146.8 (Ar $\underline{C}$-3a or Ar $\underline{C}$-7a in C_6H_3), 147.9 (Ar $\underline{C}$-3a or Ar $\underline{C}$-7a in C_6H_3), 166.0 ($\underline{C}$-2, $\underline{C}$-4, and $\underline{C}$-6 in triazine). *Anal.* Calcd for $C_{45}H_{48}N_{12}O_8$•1.4H_2O: C, 59.38; H, 5.63; N, 18.47. Found: C, 59.37; H, 5.57; N, 18.21.

Synthesis of *N*^{2},*N*$^{2'}$-(Octane-1,8-diyl)bis(*N*^{4},*N*^{6}-bis(benzo[*d*][1,3]dioxol-5-ylmethyl)-1,3,5-triazine-2,4,6-triamine) (3b-8).

To a solution of intermediate (**2b**)[13] (1.030 g, 2.50 mmol) in DMF (2 mL) were added 1,8-diaminooctane (144.3 mg, 1.00 mmol) and K_2CO_3 (691.0 mg, 5.00 mmol) at room temperature with stirring. The reaction mixture was refluxed in an oil bath for 8 h with stirring. After addition of water (20 mL), the resulting mixture was extracted with CH_2Cl_2 (20 mL×3). The combined organic layer was washed with brine (20 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residual oil was purified by silica gel column chromatography with CH_2Cl_2/MeOH as an eluent to give the desired product (**3b-8**) (874.2 mg, 97% yield) as a white solid. Mp 60-68 ℃; FAB-MS (positive) *m*/*z* 899 $(M+H)^+$. HR-FAB-MS *m*/*z* 899.3953 (Calcd for $C_{46}H_{51}N_{12}O_8^+$: 899.3947). ^{1}H-NMR ($CDCl_3$) δ: 1.28 [(8H, bs, (Ar-NH-CH_2-C$\underline{H}_2$-CH_2-CH_2-)$_2$ and/or (Ar-NH-CH_2-CH_2-C$\underline{H}_2$-CH_2-)$_2$ and/or (Ar-NH-CH_2-CH_2-CH_2-C$\underline{H}_2$-)$_2$], 1.49 [4H, s, (Ar-NH-CH_2-C$\underline{H}_2$-CH_2-CH_2-)$_2$ or (Ar-NH-CH_2-CH_2-C$\underline{H}_2$-CH_2-)$_2$ or (Ar-NH-CH_2-CH_2-CH_2-C$\underline{H}_2$-)$_2$], 3.33 [4H, bs, (Ar-NH-C$\underline{H}$2-CH2-CH2-CH2-)$_2$], 4.45 (8H, s, Ar-C$\underline{H}_2$-NH), 5.92 (8H, s, O-C$\underline{H}_2$-O), 6.55-6.99 (12H, m, Ar $\underline{H}$-4, Ar $\underline{H}$-6, Ar $\underline{H}$-7 in C_6H_3). ^{13}C-NMR ($CDCl_3$) δ: 26.8 [(Ar-NH-CH_2-$\underline{C}H_2$-CH_2-CH_2-)$_2$ or (Ar-NH-CH_2-CH_2-$\underline{C}H_2$-CH_2-)$_2$ or (Ar-NH-CH_2-CH_2-CH_2-$\underline{C}H_2$-)$_2$], 29.2 [(Ar-NH-CH_2-$\underline{C}H_2$-CH_2-CH_2-)$_2$ or (Ar-NH-

