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PREPARATION OF SOME NOVEL TRISUBSTITUTED 1,3,5-TRIAZINES AND HYBRID LINKER MODE 1,3,5-TRIAZINE DERIVATIVES AND THEIR BIOLOGICAL EVALUATION

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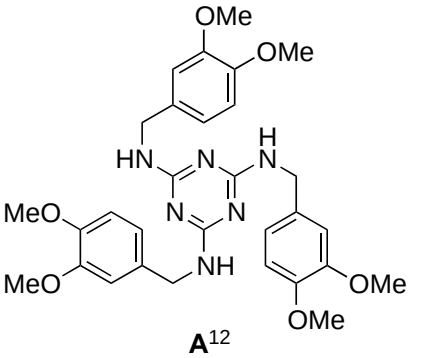
Abstract – We report a new route to the preparation of C_3-symmetrical multivalent hybrid-type molecules having a tris-aminoethylamine (TAEA) linker group and 1,3,5-triazine recognition moieties in the molecule and we also report the results of biological evaluation of their anti-herpes simplex virus type 1 (anti-HSV-1) activity and cytotoxic activity against Vero cells. Among the tested compounds, a new mid-size C_2-symmetrical multivalent hybrid-type molecule (**10aq**) showed a high level of anti-HSV-1 activity (EC_{50} = 19.7 μM) with low cytotoxicity (CC_{50} > 200 μM) against Vero cells. A new C_S-symmetrical multivalent derivative (**4ab**) also showed high anti-HSV-1 activity (EC_{50} = 1.77 μM) with low cytotoxicity (CC_{50} > 200 μM). The hybrid-type C_2-symmetrical multivalent mid-size molecule (**10aq**) seems to be an interesting new lead in the search for new hybrid-type symmetrical multivalent antiviral compounds.

INTRODUCTION

Interactions between carbohydrate-containing glycoproteins, proteoglycans and glycolipids on the cell surface are important biological stages for the processes of bacterial or viral infection and tumor metastasis.[1-3] Moreover, supramolecular interaction by macromolecules with two-fold (C_2) or three-fold (C_3) geometry is one of the common interactions in many important biological responses.[4] To develop new multivalent symmetrical bioactive compounds or leads, we have recently designed and synthesized a

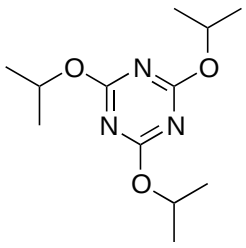
few new molecules with such geometry and evaluated their bioactivities in order to find new types of bioactive leads.[5-14] In connection with this project, we have recently reported the preparation of various C_3-symmetrical trivalent 1,3,5-triazine (TAZ) derivatives and the results of biological evaluation of the synthesized symmetrical TAZ derivatives.[7,12] Among previously targeted C_3-symmetrical TAZ derivatives, we found that C_3-symmetrical tri-substituted TAZ derivatives (**A** and **B**) showed high levels of anti-HSV-1 activity (EC_{50} = 0.98 and 1.87 μM, respectively) and considerably low levels of cytotoxic activity (CC_{50} > 200 μM) against Vero cells,[7,12] and these TAZ derivatives are considered to be potential new leads in the search for antiviral active molecules (Figure 1). Regarding the carbohydrate recognition property of TAZ derivatives with high anti-herpes simplex virus type 1 (anti-HSV-1) activity, the results of our thermodynamic experiments indicated that the C_3-type TAZ derivative (**A**) having a benzylamine group is a more promising antiviral lead than the C_3-type trialkoxy-substituted TAZ derivative (**B**).[13]

As an extension of molecular modification of these compounds, we further synthesized new symmetrical C_3 and C_S-symmetrical TAZ derivatives having arylalkylamine groups and a few new multivalent hybrid-type TAZ derivatives constructed on a symmetrical TAEA framework. In this paper, we also describe the results of evaluation of their biological activities and the structure-activity relationships (SARs) of these symmetrical TAZ-related derivatives.



