Synthesis and Biological Evaluation of Symmetrical 2,4,6-Trisubstituted 1,3,5-Triazine Derivatives

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We describe the synthesis and biological evaluation of newly designed 2,4,6-trisubstituted symmetrical 1,3,5-triazine (TAZ) derivatives. Among the tested trisubstituted symmetrical TAZ derivatives, various C_3- or C_S-symmetrical alkoxy-amino-substituted TAZ derivatives showed significant antiviral activity against herpes simplex virus type 1 (HSV-1) and/or cytotoxic activity against Vero cells. The structure–activity relationships for anti-HSV-1 activity of these symmetrical 2,4,6-trisubstituted TAZ derivatives are also described. Experimental results indicated that a C_S-symmetrical TAZ structure with introduction of two alkoxy groups and one amine moiety seems to be the minimally required structure for anti-HSV-1 activity.

Key words 1,3,5-triazine; anti-herpes simplex virus type 1; cytotoxic activity; C_3 symmetry; C_S symmetry; plaque reduction assay

Molecular recognition of two-fold (C_2) or three-fold (C_3) symmetrical geometry macromolecules is one of the common features in many important biological responses,[1,2] and we have therefore already designed a few symmetrical target molecules for the purpose of finding biologically active new leads or candidates.[3–5] With reference to the molecular symmetry, small molecules having C_3-, C_S-, or C_2-symmetrical geometry frequently appear in various biologically active compounds.[6–8] Such small symmetrical molecules are usually constructed on a corresponding symmetrical template.

From this point of view, we have recently reported some molecular modifications of tris(2-aminoethyl)amine (TAEA) derivatives to C_3- or C_S-symmetrical tripodal receptor type molecules and the results of biological evaluation of these symmetrical compounds.[3] We have also reported an interesting lectin-like property for sugar recognition of some of these tripodal receptor type TAEA molecules.[4]

In order to achieve a suprafacial three-dimensional interaction of a bioactive symmetrical molecule for its binding site, the nature of substituents in the molecule is thought to be very important for preferential interactions. Such interactions are dictated largely by van der Waals interactions or formation of hydrogen bonds. The introduction of amine (basic nitrogen atom) and/or a bivalent oxygen group such as a hydroxy or alkoxy group into a C_3-symmetrical 1,3,5-triazine (TAZ) template seems to be interesting, because it is well known that amine functionalities behave as both hydrogen acceptors and hydrogen donors in appropriate circumstances. These facts may indicate that molecules with some amine and/or bivalent oxygen functionalities on a heterocyclic C_3-symmetrical TAZ template can produce a property for suprafacial hydrogen-bonding interaction.

For an extension of our studies, we planned to investigate the synthesis of 2,4,6-trisubstituted symmetrical TAZ derivatives[9–16] as well as to evaluate their biological properties. In this paper, we report the results of new synthetic routes for C_3- or C_S-symmetrical 2,4,6-trisubstituted TAZ derivatives in the target molecules together with the results of anti-herpes simplex virus type 1 (HSV-1) activity and cytotoxic activity against Vero cell of the obtained symmetrical 2,4,6-trisubstituted TAZ derivatives.

Results and Discussion

Synthesis To begin with, we carried out a few synthetic trials for the preparation of target symmetrical triacylamino-substituted TAZ (**2**) derivatives by using 2,4,6-triamino-1,3,5-triazine (TATAZ) as a starting material. However, our attempts to separate the target products (**2x** or **2y**) after acylation reactions of TATAZ with acylating agents failed[17] (Fig. 1).

We therefore attempted using 2,4,6-trichloro-1,3,5-triazine (TCTAZ; **1**) as a starting material to prepare target molecules, and we examined substitution reactions by amine or alcohol nucleophiles under various reaction conditions shown in a synthetic review by Blotny.[18] As a result, we obtained many types of target trisubstituted symmetrical TAZ derivatives. The obtained results are summarized in Table 1.

As shown in Table 1, triamino-substituted C_3-symmetrical derivatives (**2a**,[19] **2b**, and **2d**) were obtained predominantly in good yields from reactions of TCTAZ (**1**) with the corresponding amine nucleophile (Entries 1–3).

Trials for the preparation of alkoxy-diamino-trisubstituted TAZ (**3**) by nucleophilic substitutions of TCTAZ with an aliphatic amine (**d**H) and an alcohol (**q**H, **r**H, or **s**H) as nucleophiles under various reaction conditions (Entries 4–9) resulted in the formation of a mixture of a few types of tar-

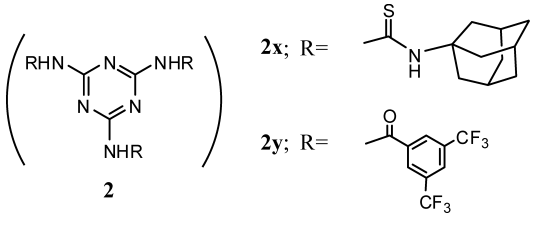

Fig. 1. Target Triacylamino-Substituted TAZ

The authors declare no conflict of interest.

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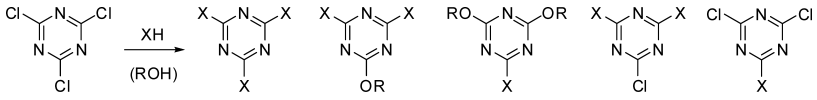
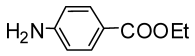
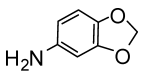
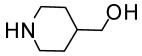
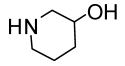
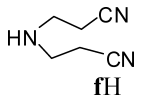
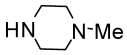
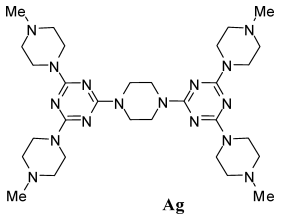
Table 1. TAZ Derivatives from Reactions of TCTAZ (**1**) and Amines (**X**H)



1 **2** **3** **4** **5** **6**

Entry	Amine **X**H	Ratio of **1** : amine : (additive)	Conditions[a]	Solvent	Products (yield %)
1	 **a**H	1 : 3.3	Reflux 15 min	AcOH	**2a** (83)
2	 **b**H	1 : 3.3	Reflux 1.5 h	AcOH	**2b**·HCl (82)
3		1 : 6	MW 50 W, 160°C, 5 min	Dioxane	**2d** (70)
4		1 : 6	MW 50 W, 100°C, 5 min	EtOH	**2d** (24), **3dq** (36), **4dqq** (4)
5	 **d**H	1 : 2	MW 50 W, 160°C, 5 min	*i*-PrOH	**3dr** (2), **5d** (12), **6d** (11)
6		1 : 4 : (10 DIPEA[b])	MW 50 W, 160°C, 10 min	*i*-PrOH	**2d** (8), **3dr** (4), **5d** (27)
7		1 : 2.5 : (5 DIPEA[b])	MW 50 W, 160°C, 10 min	*i*-PrOH	**2d** (9), **3dr** (1), **5d** (88)
8		1 : 2.5 : (5 DIPEA[b])	MW 50 W, 160°C, 10 min	*n*-HepOH	**3ds** (3), **5d** (26)
9		1 : 2 : (2 TEA[c])	0°C, 1 h to rt 17 h	CH_2Cl_2	**5d** (57)
10	 **e**H	1 : 6	180°C, 1 h		**2e** (29)
11	 **f**H	1 : 2 : (2 TEA[c])	0°C, 1 h to rt 18 h	dry CH_2Cl_2	**5f** (33)
12	 **g**H	1 : 3	rt 1 h	dry THF	**5g**·3HCl (20)
13		1 : 3.3[d]	Reflux 1 d	AcOH	**Ag** (46)

a) MW means microwave irradiation. *b*) *N*,*N*-Diisopropylethylamine. *c*) Triethylamine. *d*) The target compound could not be isolated.



Ag

get trisubstituted TAZ derivatives. Among these entries, the highest yield (88%) of diamino-chloro-trisubstituted TAZ derivative (**5d**) was obtained from microwave-assisted reaction with *i*-PrOH as a solvent in the presence of *N*,*N*-diisopropylethylamine (DIPEA) (Entry 7). Reactions of TCTAZ with an amine nucleophile (**d**H or **f**H) under mild conditions (room temperature) or reactions using an alcohol as a solvent acting as a nucleophile gave diamino-monochloro-substituted TAZ derivatives (**5d** or **5f**[20]) and monoamino-dichloro-substituted TAZ product (**6d**) (Entries 5–9, and 11).

Using the method reported by Azarifar *et al.*,[21] reactions of TCTAZ (**1**) with a racemic 3-hydroxypiperidine (**e**H) as an amine nucleophile also resulted in the formation of triamino-substituted TAZ (**2e**) in 29% yield (Entry 10).

The reaction of TCTAZ with *N*-methylpiperazine (**g**H) proceeded smoothly even at room temperature to afford the corresponding diamino-monochloro-TAZ derivative (**5g**·HCl) in 20% yield (Entry 12). Dimerization between two intermediates TAZs (**5g** and **2g**) occurred in the reaction of TCTAZ with a nucleophile (**g**H) at a high reaction temperature, resulting in the formation of dimeric triazine (**Ag**), which had a bridged structure with two TAZ rings (Entry 13, see Experimental for details). The reaction mechanism for formation of the dimerized compound **Ag** *via* triamino-TAZ (**2g**)[22] is shown in Chart 1.

In terms of selective formation of targeted symmetrical alkoxy-amino-TAZ derivatives, we found that the above-described synthetic strategy for the preparation of alkoxy-amino-substituted (trisubstituted) TAZ from TCTAZ (**1**) has disadvantages as a method for preparation of targeted symmetrical alkoxy-amino-TAZ derivatives (**3** or **4**).