CH_2-CH_2-$\underline{C}H_2$-CH_2-)$_2$ or (Ar-NH-CH_2-CH_2-CH_2-$\underline{C}H_2$-)$_2$], 29.7 [(Ar-NH-CH_2-$\underline{C}H_2$-CH_2-CH_2-)$_2$ or (Ar-NH-CH_2-CH_2-$\underline{C}H_2$-CH_2-)$_2$ or (Ar-NH-CH_2-CH_2-CH_2-$\underline{C}H_2$-)$_2$], 40.7 [(Ar-NH-$\underline{C}H_2$-CH_2-CH_2-CH_2-)$_2$], 44.6 (Ar-$\underline{C}H_2$-NH), 101.1 (O-$\underline{C}H_2$-O), 108.3 (Ar $\underline{C}$-4 or Ar $\underline{C}$-6 or Ar $\underline{C}$-7 in C_6H_3), 108.4 (Ar $\underline{C}$-4 or Ar $\underline{C}$-6 or Ar $\underline{C}$-7 in C_6H_3), 120.9 (Ar $\underline{C}$-4 or Ar $\underline{C}$-6 or Ar $\underline{C}$-7 in C_6H_3), 133.3 (Ar $\underline{C}$-5 in C_6H_3), 146.8 (Ar $\underline{C}$-3a or Ar $\underline{C}$-7a in C_6H_3), 147.9 (Ar $\underline{C}$-3a or Ar $\underline{C}$-7a in C_6H_3), 165.6 ($\underline{C}$-2, $\underline{C}$-4, and $\underline{C}$-6 in triazine). *Anal.* Calcd for $C_{46}H_{50}N_{12}O_8$•1.4H_2O: C, 59.78; H, 5.76; N, 18.19. Found: C, 59.72; H, 5.50; N, 18.45.

Synthesis of N^2,$N^{2'}$-(Nonane-1,9-diyl)bis(N^4,N^6-bis(benzo[*d*][1,3]dioxol-5-ylmethyl)-1,3,5-triazine-2,4,6-triamine) (3b-9).