A[12]

EC_{50} = 0.98 mM
CC_{50} = 292.2 mM



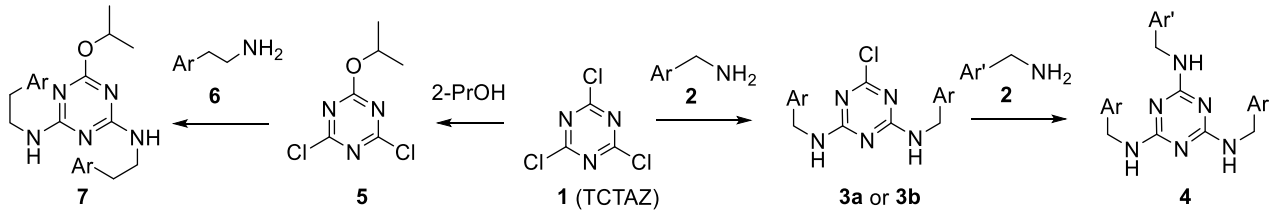
B[7]

EC_{50} = 1.87 mM
CC_{50} = 479.8 mM

Figure 1. Antiviral lead compounds (**A** and **B**)

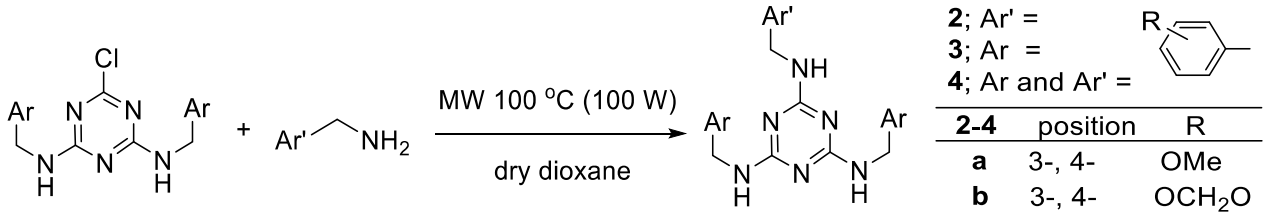
RESULTAS AND DISCUSSION

A few additional C_S-symmetrical TAZ derivatives (**4** and **7**) were synthesized from 2,4,6-trichloro-1,3,5-triazine (TCTAZ, **1**) as a starting material using a stepwise substitution reaction by nucleophiles such as benzylamine derivatives or alcohols (Scheme 1). The details for the stepwise preparation of these C_S-symmetrical TAZ derivatives (**4** and **7**) are given in EXPERIMENTAL.



Scheme 1. Synthetic pathway of target C_S-symmetrical TAZ derivatives (**4** and **7**)

Table 1. Synthesis of C_S-symmetrical tribenzylamino-substituted TAZ derivatives (**4**)[a)]



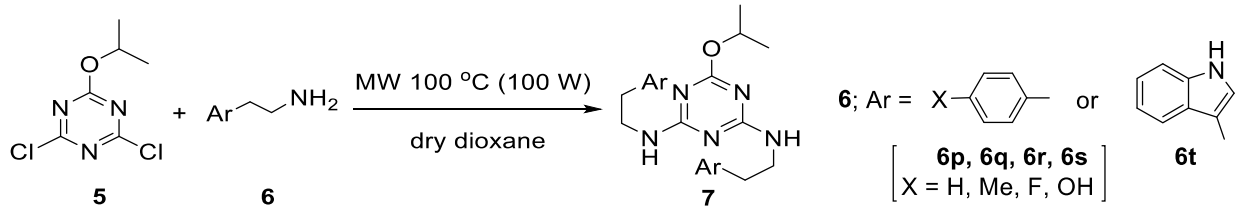
Entry	**3**	**2**	Ratio of **3** : **2**	Reaction time (min)	Product (yield %)
1	**3a**	**2b**	1 : 2.5	45	**4ab** (76)
2	**3a**	**2c**	1 : 2.5	50	**4ac** (84)
3	**3a**	**2d**	1 : 8	60	**4ad** (77)
4	**3b**	**2a**	1 : 2.5	30	**4ba** (80)
5	**3b**	**2c**	1 : 2.5	20	**4bc** (80)
6	**3b**	**2d**	1 : 2.5	30	**4bd** (92)

a) MW means microwave irradiation (100 W, 100 °C)

As can be seen in Tables 1 and 2, the yields in the procedure (entries 1~11) with the starting TCTAZ (**1**) to target C_S-symmetrical TAZ derivatives (**4** and **7**) were good, and this method for synthesis of TAZ derivatives was reproducible and was reconfirmed to be useful as a general procedure for synthesis of trivalent TAZ derivatives.[12] The presence of a phenylethylamino functionality in the C_S-type TAZ molecules (**7**) also gave a good result. The structures of the obtained new trivalent TAZ derivatives (**4** and **7**) were established by spectroscopic methods and elemental analysis. Correct molecular ion peaks were observed in high-resolution positive FAB-MS spectra of all C_S-symmetrical TAZ derivatives (**4** and **7**).