Mono- or diamino-substituted triazines generally showed poor reactivity against weak nucleophiles such as alcohols. On the other hand, alkoxy-substituted chloro-TAZs had higher reactivities as substrates in further nucleophic substitutions with amine nucleophiles than those of amine-substituted

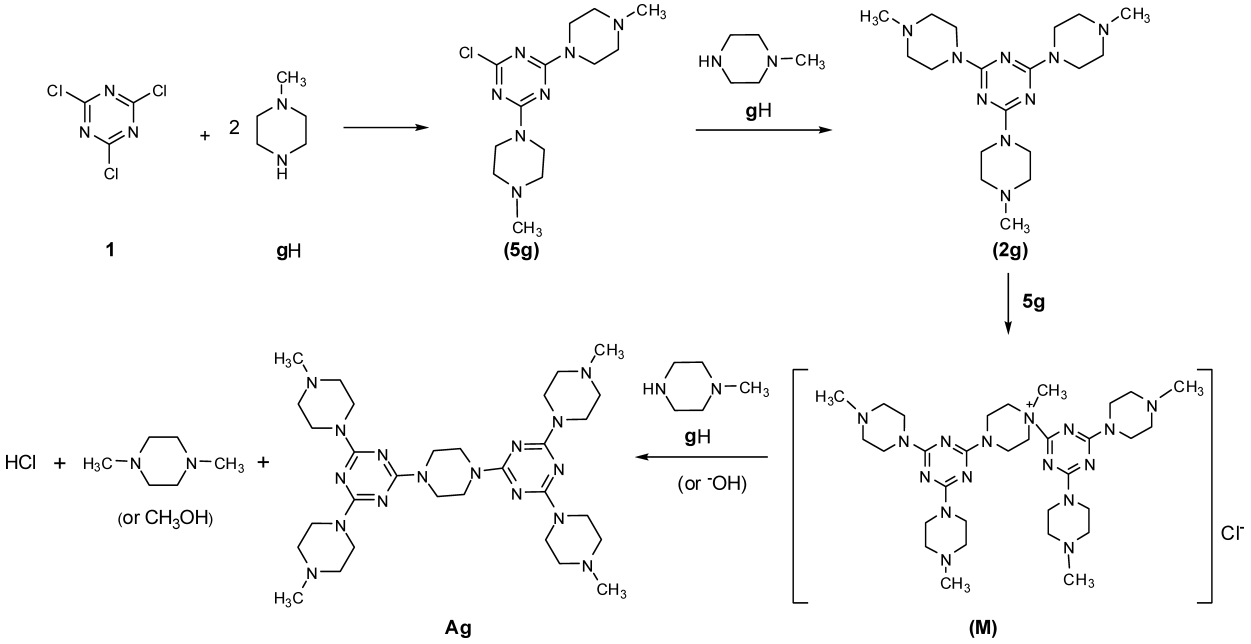


Chart 1. Formation Mechanism of Dimeric TAZ Derivative (**Ag**)

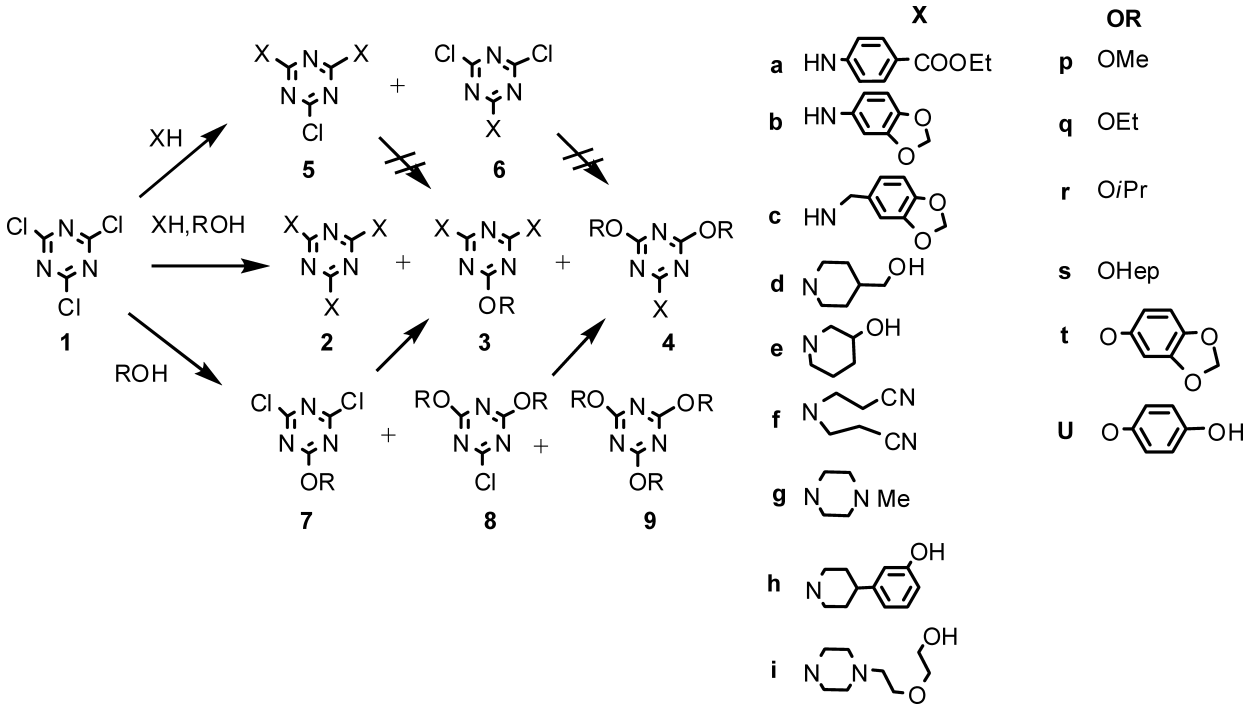


Chart 2

chloro-TAZ derivatives. Therefore, for the purpose of preparation of designed alkoxy-amino-TAZ derivatives as our target molecules, the synthetic procedure *via* alkoxy-substituted chloro-TAZ is expected to be superior to the procedure *via* amine-substituted chloro-TAZs.

Chart 2 shows the strategic point of synthetic pathways *via* alkoxy-chloro-TAZ derivatives (**7**, **8**) to alkoxy-amino-TAZ derivatives (**3**, **4**). Our method *via* alkoxy-substituted chloro-TAZ intermediates for target alkoxy-amino-TAZs consisting of stepwise nucleophilic substitutions gave moderate to excellent results as shown in Table 2.

Among the results, it is noteworthy that when using an isolated monoalkoxy-dichloro-TAZ derivative (**7s**),[23] reactions with amine nucleophiles (Entries 17–20) gave the corresponding target alkoxy-diamino-trisubstituted TAZ derivatives (**3ds**, **3es**, **3hs**, and **3is**) in moderate to excellent yields. These facts apparently indicate that the strategy is advantageous for the purpose of preparation of designed trisubstituted symmetrical alkoxy-amino-TAZ derivatives as our target molecules (**3** or **4**). The results of stepwise one-pot reactions of TCTAZ with other alcohols and then amine nucleophiles are also shown in Table 2 (Entries 21–23).

From these reactions with TCTAZ as a starting material, we could prepare many target symmetrical TAZ derivatives (**3** and **4**) including **3dq**, **3ds**, **3dt**, **3du**, **3es**, **3hs**, **3is**, **4dpp**, **4dpt**, **4dqq**, and **4dss**. In some runs, we also obtained trialkoxy-substituted TAZ derivatives (**9ppt**, **9ptt**, and **9sss**[24]).

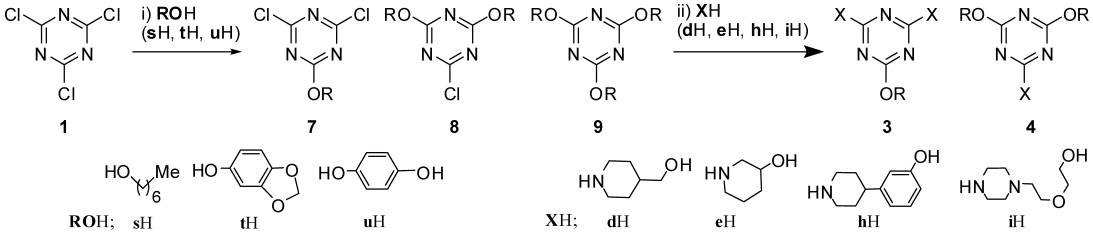
All structures of the synthesized compounds were easily confirmed by spectroscopic and analytical data. The geometries of C_3- or C_S-symmetrical structures of target TAZ derivatives in this article were also confirmed by ^{13}C-NMR spectroscopic data.

Antiviral Activity and Discussion Synthesized TAZ derivatives were evaluated for anti-HSV-1 activities by plaque reduction assays[25] and were also evaluated for their cytotoxicities against Vero cells. The results are summarized in Table 3, and aciclovir[26] is also shown as a positive control. Calculated log P values for the compounds are also shown in Table 3. There were few significant correlations between log P values and EC_{50} values (anti-HSV-1 activity) or between log P values and IC_{50} values (cytotoxicity against Vero cells) among the compounds listed in Table 3. However, regarding structural features of the evaluated 2,4,6-trisubstituted TAZ derivatives, we obtained interesting results for bioactivities of symmetrical derivatives using a TAZ template.

Among the prepared trisubstituted TAZ derivatives, C_3-symmetrical TAZ derivatives (**2a**, **2b**·HCl, **2d**, **2e**[27]) showed no significant anti-HSV-1 activity or cytotoxic activity at a concentration of less than 100 μM.

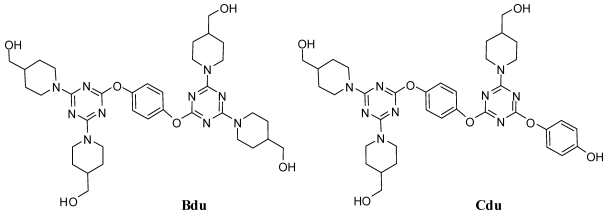
However, two C_S-symmetrical derivatives (**3ds** and **3es**[27]), in which a hydroxylated cyclic amine moiety in the C_3-symmetrical TAZ molecules (**2d** and **2e**) had been substituted with an alkoxy group (HepO), showed different properties of those bioactivities. In compound **3ds**, both the antiviral activity and cytotoxicity were increased (EC_{50} and IC_{50}=25–50 μM), but compound **3es** did not show any significant change in either of the biological activities at a concentration of less than 200 μM. In the C_S-symmetrical derivatives (**3dt**) substituted with a different alkoxy group, similar effects regarding anti-HSV-1 activity and cytotoxicity are also observed (EC_{50}=>6.3 μM and IC_{50}=42.2 μM). In the C_S-symmetrical compounds (**3dq** and **3du**) having a different alkoxy group, weak anti-HSV-1 activity also appeared in both compounds (see Table 3). In the other C_S-symmetrical derivative (**3is**) in which a hydroxylated amine moiety (**d**) in the C_S-symmetrical molecule (**3ds**) had been replaced with a different amine functionality

Table 2. Synthesis of Alkoxy-amino-TAZ Derivatives (**3** and **4**) from Reactions of TCTAZ (**1**) with Various Alcohols (**R**OH) and Amines (**X**H)