To a solution of intermediate (**2b**)[13] (1.030 g, 2.50 mmol) in DMF (2 mL) were added 1,9-diaminononane (158.3 mg, 1.00 mmol) and K_2CO_3 (691.0 mg, 5.00 mmol) at room temperature with stirring. The reaction mixture was refluxed in an oil bath for 8 h with stirring. After addition of water (20 mL), the resulting mixture was extracted with CH_2Cl_2 (20 mL×3). The combined organic layer was washed with brine (20 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residual oil was purified by silica gel column chromatography with CH_2Cl_2/MeOH as an eluent to give the desired product (**3b-9**) (668.9 mg, 73% yield) as a white solid. Mp 63-70 °C; FAB-MS (positive) *m*/*z* 913 $(M+H)^+$. HR-FAB-MS *m*/*z* 913.4119 (Calcd for $C_{47}H_{53}N_{12}O_8^+$: 913.4104). ^{1}H-NMR ($CDCl_3$) δ: 1.26 [10H, bs, (Ar-NH-CH_2-C$\underline{H}_2$-CH_2-CH_2)$_2$$CH_2$ and/or (Ar-NH-CH_2-CH_2-C$\underline{H}_2$-CH_2)$_2$$CH_2$ and/or (Ar-NH-CH_2-CH_2-CH_2-C$\underline{H}_2$)$_2$$CH_2$ and (Ar-NH-CH_2-CH_2-CH_2-CH_2)$_2$C$\underline{H}_2$], 1.50 [4H, bs, (Ar-NH-CH_2-C$\underline{H}_2$-CH_2-CH_2)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-C$\underline{H}_2$-CH_2)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-CH_2-C$\underline{H}_2$)$_2$$CH_2$], 3.33 [4H, bs, (Ar-NH-C$\underline{H}_2$-CH_2-CH_2-CH_2)$_2$$CH_2$], 4.45 (8H, s, Ar-C$\underline{H}_2$-NH), 5.91 (8H, s, O-C$\underline{H}_2$-O), 6.63-6.95 (12H, m, Ar $\underline{H}$-4, Ar $\underline{H}$-6, Ar $\underline{H}$-7 in C_6H_3). ^{13}C-NMR ($CDCl_3$) δ: 26.9 [(Ar-NH-CH_2-$\underline{C}H_2$-CH_2-CH_2)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-$\underline{C}H_2$-CH_2)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-CH_2-$\underline{C}H_2$)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-CH_2-CH_2)$_2$$\underline{C}H_2$], 29.2 [(Ar-NH-$CH_2$-$\underline{C}H_2$-$CH_2$-$CH_2$)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-$\underline{C}H_2$-CH_2)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-CH_2-$\underline{C}H_2$)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-CH_2-CH_2)$_2$$\underline{C}H_2$], 29.4 [(Ar-NH-$CH_2$-$\underline{C}H_2$-$CH_2$-$CH_2$)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-$\underline{C}H_2$-CH_2)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-CH_2-$\underline{C}H_2$)$_2$$CH_2$], 29.8 [(Ar-NH-$CH_2$-$\underline{C}H_2$-$CH_2$-$CH_2$)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-$\underline{C}H_2$-CH_2)$_2$$CH_2$ or (Ar-NH-CH_2-CH_2-CH_2-$\underline{C}H_2$)$_2$$CH_2$], 40.8 [(Ar-NH-$\underline{C}H_2$-$CH_2$-$CH_2$-$CH_2$)$_2$$CH_2$], 44.6 (Ar-$\underline{C}H_2$-NH), 101.1 (O-$\underline{C}H_2$-O), 108.3 (Ar $\underline{C}$-4 or Ar $\underline{C}$-6 or Ar $\underline{C}$-7 in C_6H_3), 108.4 (Ar $\underline{C}$-4 or Ar $\underline{C}$-6 or Ar $\underline{C}$-7 in C_6H_3), 120.9 (Ar $\underline{C}$-4 or Ar $\underline{C}$-6 or Ar $\underline{C}$-7 in C_6H_3), 133.3 (Ar $\underline{C}$-5 in C_6H_3), 146.8 (Ar $\underline{C}$-3a or Ar $\underline{C}$-7a in C_6H_3), 147.9 (Ar $\underline{C}$-3a or Ar $\underline{C}$-7a in C_6H_3), 165.9 ($\underline{C}$-2, $\underline{C}$-4, and $\underline{C}$-6 in triazine). *Anal.* Calcd for $C_{47}H_{52}N_{12}O_8$•1.3H_2O: C, 60.28; H, 5.88; N, 17.95. Found: C, 60.26; H, 5.66; N, 18.04.

Antiviral Activity Assay and Cytotoxicity

The anti-HSV-1 activities (EC_{50}) of the synthesized hybrid linker mode C_2-symmetrical TAZ derivatives (**3**) were measured by using a plaque reduction assay,[20] and their cytotoxicity against Vero cells (CC_{50}) was

also evaluated as we described previously. The results are summarized in Table 1 together with data for aciclovir.[21]