For the preparation of various new target multivalent hybrid-type TAZ mid-size molecules, we also show a few effective synthetic strategies consisting of stepwise coupling of three kinds of motif linkers (see Schemes 2 and 3, and Table 3).

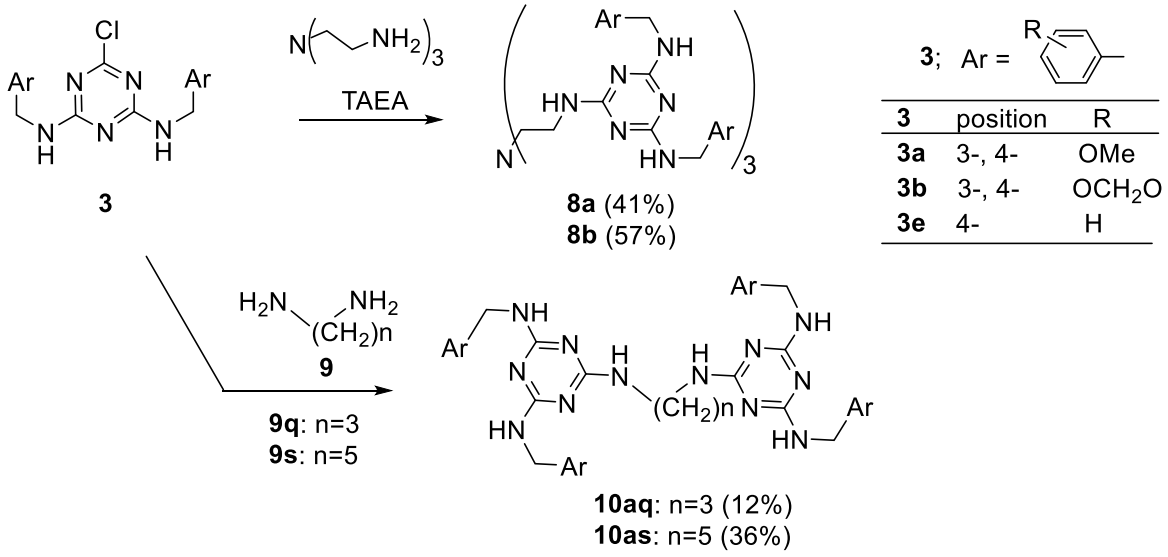
Table 2. Synthesis of C_S-symmetrical isopropoxy-diarylalkylamino-TAZ derivatives (**7**)