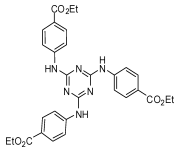
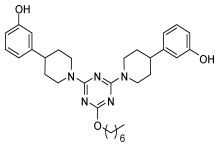
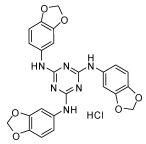
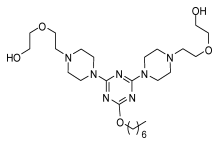
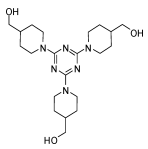
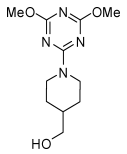
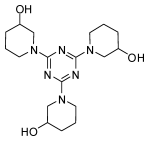
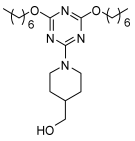
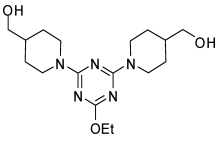
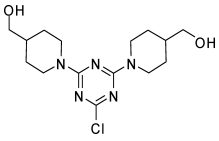
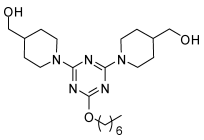
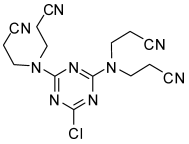
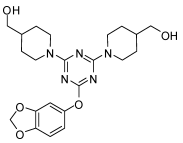
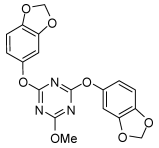
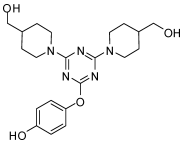
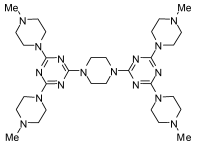
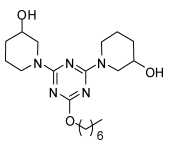
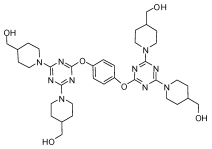
Entry	Reagents	Ratio of reagents and/or (additive)[a]	Conditions[b]	Solvent	Products (yield %)[c]
14	i) **1**, **s**H	**1**:**s**H:**d**H:(collidine) =	i) Collidine, 0°C, 1 h	Dry acetone	**3ds** (73), **4dss** (4), **9sss** (1)
	ii) **d**H	**1**:1.3:4:(1)	ii) MW 50 W, 160°C, 10 min	Dry dioxane	
15	i) **1**, **s**H	**1**:**s**H:**d**H:(collidine:DIPEA)=	i) Collidine, 0°C, 1 h	Dry acetone	**3ds** (1), **4dss** (47)
	ii) **d**H	**1**:2.6:2:(2:2)	ii) DIPEA, rt 6 h	Dry acetonitrile	
16	**1**, **s**H	**1**: **s**H:(collidine)=1:1.3:(1)	0°C, 1 h	Dry acetone	**7s** (70), **9sss** (1)
17	**7s**, **d**H	**7s**:**d**H=1:6.3	MW 50 W, 160°C, 10 min	Dry dioxane	**3ds** (85)
18	**7s**, **e**H	**7s**:**e**H:(DIPEA)=1:3:(3)	rt 2 h	Dry acetonitrile	**3es** (92)
19	**7s**, **h**H	**7s**:**h**H:(DIPEA)=1:2:(3)	rt 20 h	Dry acetonitrile	**3hs** (69)
20	**7s**, **i**H	**7s**:**i**H:(DIPEA)=1:3:(3)	rt 21 h	Dry acetonitrile	**3is** (37)
21	i) **1**, **t**H	**1**:**t**H:**d**H:(collidine)=	i) Collidine, rt 3 h	Dry acetone	**3dt** (74)
	ii) **d**H	**1**:1.3:4:(1)	ii) MW 300 W, 160°C, 10 min	Dry dioxane	
22	i) **1**, **t**H	**1**:**t**H:**d**H:(NaOH)=	i) Aq. NaOH, rt 2 h	MeOH	**4dpp** (20), **4dpt** (8),
	ii) dH	1.1:1:5:(4)	ii) MW 50 W, 150°C, 15 min	Dry dioxane	**9ppt** (21),[d] **9ptt** (22)[d]
23	i) **1**, **u**H	**1**:**u**H:**d**H:(collidine)=	i) Collidine, rt 3 h	Dry acetone	**3du** (29), **Bdu** (9), **Cdu** (3)
	ii) dH	**1**:1.3:4:(1)	ii) MW 300 W, 160°C, 10 min	Dry dioxane	

a) DIPEA stands for *N*,*N*-diisopropylethylamine. *b*) MW stands for microwave irradiation. *c*) Yield obtained from TCTAZ (**1**). *d*) Yields of **9ppt** and **9ptt** based on **t**H were 23% and 49%, respectively.



(**i**) bearing an ether-linked alcohol, both anti-HSV-1 activity and increased cytotoxicity were observed (EC_{50}=>3.1 μM and IC_{50}=21.4 μM). C_S-Symmetrical compound **3hs** also showed both anti-HSV-1 activity and cytotoxicity (EC_{50}=>50 μM and IC_{50}=55.3 μM) comparable to those of compound **3ds**. These results suggest the importance of the presence of hydroxy

Table 3. Antiviral Activity (EC_{50}), Cytotoxicity (IC_{50}) against HSV-1, and Calculated Log P[a)]

Compound		EC_{50} (μM)	IC_{50} (μM)	Log P	Compound		EC_{50} (μM)	IC_{50} (μM)	Log P
	**2a**	>100	>200	6.64		**3hs**	>50	55.3	8.43
	**2b**·HCl	>100[c)]	>100[d)]	5.51[e)]		**3is**	>3.1	21.4	2.88
	**2d**	>100	>100	2.43		**4dpp**	92.1	>200	1.74
	**2e**	>100	>200	1.96		**4dss**	38.0	178.7	6.72
	**3dq**	395.6	>200	2.42		**5d**	247.5	266.0	2.39
	**3ds**	25–30	25–30	4.57		**5f**	>200	>200	2.67
	**3dt**	>6.3	42.2	3.52		**9ptt**	>200	>200	4.28
	**3du**	123.5	>200	3.36		**Ag**	112.1	>200	3.79
	**3es**	>200	>200	4.27		**Bdu**	>200	>200	5.03[f)]
					Aciclovir[b)]		1.1	>444	−0.76

a) Log P was calculated by using ChemDraw Ultra 10.0. *b*) Data were taken from ref. 26. *c*) Compound (**2b**·HCl) at a concentration of 100 μM reduced plaque formation by *ca.* 10%. *d*) Compound (**2b**·HCl) showed cytotoxicity at a concentration of 200 μM. *e*) A value of the free amine (**2b**). *f*) Log P was calculated by using CAChe 6.1.12.

groups and also the importance of the introduction of an alkoxy group for each biological activity.

Regarding antiviral activities of these symmetrical derivatives, comparison of the activities of two C_S-symmetrical compounds (**3ds** and **4dss**) is particularly interesting. C_S-Symmetrical compound **4dss**, modified by additional introduction of the same alkoxy group (**s**: HepO) into the TAZ ring of **3ds** instead of an amino moiety (**d**), showed almost the same level of antiviral activity (EC_{50}=38.0 μM) and decreased cytotoxicity (IC_{50}=178.7 μM). The results indicate that this modification of **3ds** to **4dss** gave a better selectivity index ($SI=IC_{50}/EC_{50}$) for the antiviral compound, though obtained SI value was still small, providing an easy way for generating an antiviral lead of this 2,4,6-trisubstituted TAZ series. With respect to functional groups included in the molecule, the observed anti-HSV-1 activity of this molecule **4dss** indicates that the distance of one set of two functional groups [an amine moiety containing a hydroxy group and an alkoxy group] seems to be important for a preferential required structure for anti-HSV-1 activity. In fact, compound **4dpp** in which two long-chain alkoxy groups of **4dss** were replaced by two methoxy groups still had considerable activity (EC_{50}=92.1 μM) with low cytotoxicity (IC_{50}=>200 μM). In addition, both the observed anti-HSV-1 and cytotoxic activities of compound **5d** were weak (EC_{50}=247.5 μM and IC_{50}=266.0 μM) and neither of the TAZ derivatives (**5f** and **9ptt**) showed any significant anti-HSV-1 or cytotoxic activity at a concentration of less than 200 μM. These results suggest the importance of the presence of hydroxy groups and an alkoxy group in these C_S-symmetrical TAZ molecular structures for the development of anti-HSV-1 agents.

Concerning the biological activities of dimeric TAZ derivatives, compound **Ag** showed only weak anti-HSV-1 activity (EC_{50}=112.1 μM) and no cytotoxic activity at a concentration of less than 200 μM, but dimeric TAZ derivative **Bdu** did not show any significant biological activities at a concentration of less than 200 μM. Although there is still some uncertainty, the results seem to indicate that the tested dimeric symmetrical TAZ derivatives have a different mode of antiviral or cytotoxic activity.

Regarding biological activities, the obtained results in this TAZ series provide interesting information for further molecular modifications targeting antiviral compounds. Thus, the TAZ template seems to be a preferable template for antiviral compounds rather than the TAEA template,[3] because antiviral activities of most of the C_S-symmetrical compounds in this study were observed at lower concentrations than those of the corresponding cytotoxicities. In addition, many trisubstituted target C_S-symmetrical TAZ derivatives described in this paper showed wide ranges of antiviral (anti-HSV-1) activities.

In the search for new antiviral active candidates or new leads, the results indicate that this heterocyclic TAZ template is a potential new scaffold for designing antiviral active molecules. Considering the nature of an introduced substituent characterizing the lipophilicity of a molecule, further modifications for finding more promising antiviral leads with better selectivity indexes are now under investigation. Based on the results of our previous studies on a few types of symmetrical compounds,[3–5] we speculate that a symmetrical molecule constructed on a symmetric template or with a linker may be an efficient structural feature. For the elucidation of sugar recognition properties of some of the highly bioactive symmetrical compounds such as **3ds**, **3dt**, **3is**, and **4dss** described in this article, we are also planning to carry out calorimetric experiments.

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 JEOL JNM A-500. Chemical shifts were 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), CD_3OD (49.00 ppm), DMSO-d_6 (39.50 ppm), and pyridine-d_5 (149.80 ppm)] for ^{13}C-NMR. 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). Microanalyses were performed with a Yanaco MT-6 CHN corder. Routine monitoring of reactions was carried out using precoated Kieselgel 60F_{254} plates (E. Merck). Microwave irradiation experiments were carried out in a CEM Discover Focused Microwave System. Centrifugal or flash column chromatography was performed on silica gel (Able-Biott, Fuji Silysia FL-60D, or Kanto 60N) with a UV detector. Commercially available starting materials were used without further purification.