REFERENCES AND NOTES

1. 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 edn., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N. Y., 2009 and related references cited therein.
2. S. Reitsma, D. W. Slaaf, H. Vink, M. A. M. J. van Zandvoort, and M. G. A. oude Egbrink, *Pflugers Arch. Eur. J. Physiol.*, 2007, **454**, 345.
3. F. Sansone and A. Casnati, *Chem. Soc. Rev.*, 2013, **42**, 4623.
4. A. M. Duran and J. Meiler, *Comput. Struct. Biotechnol. J.*, 2013, **8**, e201308004.
5. K. Sumoto, *YAKUGAKU ZASSHI*, 2020, **140**, 529, and related references cited therein.
6. N. Mibu, K. Yokomizo, W. Uchida, S. Takemura, J. Zhou, H. Aki, T. Miyata, and K. Sumoto, *Chem. Pharm. Bull.*, 2012, **60**, 408.
7. 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.
8. N. Mibu, K. Yokomizo, A. Koga, M. Honda, K. Mizokami, H. Fujii, N. Ota, A. Yuzuriha, K. Ishimaru, J. Zhou, T. Miyata, and K. Sumoto, *Chem. Pharm. Bull.*, 2014, **62**, 1032.
9. N. Mibu, K. Yokomizo, H. Aki, N. Ota, H. Fujii, A. Yuzuriha, S. Saneyoshi, A. Tanaka, A. Koga, J. Zhou, T. Miyata, and K. Sumoto, *Chem. Pharm. Bull.*, 2015, **63**, 935.
10. N. Mibu, K. Yokomizo, K. Murakami, Y. Ono, M. Ishimaru, M. Otsubo, H. Inao, Y. Ono, J.-R. Zhou, and K. Sumoto, *Chem. Pharm. Bull.*, 2016, **64**, 1769.
11. M. Furutachi, T. Gondo, S. Goto, S. Fuchigami, K. Ako, Y. Oowada , K. Yokomizo, J.-R. Zhou, T. Ishizaki, T. Koga, N. Kashige, F. Miake, and K. Sumoto, *Heterocycles*, 2017, **94**, 1748.
12. M. Furutachi, S. Fuchigami, K. Ako, S. Goto, T. Gondo, M. Takuse, M. Yoshida, K. Yokomizo, J.-R. Zhou, A. Matsunaga, N. Hiraga, N. Kashige, F. Miake, and K. Sumoto, *Heterocycles*, 2018, **96**, 144.
13. N. Mibu, K. Yokomizo, M. Sano, Y. Kawaguchi, K. Morimoto, S. Shimomura, R. Sato, N. Hiraga, A. Matsunaga, J.-R. Zhou, T. Ohata, H. Aki, and K. Sumoto, *Chem. Pharm. Bull.*, 2018, **66**, 830.
14. N. Mibu, T. Ohata, M. Sano, J.-R. Zhou, K. Yokomizo, H. Aki, and K. Sumoto, *J. Therm. Anal. Calorim.*, 2019, **135**, 2807.
15. N. Mibu, K. Yokomizo, A. Yuzuriha, M. Otsubo, Y. Kawaguchi, M. Sano, I. Sakai, K. Nakayama, J. -R. Zhou, and K. Sumoto, *Heterocycles*, 2017, **94**, 1653.
16. S. Shimomura, Y. Inoue, Y. Kawano, Y. Fujita, K. Yamada, Y. Matsumoto, K. Yokomizo, J.-R. Zhou, K. Ota, N. Mibu, M. Furutachi, and K. Sumoto, *Heterocycles*, 2020, **100**, 1657.

17. N. Mibu, K. Yokomizo, K. Yamada, J. Matsuyama, S. Tomonaga, I. Sakai, R. Sato, Y. Kawano, Y. Matsumoto, Y. Fujita, Y. Inoue, M. Iida, K. Hashiguchi, J.-R. Zhou, M. Furutachi, and K. Sumoto, *Heterocycles*, 2019, **98**, 489.
18. Trisubstituted TAZ scaffolds have been applied in the search for many bioactive compounds. For example, see P. Singla, V. Luxami, and K. Paul, *Eur. J. Med. Chem.*, 2015, **102**, 39.
19. N. Mibu, M. Furutachi, Y. Inoue, Y. Fujita, Y. Matsumoto, Y. Kawano, S. Tomonaga, J. Matsuyama, K. Yamada, R. Sato, K. Yokomizo, J.-R. Zhou, S. Shimomura, K. Ota, and K. Sumoto, *Heterocycles*, 2019, **98**, 1580.
20. R. F. Schinazi, J. Peters, C. C. Williams, D. Chance, and A. J. Nahmias, *Antimicrob. Agents Chemother.*, 1982, **22**, 499.
21. T. Ikeda, K. Yokomizo, M. Okawa, R. Tsuchihashi, J. Kinjo, T. Nohara, and M. Uyeda, *Biol. Pharm. Bull.*, 2005, **28**, 1779.