General Procedure for Substitution Reactions of TCTAZ with Amines TCTAZ (**1**, 1–10 mmol) was added to a stirred solution of an amine in an appropriate solvent (6–75 mL) with or without an additive, and the resulting mixture was refluxed immediately or stirred or was subjected to microwave irradiation (MW) under the conditions shown in Table 1. The obtained products were purified by chromatography or recrystallization from appropriate solvents, and the yields are also summarized in Table 1. Typical protocols for the preparation of triamino-TAZ derivatives **2a** (Entry 1) and **2d** (Entry 3) are shown below in detail.

4,4′,4″-(1,3,5-Triazine-2,4,6-triyltriimino)trisbenzoic Acid 1,1′,1″-Triethylester (2a) [96474-94-1][19] Entry 1: TCTAZ (**1**; 1.84 g, 10 mmol) was added to a stirred solution of ethyl 4-aminobenzoate (**a**H, 5.45 g, 33 mmol) in glacial acetic acid (AcOH, 75 mL) and the resulting solution was refluxed immediately for 15 min. The precipitated white solids were collected by filtration, washed with boiling water (*ca.* 20 mL×3), and dried at 90°C *in vacuo* to afford product **2a** (4.74 g, 83% yield) with high purity (>98% confirmed by NMR). Purification by recrystallization from *i*-PrOH gave an analytically pure product **2a** (3.06 g, 54% yield) as colorless crystals: mp 222–225°C (from *i*-PrOH) [lit.[19] mp 158°C (EtOH)]. IR (KBr) cm^{-1}: 3450 (NH of amine), 1720 (C=O), 1280, 1105 (C–O). ^{1}H-NMR (DMSO-d_6) δ: 1.34 (9H, t, J=7.0 Hz, CH_3), 4.31 (6H, q, J=7.0 Hz, CH_2), 7.92 (6H, dm, J=8.7 Hz, H3, 5), 8.00 (6H, t, J=8.7 Hz, H2, 6), 9.90 (3H, s, NH). ^{13}C-NMR (DMSO-d_6) δ: 14.15 (CH_3), 60.23 (CH_2), 119.44 (C2, 6), 123.14 (C4), 129.75 (C3, 5), 144.13 (C1), 163.66 (C=N), 165.40 (C=O). Positive-ion FAB-MS m/z: 571($M+H^+$).

HR-FAB-MS *m/z*: 571.2303 (Calcd for $C_{30}H_{31}N_6O_6$: 571.2305). *Anal.* Calcd for $C_{30}H_{30}N_6O_6 \cdot 2.5H_2O$: C, 58.53; H, 5.73; N, 13.65. Found: C, 58.51; H, 5.44; N, 13.67.

***N*²,*N*⁴,*N*⁶-Tris(1,3-benzodioxol-5-yl)-1,3,5-triazine Hydrochloride (2b·HCl)** Entry 2: In the same manner as that for the preparation of **2a** (Entry 1), by the reaction of **1** and 3,4-methylenedioxyaniline (**b**H), product **2b**·HCl (82%) with high purity (>98% confirmed by NMR) was obtained. Recrystallization from MeOH gave an analytically pure product **2b**·HCl (42%) as a white powder: mp 272–274°C (from MeOH). IR (KBr) cm^{-1}: 3410 (NH of amine), 1240 (C–N), 1040 (C–O). ^{1}H-NMR (DMSO-d_6) δ: 6.01 (6H, s, H2), 6.87 (3H, d, J=8.2 Hz, H7), 6.99 (3H, d, J=8.2 Hz, H6), 7.35 (3H, br s, H4), 10.14 (3H, brs, NH). ^{13}C-NMR (DMSO-d_6) δ: 101.13 (C2), 104.12 (C4), 107.85 (C7), 114.92 (C6), 131.72 (C5), 143.82 (C7a), 147.20 (C3a). ^{1}H-NMR (pyridine-d_5) δ: 5.95 (6H, s, H2), 6.88 (3H, d, J=8.2 Hz, H7), 7.41 (3H, dd, J=8.2, 1.5 Hz, H6), 7.84 (3H, s, H4), 8.64 (3H, brs, NH or HCl), 10.22 (3H, brs, HCl or NH). ^{13}C-NMR (pyridine-d_5, 149.80 ppm) δ: 101.44 (C2), 104.39 (C4), 108.23 (C7), 114.34 (C6), 135.47 (C5), 143.47 (C7a), 148.11 (C3a), 165.46 (C2′). Positive-ion FAB-MS *m/z*: 487 (M+H$^+$). HR-FAB-MS *m/z*: 487.1365 (Calcd for $C_{24}H_{19}N_6O_6$: 487.1366). *Anal.* Calcd for $C_{24}H_{18}N_6O_6 \cdot HCl \cdot 0.7H_2O$: C, 53.83; H, 3.84; N, 15.69. Found: C, 53.88; H, 3.83; N, 15.49.

1,1′,1″-(1,3,5-Triazine-2,4,6-trityl)tris[(piperidine-4-yl)-methanol] (2d) Entry 3: A mixture of **1** (0.74 g, 4.0 mmol) and 4-piperidinemethanol (**d**H, 2.76 g, 24 mmol) in dioxane (8 mL) was subjected to MW at 160°C (50 W) for 5 min with stirring. After evaporation of the solvent, the residue was dissolved in a mixture of EtOAc (40 mL) and aqueous saturated $NaHCO_3$ (40 mL) and then separated. The aqueous layer was extracted with EtOAc (40 mL×2). The combined organic layer was dried ($MgSO_4$). Evaporation of the solvent gave product **2d** (1.17 g, 70%). Recrystallization from propionitrile gave **2d** (0.86 g, 51%) as colorless crystals: mp 198–201°C (from EtCN). IR (KBr) cm^{-1}: 3400 (OH of alcohol), 1250 (C–N of *t*-amine), 1040 (C–O of alcohol). ^{1}H-NMR (DMSO-d_6) δ: 0.99 (6H, dm, J=12.5 Hz, H3′β, 5′β), 1.58 (3H, m, H4′), 1.66 (6H, dm, J=12.5 Hz, H3′α, 5′α), 2.70 (6H, dt, J=12.5, 2.1 Hz, H2′β, 6′β), 3.25 (6H, d, J=5.6 Hz, H1), 4.40 (3H, t, J=5.3 Hz, OH), 4.60 (6H, brd, J=12.5 Hz, H2′α, 6′α). ^{13}C-NMR (DMSO-d_6) δ: 28.38 (C3′, 5′), 38.74 (C4′), 42.60 (C2′, 6′), 65.74 (C1), 164.68 (C2″). Positive-ion FAB-MS *m/z*: 421 (M+H$^+$). HR-FAB-MS *m/z*: 421.2929 (Calcd for $C_{21}H_{37}N_6O_3$: 421.2927). *Anal.* Calcd for $C_{21}H_{36}N_6O_3$: C, 59.98; H, 8.63; N, 19.98. Found: C, 59.92; H, 8.59; N, 19.98.

1,1′-(6-Ethoxy-1,3,5-triazine-2,4-diyl)bis[(piperidin-4-yl)methanol] (3dq) and 1-(4,6-Diethoxy-1,3,5-triazine-2-yl)-(piperidine-4-yl)-methanol (4dqq) Entry 4: In the same manner as that for the preparation of **2d** (Entry 3), the reaction of **1** and **d**H was carried out in EtOH. After evaporation, the residue was purified by flash chromatography (CH_2Cl_2 : EtOH=90 : 10) to give **2d** (24%), **3dq** (36%), and **4dqq** (4%) as a colorless oil. An analytical sample **3dq** was obtained by recrystallization from AcOEt.

3dq: Colorless crystals, mp 133–134°C (from AcOEt). IR (KBr) cm^{-1}: 3345 (OH of alcohol), 1190, 1145 (C–N of *t*-amine), 1025 (C–O of alcohol). ^{1}H-NMR (CD_3OD) δ: 1.13 (4H, m, H3′β, 5′β), 1.33 (3H, t, J=7.0 Hz, H2‴), 1.73 (2H, m, H4′), 1.75 (4H, brt, J=12 Hz, H3′α, 5′α), 2.82 (4H, dt, J=12.8, 2.3 Hz, H2′β, 6′β), 3.41 (4H, d, J=6.1 Hz, H1), 4.33 (2H, q, J=7.0 Hz, H1‴), 4.71 (4H, brd, J=13 Hz, H2′α, 6′α). ^{13}C-NMR (CD_3OD) δ: 14.86 (C2‴), 29.79 (C3′, 5′), 40.31 (C4′), 44.54 (C2′, 6′), 63.28 (C1‴), 67.79 (C1), 166.96 (C2″, 4″), 172.10 (C6″). Positive-ion FAB-MS *m/z*: 352 (M+H$^+$). HR-FAB-MS *m/z*: 352.2347 (Calcd for $C_{17}H_{30}N_5O_3$: 352.2349). *Anal.* Calcd for $C_{17}H_{29}N_5O_3$: C, 58.10; H, 8.32; N, 19.93. Found: C, 57.89; H, 8.24; N, 19.76.

4dqq: ^{1}H-NMR (CD_3OD) δ: 1.19 (2H, m, H3′β, 5′β), 1.38 (6H, q, J=7.0 Hz, H2‴), 1.75 (1H, m, H4′α), 1.80 (2H, m, H3′α, 5′α), 2.92 (2H, dt, J=10.8, 2.4 Hz, H2′β, 6′β), 3.42 (2H, d, J=7.0 Hz, H1), 4.36 (4H, q, J=7.0 Hz, H1‴), 4.76 (2H, m, H2′α, 6′α). ^{13}C-NMR (CD_3OD) δ: 14.67 (C2‴), 29.69 (C3′, 5′), 40.06 (C4′), 44.82 (C2′, 6′), 64.23 (C1‴), 67.55 (C1), 167.40 (C2″), 172.90 (C4″, 6″). Positive-ion FAB-MS *m/z*: 283 (M+H$^+$). HR-FAB-MS *m/z*: 283.1778 (Calcd for $C_{13}H_{23}N_4O_3$; 283.1770).

1-(4,6-Dichloro-1,3,5-triazine-2-yl)-4-piperidinemethanol (6d) Entry 5: In the same manner as that for the preparation of **2d** (Entry 3), the reaction of **1** and **d**H was carried out in *i*-PrOH. After removal of the white precipitated solid (**d**H·HCl), the residue obtained by evaporation was purified by flash chromatography (CH_2Cl_2 : 95% EtOH : 28% NH_3=97 : 2.7 : 0.3→93 : 6.5 : 0.5) to give products **6d** (11%) as a yellow oil, **5d** (12%), and **3dr** (2%).

6d: Positive-ion FAB-MS *m/z*: 263 (M+H$^+$). HR-FAB-MS *m/z*: 263.0460 (Calcd for $C_9H_{13}Cl_2N_4O$: 263.0466). ^{1}H-NMR ($CDCl_3$) δ: 1.26 (2H, m, H3′β, 5′β), 1.44 (0.5H, brs, OH), 1.58 (0.5H, brs, OH), 1.84 (1H, m, H4′α), 1.89 (2H, dm, J=13.4 Hz, H3′α, 5′α), 2.97 (2H, dt, J=13.0, 2.7 Hz, H2′β, 6′β), 3.55 (2H, d, J=6.1 Hz, H1), 4.78 (2H, dt, J=6.7, 2.3 Hz, H2′α, 6′α). ^{13}C-NMR ($CDCl_3$) δ: 28.40 (C3′, 5′), 38.50 (C4′), 44.26 (C2′, 6′), 67.01 (C1), 163.75 (C2″), 170.26 (C4″, 6″).

1,1′-(6-Isopropoxy-1,3,5-triazine-2,4-diyl)bis[(piperidin-4-yl)methanol] (3dr) Entry 6: In the same manner as that for the preparation of **2d** (Entry 3), the reaction of **1** and **d**H was carried out with DIPEA in *i*-PrOH. After evaporation of the solvent, the resulting residue was purified by centrifugal chromatography (CH_2Cl_2 : 95% EtOH : 28% NH_3=93 : 6.5 : 0.5) to give **5d** (27%), **2d** (8%), and **3dr** (4%).

3dr: Positive-ion FAB-MS *m/z*: 366 (M+H$^+$). HR-FAB-MS *m/z*: 366.2509 (Calcd for $C_{18}H_{32}N_5O_3$: 366.2505). ^{13}C-NMR ($CDCl_3$) δ: 21.93 (Me), 28.47 (C3′, 5′), 39.10 (C4′), 43.22 (C2′, 6′), 67.66 (C1), 69.02 (C1‴), 165.79 (C2″, 4″), 171.03 (C6″).

1,1′-(6-Chloro-1,3,5-triazine-2,4-diyl)bis[(piperidin-4-yl)methanol] (5d) Entry 7: In the same manner as that described in Entry 6 except for the ratio of reagents (**d**H and DIPEA), the reaction was carried out under the conditions shown in Table 1. Purification by open column chromatography (*n*-hexane : EtOAc=20 : 80→0 : 100) gave **5d** (88%), **2d** (9%), and **3dr** (1%). An analytical sample **5d** was obtained by recrystallization from CH_2Cl_2 as white powder.

Entry 8: In the same manner as that in Entry 7 except for the use of *n*-heptanol instead of *i*-PrOH, the reaction was carried out. Purification of the products by open column chromatography (*n*-hexane : EtOAc=20 : 80→0 : 100) gave **5d** (26%) and **3ds** (3%).

Entry 9: To a solution of **1** (10.0 mmol) in dry CH_2Cl_2 (20 mL) was added a solution of **d**H (20 mmol) and TEA (20 mmol) in dry CH_2Cl_2 (20 mL). After stirring for 1 h at 0°C, the reaction mixture was allowed to warm up to room temperature and then stirred for another 17 h. After addition of

a solution of KOH (100 mmol) in water (60 mL), the resulting mixture was extracted with CH_2Cl_2 (30 mL×2) and then the organic layer was washed with aqueous $NaHCO_3$ (20 mL) and brine (20 mL×2). The organic layer was dried and the solvent was evaporated to give crude **5d** as an oil, which was crystallized by addition of CH_2Cl_2 to form a white solid. Recrystallization of crude **5d** from CH_2Cl_2 gave an analytical pure sample **5d** (57%) as a white powder.

5d: mp 154–155°C (from CH_2Cl_2). IR (KBr) cm^{-1}: 3400 (OH), 1570 (N=C). ^{1}H-NMR ($CDCl_3$) δ: 1.20 (4H, dq, J=7.3, 4.3 Hz, H3′β, 5′β), 1.45 (2H, br s, OH), 1.76 (2H, m, H4′α), 1.79 (4H, t, J=11.9 Hz, H3′α, 5′α), 2.83 (4H, dt, J=13.1, 2.1 Hz, H2′β, 6′β), 3.52 (4H, d, J=5.8 Hz, H1), 4.73 (4H, d, J=13.1 Hz, H2′α, 6′α). ^{13}C-NMR ($CDCl_3$) δ: 28.53 (C3′, 5′), 38.94 (C4′), 43.46 (C2′, 6′), 67.48 (C1), 164.32 (C2″, 4″), 169.61 (C6″). Positive-ion FAB-MS m/z: 342 ($M+H^+$). HR-FAB-MS m/z: 342.1689 (Calcd for $C_{15}H_{25}ClN_5O_2$: 342.1697). *Anal.* Calcd for $C_{15}H_{24}ClN_5O_2$: C, 52.70; H, 7.08; N, 20.49. Found: C, 52.58; H, 7.12; N, 20.20.

1,1′,1″-(1,3,5-Triazine-2,4,6-triyl)tris-3-piperidinol (2e[27]) Entry 10: A mixture of **1** (10 mmol) and 3-hydroxypiperidine (**e**H, 60 mmol) was heated. After addition of water (100 mL) and then ether (100 mL), the insoluble solid material was filtered and then the obtained product was dissolved in MeOH (300 mL). After addition of ether (100 mL), the resulting precipitates were collected. Recrystallization of the crude product from EtOH gave pure product **2e** (29%) as colorless crystals: mp 264–265°C (from EtOH). IR (KBr) cm^{-1}: 3340 (OH of alcohol), 1230 (C–N of *t*-amine), 1060 (C–O of alcohol). ^{1}H-NMR (DMSO-d_6) δ: 1.32 (6H, m, H4, 5), 1.67 (3H, m, H5), 1.88 (3H, m, H4), 2.68 (3H, m, H2), 2.83 (3H, m, H6), 3.38 (3H, m, H3), 4.28 (3H, m, H6), 4.43 (3H, m, H2), 4.79 (3H, m, OH). ^{13}C-NMR (DMSO-d_6) δ: 22.90 (C5), 33.50 (C4), 42.46 (C6), 49.91 (C2), 65.27 (C3), 164.72 (C2′). Positive-ion FAB-MS m/z: 379 ($M+H^+$). HR-FAB-MS m/z: 379.2456 (Calcd for $C_{18}H_{31}N_6O_3$: 379.2458). *Anal.* Calcd for $C_{18}H_{30}N_6O_3$: C, 57.12; H, 7.99; N, 22.21. Found: C, 57.03; H, 7.96; N, 22.01.

3,3′,3″,3‴-[(6-Chloro-1,3,5-triazine-2,4-diyl)-dinitrilo]-tetrakispropanenitrile (5f) [856812-02-7][20)] Entry 11: In a manner similar to that described in Entry 9, the reaction of **1** with **f**H was carried out. Evaporation of the solvent gave crude product **5f** as a pale yellow solid, which was washed with CH_2Cl_2 (15 mL) to give **5f** (33%) as a white solid. An analytical sample **5f** was obtained by recrystallization from CH_2Cl_2 as colorless needles: mp 156–157°C (from CH_2Cl_2) [lit.[20)] mp 149–151°C]. IR (KBr) cm^{-1}: 2250 (CN), 805 (C–Cl). ^{1}H-NMR (DMSO-d_6) δ: 2.84 (4H, t, J=6.7 Hz, $H2_A$), 2.88 (4H, t, J=6.7 Hz, $H2_B$), 3.84 (4H, t, J=6.7 Hz, $H3_A$), 3.89 (4H, t, J=6.7 Hz, $H3_B$). ^{13}C-NMR (DMSO-d_6) δ: 15.52 ($C2_B$), 15.79 ($C2_A$), 42.86 ($C3_A$), 43.06 ($C3_B$), 118.84 (CN_A), 119.08 (CN_B), 164.34 (C2′), 168.58 (C6′). Positive-ion FAB-MS m/z: 358 ($M+H^+$). HR-FAB-MS m/z: 358.1299 (Calcd for $C_{15}H_{17}N_9Cl$: 358.1295). *Anal.* Calcd for $C_{15}H_{16}N_9Cl\cdot0.5H_2O$: C, 49.12; H, 4.67; N, 34.37. Found: C, 48.95; H, 4.47; N, 34.60.

2-Chloro-4,6-bis(4-methyl-1-piperazinyl)-1,3,5-triazine Trihydrochloride (5g·3HCl) Entry 12: To a solution of **1** (1.0 mmol) in dry tetrahydrofuran (THF, 6 mL) was added 1-methylpiperazine (**g**H, 3.0 mmol) with stirring at room temperature. After removal of the precipitated solid, 1 M HCl/EtOH was added to the filtrate, and filtration of the resulting material gave product **5g**·3HCl in 20% yield as colorless crystals.

5g·3HCl: ^{1}H-NMR ($CDCl_3$) δ: 2.35 (6H, s, CH_3), 2.73 (8H, m, H3, 5), 3.22 (8H, m, H2, 6). ^{13}C-NMR ($CDCl_3$) δ: 43.37 (C2, 6), 45.71 (CH_3), 51.50 (C3, 5), 164.34 (C2′, 4′), 169.57 (C6′). Positive-ion FAB-MS m/z: 312 ($M+H^+$). HR-FAB-MS m/z: 312.1710 (Calcd for $C_{13}H_{23}N_7Cl$ for 312.1703).

2,2′-(1,4-Piperazinediyl)bis[4,6-di(4-methyl-1-piperazinyl)-1,3,5-triazine] (Ag) Entry 13: To a solution of **g**H (33.0 mmol) in AcOH (70 mL) was added **1** (1.84 g, 10.0 mmol), and the resulting mixture was refluxed for 1 d. The precipitated solids were collected and washed with hot water (20 mL×2). The obtained precipitate was dissolved in 10% NaOH (20 mL) and the resulting solution was extracted with CH_2Cl_2 (40 mL×2). The organic layer was washed with brine (30 mL) and dried over $MgSO_4$. After removal of the solvent, **Ag** (46%) was obtained as a pale yellow solid. Recrystallization from EtOH–H_2O gave the dimeric TAZ derivative **Ag** as a white powder.

Ag: mp 255–257°C decn. (from EtOH–H_2O). ^{1}H-NMR ($CDCl_3$) δ: 2.31 (12H, s, CH_3), 2.40 (16H, t, J=5.0 Hz, H3′, 5′), 3.78a) (8H, s, Ha), 3.80a) (16H, m, H2′, 6′). ^{13}C-NMR ($CDCl_3$) δ: 43.04 (C2′, 6′), 43.14 (Ca), 46.23 (CH_3), 55.00 (C3′, 5′), 165.39 (C4, 6), 165.53 (C2). Positive-ion FAB-MS m/z: 637 ($M+H^+$). HR-FAB-MS m/z: 637.4651 (Calcd for $C_{30}H_{53}N_{16}Cl$ for 637.4639).

General Procedure for Stepwise Substitution of TCTAZ with Alcohols and Amines (Step 1) To a solution of **1** (5–20 mmol) in dry acetone (7–60 mL) were added an alcohol (**R**OH) and collidine. After stirring for 1–3 h at 0°C or at room temperature, the precipitated collidine·HCl was removed by filtration. Evaporation of the solvent gave crude alkoxy-chloro-TAZ (**7** or **8**). (Step 2) This crude product was dissolved in dry dioxane (7–60 mL), and an amine with or without DIPEA was added. Then stirring was continued at room temperature, or the resulting mixture was subjected to MW at 150–160°C (50 W) under the conditions shown in Table 2. After evaporation of the solvent, the residue was purified by chromatography or recrystallization. A typical protocol for the preparation of compound **3ds** (Entry 14) is shown below in detail.

1,1′-(6-Heptoxy-1,3,5-triazine-2,4-diyl)bis[(piperidin-4-yl)methanol] (3ds), [1-[4,6-Bis(heptyloxy)-1,3,5-triazin-2-yl]piperidin-4-yl]methanol (4dss), and 2,4,6-Tris(heptyloxy)-1,3,5-triazine (9sss) [37068-43-2][24)] Entry 14: (Step 1) To a solution of **1** (1.02 g, 5.5 mmol) in dry acetone (7 mL) were added **s**H (0.843 g, 7.25 mmol) and collidine (0.69 g, 5.7 mmol) at 0°C. After stirring for 1 h at 0°C, the resulting white precipitated salt (collidine·HCl) was removed by filtration. After evaporation of the solvent, a dark orange solid was obtained. (Step 2) This material was dissolved in dry dioxane (5 mL), and **d**H (2.53 g, 22.0 mmol) was added, and then the resulting mixture was subjected to MW at 160°C (50 W) for 10 min with stirring. After evaporation of the solvent, the residue was purified by flash chromatography (CH_2Cl_2 : 95%EtOH : 28%NH_3 = 95 : 4.5 : 0.5→93 : 6.5 : 0.5) to give **3ds** (1.69 g, 73% yield) as a white solid, **4dss** (93 mg, 4% yield), and **9sss** (23 mg, 1% yield).

3ds: mp 122–123°C (from CH_3CN). IR (KBr) cm^{-1}: 3420 (OH of alcohol), 1355, 1050 (C–N of *t*-amine). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.0 Hz, H7‴), 1.18 (4H, m, H3′β, 5′β), 1.29 (6H, m, H5‴, 6‴, 4‴), 1.40 (2H, m, H3‴), 1.47 (2H, br s, OH), 1.76 (8H, m, H2‴, 4′α, 3′α, 5′α), 2.80 (4H, dt,

J=12.8, 2.1 Hz, H2′β, 6′β) 3.51 (4H, d, J=5.8 Hz, H1) 4.26 (2H, t, J=6.9 Hz, H1‴), 4.79 (4H, brd, J=12.8 Hz, H2′α, 6′α). ^{13}C-NMR ($CDCl_3$) δ: 14.06 (C7‴), 22.58 (C6‴), 25.96 (C3‴), 28.57 (C3′, 5′), 28.93, 29.07 (C2‴, 4‴), 31.75 (C5‴), 39.12 (C4′), 43.24 (C2′, 6′), 66.57 (C1‴), 67.69 (C1), 165.82 (C2″, 4″), 170.91 (C6″). Positive-ion FAB-MS m/z: 422 ($M+H^+$). HR-FAB-MS m/z: 422.3141 (Calcd for $C_{22}H_{40}N_5O_3$: 422.3131). *Anal.* Calcd for $C_{22}H_{39}N_5O_3$: C, 62.68; H, 9.32; N, 16.61. Found: C, 62.45; H, 9.15; N, 16.60.

4dss: mp 68–70°C (from CH_3CN). IR (KBr) cm^{-1}: 3365 (OH of alcohol), 1250, 1130, 1045 (C–O alcohol and ether). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (6H, t, J=7.0 Hz, H7‴), 1.20 (2H, m, H3′β, 5′β), 1.25–1.35 (12H, m, H4‴, 5‴, 6‴), 1.41 (4H, m, H3‴), 1.60 (1H, brs, OH), 1.73–1.83 (7H, m, H2‴, 4′α, 3′α, 5′α), 2.86 (2H, dt, J=13.1, 2.1 Hz, H2′β, 6′β), 3.52 (2H, d, J=6.1 Hz, H1), 4.31 (4H, t, J=6.9 Hz, H1‴), 4.81 (2H, dm, J=13.1 Hz, H2′α, 6′α). ^{13}C-NMR ($CDCl_3$) δ: 14.04 (C7‴), 22.57 (C6‴), 25.87 (C3‴), 28.53, 28.79, 29.00 (C3′, 5′, 2‴, 4‴), 31.73 (C5‴), 38.95 (C4′), 43.55 (C2′, 6′), 67.49 (C1), 67.49 (C1‴), 166.39 (C2″, 4″), 171.90 (C6″). Positive-ion FAB-MS m/z: 423 ($M+H^+$). HR-FAB-MS m/z: 423.3339 (Calcd for $C_{23}H_{43}N_4O_3$: 423.3335). *Anal.* Calcd for $C_{23}H_{42}N_4O_3$: C, 65.37; H, 10.02; N, 13.26. Found: C, 65.43; H, 10.05; N, 13.08.

9sss: Positive-ion FAB-MS m/z: 424 ($M+H^+$). HR-FAB-MS m/z: 424.3538 (Calcd for $C_{24}H_{46}N_3O_3$: 424.3539). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (9H, t, J=7.0 Hz, H7′), 1.25–1.35 (18H, m, H5′, 6′, 4′), 1.43 (6H, m, H3′), 1.78 (6H, m, H2′), 4.38 (6H, t, J=6.7 Hz, H1′). ^{13}C-NMR ($CDCl_3$) δ: 13.96 (C7′), 22.53 (C6′), 25.75 (C3′), 28.64 (C2′), 28.91 (C4′), 31.69 (C5′), 68.43 (C1′), 173.15 (C2, 4, 6).

Entry 15: (Step 1) The reaction was carried out in the same manner as that described above procedure (Entry 14, Step 1) except for the ratio of reagents [alcohol (**s**H) and collidine]. (Step 2) The residue was dissolved in dry acetonitrile, and **d**H and DIPEA were added, and then the resulting mixture was stirred at room temperature for 6 h. After evaporation of the solvent, the residue was purified by flash chromatography (n-hexane : EtOAc=70 : 30→60 : 40) to give **3ds** (1%) as a white solid and **4dss** (47%). Analytical samples of **3ds** and **4dss** were obtained by recrystallization from acetonitrile as colorless crystals.

2,4-Dichloro-6-(heptyloxy)-1,3,5-triazine (7s) [107392-85-8][23] Entry 16: In a manner similar to that for preparation of compound **3ds** (Entry 14, Step 1), the reaction of **1** (22 mmol), **s**H (29 mmol) and collidine (23 mmol) was carried at 0°C for 1 h. After removal of the salt (collidine·HCl), ice-water (40 mL) was added to the filtrate and the mixture was extracted with CH_2Cl_2 (20 mL×3). The organic layer was dried, and filtrated. The filtrate was evaporated and the residue was purified by open column chromatography (CH_2Cl_2) to give **7s** (70%) as a colorless oil and **9sss** (1%) as a white solid.

7s: ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.0 Hz, H7′), 1.31 (4H, m, H5′, 6′), 1.35 (2H, m, H4′), 1.44 (2H, m, H3′), 1.82 (2H, m, H2′), 4.49 (2H, t, J=6.6 Hz, H1′). ^{13}C-NMR ($CDCl_3$) δ: 13.99 (C7′), 22.51 (C6′), 25.55 (C3′), 28.27 (C2′), 28.77 (C4′), 31.60 (C5′), 70.68 (C1′), 171.05 (C1), 172.45 (C3, 5). Positive-ion FAB-MS m/z: 264 ($M+H^+$). HR-FAB-MS m/z: 264.0618 (Calcd for $C_{10}H_{16}Cl_2N_3O$: 264.0670).

Reactions of 7s with Amines The reaction of **7s** with various nucleophiles (**d**H, **e**H, **h**H, and **i**H) under the conditions shown in Table 2 afforded compound **3ds** (85%), **3es** (92%), **3hs** (69%), and **3is** (37%), respectively (see Entries 17–20). A typical protocol for the preparation of **3ds** is shown below in detail. Physical and spectroscopic data of these compounds are shown below.

Entry 17: A solution of **7s** (12.0 mmol) and **d**H (75.7 mmol) in dry dioxane (15 mL) was subjected to MW with stirring. The obtained product was separated by flash chromatography (n-hexane : EtOAc=40 : 60→20 : 80) to give **3ds** (85%) as a white solid.

1,1′-[6-(Heptyloxy)-1,3,5-triazine-2,4-diyl]bis(piperidin-3-ol) (3es[27]**)** Entry 18: Colorless crystals, mp 126–127°C (CH_3CN). IR (KBr) cm^{-1}: 3420 (OH of alcohol), 1375, 1510 (C–N of t-amine), 1105 (C–O). ^{1}H-NMR (pyridine-d_5) δ: 0.83 (3H, t, J=7.0, H7″), 1.15–1.25 (6H, m, H4″, 5″, 6″), 1.38 (2H, m, H3″), 1.50 (2H, m, H5α or β), 1.65–1.85 (6H, m, H2″, 4α or β, 5β or α), 2.13 (2H, m, H4β or α), 3.19 (2H, m, H6α or β), 3.38 (2H, m, H2α or β), 3.96 (2H, m, H3), 4.36 (2H, brs, H1″), 4.50 (2H, brs, H6β or α), 4.87 (2H, brd, J=10.4 Hz, H2β or α), 4.90 (2H, brs, OH). ^{13}C-NMR (pyridine-d_5) δ: 14.11 (C7″), 22.71 (C6″), 23.53 (C5), 26.29 (C3″), 29.20, 29.42 (C2″, 4″), 31.88 (C5″), 34.28 (C4), 43.65 (C6), 51.23 (C2), 66.28, 66.36 (C1″, 3), 166.82 (C2′, 4′), 171.63 (C6′). Positive-ion FAB-MS m/z: 394 ($M+H^+$). HR-FAB-MS m/z: 394.2822 (Calcd for $C_{20}H_{36}N_5O_3$: 394.2818). *Anal.* Calcd for $C_{20}H_{35}N_5O_3$: C, 58.89; H, 9.04; N, 17.17. Found: C, 58.95; H, 9.04; N, 17.11.

3,3′-[1,1′-(6-(Heptyloxy)-1,3,5-triazine-2,4-diyl)bis-(piperidine-4,1-diyl)]diphenol (3hs) Entry 19: White solid, mp 79–80°C. IR (KBr) cm^{-1}: 3400 (O–H of ArOH), 1575, 1515 (C–N of t-amine). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, t, J=6.9 Hz, H7‴), 1.26 (6H, m, H4‴, 5‴, 6‴), 1.39 (2H, m, H3‴), 1.61 (4H, m, H3′, 5′), 1.73 (2H, m, H2‴), 1.85 [6H, brd, J=12.5 Hz, H3′, 5′ (4H), OH (2H)], 2.68 (2H, brt, J=12.5 Hz, H4′), 2.86 (4H, t, J=12.5 Hz, H2′β, 6′β), 4.28 (2H, t, J=6.9 Hz, H1‴), 4.90 (4H, brd, J=13.1 Hz, H2′α, 6′α), 5.74 (1H, brs, H_2O), 6.66 (2H, s, H2), 6.67 (2H, d, J=7.6 Hz, H4), 6.74 (2H, d, J=7.6 Hz, H6), 7.14 (2H, t, J=7.6 Hz, H5). ^{13}C-NMR ($CDCl_3$) δ: 14.02 (C7‴), 22.57 (C6‴), 25.95 (C3‴), 28.95 (C2‴ or C4‴), 29.05 (C4‴ or C2‴), 31.74 (C5‴), 33.08 (C3′, 5′), 42.96 (C4′), 44.10 (C2′, 6′), 66.73 (C1‴), 113.37 (C4), 113.81 (C2), 119.07 (C6), 129.58 (C5), 147.76 (C1), 156.02 (C3), 165.80 (C2″, 4″), 170.99 (C6″). Positive-ion FAB-MS m/z: 546 ($M+H^+$). HR-FAB-MS m/z: 546.3441 (Calcd for $C_{32}H_{44}N_5O_3$: 546.3444). *Anal.* Calcd for $C_{32}H_{43}N_5O_3\cdot 0.5H_2O$: C, 69.29; H, 7.99; N, 12.62. Found: C, 69.16; H, 8.01; N, 12.43.

4,4′-[6-(Heptyloxy)-1,3,5-triazine-2,4-diyl]bis[2-[2-(1-piperazinyl)-ethoxy]ethanol] (3is) Entry 20: Yellow oil. IR (KBr) cm^{-1}: 3375 (OH of alcohol), 1570, 1525 (C–N of t-amine), 1120 (C–O). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.0 Hz, H7‴), 1.29 (6H, m, H4‴, 5‴, 6‴), 1.40 (2H, m, H3‴), 1.74 (2H, m, H2‴), 2.54 (8H, t, J=5.0 Hz, H3′, 5′), 2.62 (4H, t, J=5.2 Hz, H5), 2.93 (2H, brs, OH), 3.61 (4H, t, J=4.6 Hz, H2), 3.68 (4H, t, J=5.2 Hz, H4), 3.71 (4H, t, J=4.6 Hz, H1), 3.83 (8H, t, J=5.0 Hz, H2′, 6′), 4.25 (2H, t, J=6.9 Hz, H1‴). ^{13}C-NMR ($CDCl_3$) δ: 14.00 (C7‴), 22.55 (C6‴), 25.94 (C3‴), 28.90 (C2‴ or C4‴), 29.02 (C4‴ or C2‴), 31.73 (C5‴), 42.93 (C2′, 6′), 53.20 (C3′, 5′), 57.99 (C5), 61.91 (C1), 66.69 (C1‴), 67.75 (C4), 72.39 (C2), 165.97 (C2″, 4″), 170.95 (C6″). Positive-ion FAB-MS m/z: 540 ($M+H^+$). HR-FAB-MS m/z: 540.3881 (Calcd for $C_{26}H_{50}N_7O_5$: 540.3873). *Anal.* Calcd for $C_{26}H_{49}N_7O_5\cdot 0.2H_2O$: C, 57.48; H, 9.16; N, 18.05. Found: C, 57.38; H, 9.37; N, 18.15.

1,1′-[6-(1,3-Benzodioxol-5-yloxy)-1,3,5-triazine-2,4-diyl]-bis-4-piperidinemethanol (3dt) Entry 21: This compound was prepared in a manner similar to that for compound **3ds** (Entry 14). Purification by flash chromatography (CH_2Cl_2 : EtOH=95 : 5→93 : 7) gave **3dt** (74%) as a yellow solid. An analytical sample was obtained by recrystallization from propionitrile as colorless crystals: mp 165–166°C (from C_2H_5CN). IR (KBr) cm^{-1}: 1585, 1505 (C–N of *t*-amine) 1035 (C–O of alcohol). ^{1}H-NMR ($CDCl_3$) δ: 1.18 (4H, m, H3′β, 5′β), 1.52 (2H, brs, OH), 1.75 (6H, m, H4′α, 3′α, 5′α), 2.78 (4H, t, J=12.5 Hz, H2′β, 6′β), 3.50 (4H, d, J=6.1 Hz, H1), 4.68 (4H, brs, H2′α, 6′α), 5.97 (2H, s, H2‴), 6.62 (1H, d, J=2.4, 8.5 Hz, H6‴), 6.70 (1H, d, J=2.4 Hz, H4‴), 6.74 (1H, d, J=8.5 Hz, H7‴). ^{13}C-NMR ($CDCl_3$) δ: 28.53 (C3′, 5′), 39.06 (C4′), 43.34 (C2′, 6′), 67.61 (C1), 101.39 (C2‴), 104.28 (C4‴), 107.44 (C7‴), 114.29 (C6‴), 144.35 (C7a‴), 147.23 (C3a‴ or 5‴), 147.45 (C5‴ or 3a‴), 165.89 (C2″, 4″), 171.20 (C6″). Positive-ion FAB-MS m/z: 444 ($M+H^+$). HR-FAB-MS m/z: 444.2251 (Calcd for $C_{22}H_{30}N_5O_5$: 444.2247). *Anal.* Calcd for $C_{22}H_{29}N_5O_5$: C, 59.58; H, 6.59; N, 15.79. Found: C, 59.57; H, 6.70; N, 15.95.

1-(4,6-Dimethoxy-1,3,5-triazine-2-yl)-4-piperidinemethanol (4dpp), 1-[4-(1,3-Benzodioxol-5-yloxy)-6-methoxy-1,3,5-triazine-2-yl]-4-piperidinemethanol (4dpt), 2-(1,3-Benzodioxol-5-yloxy)-4,6-dimethoxy-1,3,5-triazine (9ppt), and 2,4-Bis(1,3-benzodioxol-5-yloxy)-6-methoxy-1,3,5-triazine (9ptt) Entry 22: (Step 1) To a solution of **1** (4.06 g, 22 mmol) in MeOH (60 mL) were added **t**H (2.76 g, 20 mmol) and NaOH (3.20 g, 80 mmol) in water (40 mL) at room temperature, and the resulting mixture was stirred for 2 h. The separated solid was filtrated. (Step 2) The mixture of this solid and **d**H (1.15 g, 100 mmol) in dry dioxane (30 mL) was subjected to MW with stirring. After evaporation of the solvent, $CHCl_3$ and MeOH (both 30 mL) were added to the residue and stirred vigorously. The separated solid was removed by filtration and then the solvent was evaporated. Purification of the residue by flash chromatography (CH_2Cl_2 : 95% EtOH : 28% NH_3=997 : 2.7 : 0.3→970 : 27 : 3) gave **9ppt** (1.24 g, 21%) as a white solid, **9ptt** (1.86 g, 22%) as a white solid, **4dpt** (638 mg, 8% yield) as a pale yellow solid, and **4dpp** (1.11 g, 20% yield) as a white solid. An analytical sample **9ppt** was obtained by recrystallization from MeOH.

4dpp: mp 116–118°C. IR (KBr) cm^{-1}: 3335 (OH of alcohol), 1360, 1130 (C–N of *t*-amine). ^{1}H-NMR ($CDCl_3$) δ: 1.2 (2H, m, H3′β, 5′β), 1.63 (1H, brs, OH), 1.8 (3H, m, H3′α, 4′α, 5′α), 2.88 (2H, dt, J=13.1, 2.7 Hz, H2′β, 6′β), 3.53 (2H, d, J=6.1 Hz, H1), 3.95 (6H, s, MeO), 4.82 (2H, dm, J=13.1 Hz, H2′α, 6′α). ^{13}C-NMR ($CDCl_3$) δ: 28.49 (C3′, 5′), 38.91 (C4′), 43.59 (C2′, 6′), 54.40 (MeO), 67.40 (C1), 166.32 (C2″), 172.27 (C4″, 6″). Positive-ion FAB-MS m/z: 255 ($M+H^+$). HR-FAB-MS m/z: 255.1454 (Calcd for $C_{11}H_{19}N_4O_3$: 255.1457). *Anal.* Calcd for $C_{11}H_{18}N_4O_3$: C, 51.96; H, 7.13; N, 22.03. Found: C, 51.97; H, 7.17; N, 21.79.

4dpt: ^{1}H-NMR ($CDCl_3$) δ: 1.19 (2H, m, H3′β, 5′β), 1.75–1.85 (3H, m, H3′α, 4′α, 5′α), 2.86 (2H, m, H2′β, 6′β), 3.52 (2H, d, J=6.1 Hz, H1), 3.90 (3H, s, OMe), 4.65 (1H, d, J=13.1 Hz, H2′α or 6′α), 4.81 (1H, d, J=13.1 Hz, H6′α or 2′α), 5.98 (2H, s, H2‴), 6.61 (1H, dd, J=8.5, 2.4 Hz, H6‴), 6.68 (1H, d, J=2.4 Hz, H4‴), 6.76 (1H, d, J=8.5 Hz, H7‴). ^{13}C-NMR ($CDCl_3$) δ: 28.42 (C3′, 5′), 38.76 (C4′), 43.64 (C2′, 6′), 54.50 (MeO), 67.25 (C1), 101.53 (C2‴), 103.96 (C4‴), 107.69 (C7‴), 114.08 (C6‴), 144.89 (C7a‴), 146.50 (C5‴), 147.70 (C3a‴), 166.30 (C2″), 172.22 (C4″ or C6″), 172.38 (C6″ or C4″). Positive-ion FAB-MS m/z: 361 ($M+H^+$). HR-FAB-MS m/z: 361.1516 (Calcd for $C_{17}H_{21}N_4O_5$: 361.1512).

9ppt: ^{1}H-NMR ($CDCl_3$) δ: 4.01 (6H, s, OCH_3), 6.00 (2H, s, H2), 6.62 (1H, dd, J=8.2, 2.4 Hz, H6), 6.68 (1H, d, J=2.4 Hz, H4), 6.79 (1H, d, J=8.2 Hz, H7). ^{13}C-NMR ($CDCl_3$) δ: 55.47 (OCH_3), 101.75 (C2), 103.71 (C4), 107.96 (C7), 113.91 (C6), 145.51 (C7a), 146.05 (C5), 148.03 (C3a), 173.55 (C4′, 6′), 174.00 (C2′). Positive-ion FAB-MS m/z: 278 ($M+H^+$). HR-FAB-MS m/z: 278.0775 (Calcd for $C_{12}H_{12}N_3O_5$: 278.0777).

9ptt: mp 156–157°C (from MeOH). IR (KBr) cm^{-1}: 1355, 1170 (C–N of *t*-amine). ^{1}H-NMR ($CDCl_3$) δ: 3.96 (3H, s, OCH_3), 5.99 (4H, s, H2), 6.61 (2H, dd, J=8.5, 2.4 Hz, H6), 6.66 (2H, d, J=2.4 Hz, H4), 6.78 (2H, d, J=8.5 Hz, H7). ^{13}C-NMR ($CDCl_3$) δ: 55.63 (OCH_3), 101.78 (C2), 103.68 (C4), 107.98 (C7), 113.88 (C6), 145.58 (C7a), 145.99 (C5), 148.04 (C3a), 173.81 (C6′) 176.26 (C2′, 4′). Positive-ion FAB-MS m/z: 384 ($M+H^+$). HR-FAB-MS m/z: 384.0829 (Calcd for $C_{18}H_{14}N_3O_7$: 384.0832). *Anal.* Calcd for $C_{18}H_{13}N_3O_7$: C, 56.40; H, 3.42; N, 10.96. Found: C, 56.18; H, 3.59; N, 11.09.

[1,1′-[6-(4-Hydroxyphenoxy)-1,3,5-triazine-2,4-diyl]-bis(piperidine-4,1-diyl)]dimethanol (3du), [1,1′,1″,1‴-[6,6′-[1,4-Phenylenebis(oxy)]-bis(1,3,5-triazine-6,4,2-triyl)]-tetrakis(piperidine-4,1-diyl)]tetramethanol (Bdu) and [1,1′-[6-[4-[[4-[4-(Hydroxymethyl)piperidin-1-yl]-6-(4-hydroxyphenoxy)-1,3,5-triazin-2-yl]oxy]phenoxy]-1,3,5-triazine-2,4-diyl]-bis(piperidine-4,1-diyl)]dimethanol (Cdu) Entry 23: This compound was prepared in a manner similar to that for compound **3ds** (Entry 14). Purification of products by flash chromatography (CH_2Cl_2 : EtOH=90 : 10→85 : 15→80 : 20) gave **3du** (29%) as a brown solid, **Bdu** (9%) as a white solid, and **Cdu** (3%) as a brown solid.

3du: mp 228–229°C. IR (KBr) cm^{-1}: 3400 (OH of alcohol), 1580, 1500 (C–N of *t*-amine), 1200, 1035 (C–O). ^{1}H-NMR (DMSO-d_6) δ: 1.01 (4H, m, H3′β, 5′β), 1.62 (2H, m, H4′α), 1.64 (4H, m, H3′α, 5′α), 2.50 (4H, s, H2′β, 6′β), 3.25 (4H, t, J=5.6 Hz, H1), 4.4 (2H, brs, H2′α, 6′α), 4.41 (2H, t, J=5.3 Hz, C1-OH), 4.57 (2H, brs, H2′α, 6′α), 6.73 (2H, d, J=9.0 Hz, H3‴, 5‴), 6.92 (2H, d, J=9.0 Hz, H2‴, 6‴), 9.25 (1H, s, ArOH). ^{13}C-NMR (DMSO-d_6) δ: 28.26 (C3′, 5′), 38.48 (C4′), 42.77 (C2′, 6′), 65.54 (C1), 115.14 (C3‴, 5‴), 122.32 (C2‴, 6‴), 144.52 (C1‴), 154.02 (C4‴), 165.34 (C2″, 4″), 170.83 (C6″). Positive-ion FAB-MS m/z: 416 ($M+H^+$). HR-FAB-MS m/z: 416.2303 (Calcd for $C_{21}H_{30}N_5O_4$: 416.2303). *Anal.* Calcd for $C_{21}H_{29}N_5O_4$: C, 60.71; H, 7.04; N, 16.86. Found: C, 60.45; H, 7.27; N, 16.57.

Bdu: mp 249–251°C. IR (KBr) cm^{-1}: 3385 (OH of alcohol), 1580, 1490 (C–N of *t*-amine), 1195, 1040 (C–O).^{1}H-NMR (DMSO-d_6) δ: 1.01 (8H, brs, H3′β, 5′β), 1.62 (12H, m, H3′α, 4′α, 5′α), 2.77 (8H, brs, H2′β, 6′β), 3.25 (8H, t, J=5.5 Hz, H1), 4.42 (4H, t, J=5.5 Hz, OH), 4.4 (4H, brs, H2′α, 6′α), 4.59 (4H, brs, H2′α, 6′α), 7.14 (4H, s, H2‴, 3‴, 5‴, 6‴). ^{13}C-NMR (DMSO-d_6) δ: 28.26 (C3′, 5′), 38.45 (C4′), 42.80 (C2′, 6′), 65.51 (C1), 122.07 (C2‴, 3‴), 148.85 (C1‴, 4‴), 165.29 (C2″, 4″), 170.51 (C6″). Positive-ion FAB-MS m/z: 721 ($M+H^+$). HR-FAB-MS m/z: 721.4150 (Calcd for $C_{36}H_{53}N_{10}O_6$: 721.4144).

Cdu: ^{1}H-NMR (DMSO-d_6) δ: 1.0 (6H, m, H3, 5 in A, B), 1.65 (9H, m, H4, 3, 5 in A, B), 2.75 (6H, m, H2, 6 in A, B), 3.25 (6H, brs, C$\underline{H_2}$OH), [4.4 (m) and 4.6 (m) (6H, H2, 6 in A, B)], 4,43 (3H, brs, $CH_2O\underline{H}$), 6.76 (2H, d, J=9.0 Hz, H3, 5 in E), 6.98 (2H, d, J=9.0 Hz, H2, 6 in E), 7.19 (4H, m, H2, 3, 5, 6 in F), 9.37 (1H, brs, ArOH). ^{13}C-NMR (DMSO-d_6) δ: 28.10

(C3, 5 in A), 28.26 (C3, 5 in B), 38.13 (C4 in A), 38.46 (C4 in B), 43.08, 43.12 (C2, 6 in A, B), 65.30 (CH_2OH in A), 65.53 (CH_2OH in B),115.37 (C3, 5 in E), 122.02 (C2, 3, 5, 6 in F), 122.23 (C2, 6 in E), 144.04 (C1 in E), 148.36, 149.35 (C1, 4 in F), 154.61 (C4 in E), 165.28 (C2, 4 in D), 165.75 (C2 in C), 170.48, 171.75, 172.15 (C4, 6 in C, C6 in D). Positive-ion FAB-MS *m*/*z*: 716 ($M+H^+$). HR-FAB-MS *m*/*z*: 716.3520 (Calcd for $C_{36}H_{46}N_9O_7$: 716.3522).

Antiviral Activity Assay and Cytotoxicity of Target Compounds The antiviral activities of synthesized compounds were measured by using a plaque reduction assay[25] as described in our previous paper.[3] Results for antiviral activity (EC_{50}) and cytotoxicity (IC_{50}) with Vero cells are summarized in Table 3.

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27) We used a racemic 3-hydroxylated piperizine derivative (**e**H) as a starting material in the synthesis of C_3- or C_S-symmetric type target TAZ derivatives. The obtained symmetric products (**2e**, **3es**) showed very simple symmetric ^{13}C-NMR in DMSO-d_6 or pyridine-d_5, indicating little difference with respect to the signals assignable to symmetric trisubstituted TAZs. From a stereochemical viewpoint, however, the obtained C_3-type product (**2e**) can be considered to be a mixture of four stereoisomers, *i.e.*, two C_3-symmetric molecules that have the same absolute configuration regarding three introduced chiral piperidines (*R*,*R*,*R* or *S*,*S*,*S*) in the molecules and a set of two enantiomers (*R*,*R*,*S* and *S*,*S*,*R*). The trisubstituted symmetric TAZ derivative (**3es**) that has two chiral piperidines in the molecule is also expected to be a mixture of three stereoisomers, *i.e.*, a C_S-symmetrical *meso*-compound having different absolute configurations (*R* and *S*) with reference to the two chiral carbons and two enantiomeric molecules that have the same absolute configuration regarding two introduced piperidine rings in each molecule. The obtained diastereomeric mixture exhibited very simple symmetrical ^{13}C-NMR in pyridine-d_5, showing little difference magnetically with respect to all of the signals assignable to trisubstituted TAZ. Since these chiral compounds (**2e** and **3es**) as a mixture of stereoisomers showed no significant anti-HSV-1 activity or cytotoxicity at a concentration of less than 100 μM, we did not carry out further detailed experiments for isolation or determination of the absolute configurations of these stereoisomers. We have already reported some examples of the formation of theoretical stereoisomers from a reaction using a racemic reagent as the starting material for the construction of similar symmetrical molecules (see ref. 5).