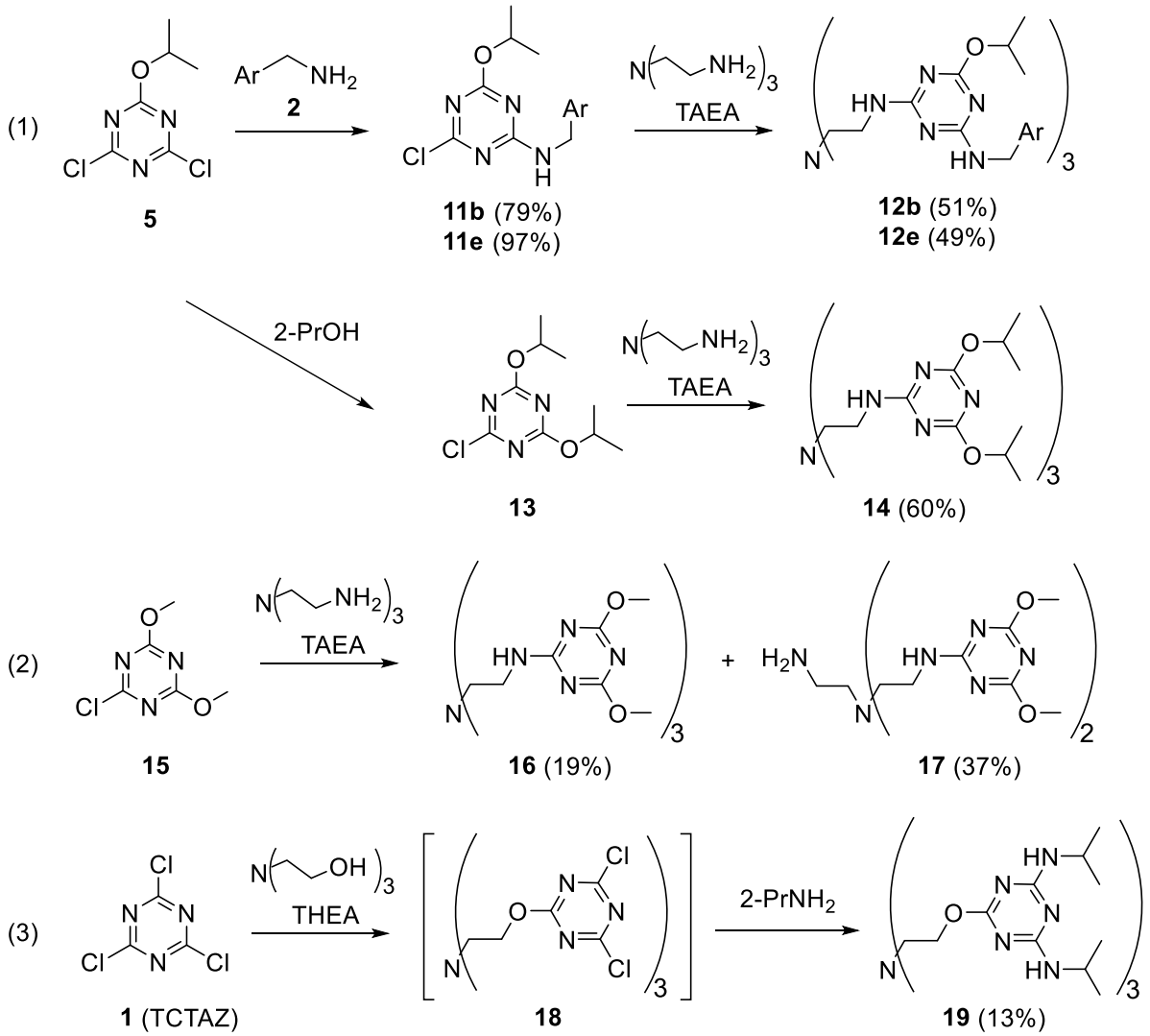
5 **6** **7**

Entry	**6**	Reaction time[a] (min)	Product (yield %)
7	**6p**	30	**7p** (86)[b]
8	**6q**	60	**7q** (83)[b]
9	**6r**	10	**7r** (94)[b]
10	**6s**	30	**7s** (50)
11	**6t**	30	**7t** (78)

a) MW means microwave irradiation (100 W, 100 °C). In all entries, reactions were conducted with stirring at 0 °C (10 min) and at rt (20 min) before MW and with the ratio of **5** : **6** = 1 : 5. *b)*Yields after recrystallization.



Scheme 2. Synthesis of C_3- and C_2-symmetrical multivalent hybrid-type TAZ derivatives (**8** and **10**) starting with compound **3** and TAEA or diaminoalkanes (**9**)



Scheme 3. (1) Stepwise synthesis of C_3-symmetrical multivalent hybrid-type TAZ derivatives (**12** and **14**) starting from monoisopropoxy-substituted TAZ derivative (**5**). (2) Synthesis of C_3-symmetrical hybrid-type TAZ derivative **16** from dimethoxy-substituted TAZ derivative **15** and TAEA. (3) Two-step synthesis of C_3-symmetrical hybrid-type TAZ derivative **19** from TCTAZ (**1**).

The anti-HSV-1 activities (EC_{50}) determined by plaque reduction assays[15] and cytotoxicity (CC_{50}) of single-drug type TAZ derivatives (**4** and **7**) against Vero cells are summarized in Table 4. The calculated log *P*[16] values for synthesized compounds are also shown in Table 4. Among the tri-substituted symmetrical TAZ derivatives tested (**4ab**~**4bd** and **7p**~**7t**), the *Cs*-symmetrical derivative **4ab** having three substituted benzylamino groups showed the highest anti-HSV-1 activity (EC_{50} = 1.77 μM) and low cytotoxity (CC_{50} > 200 μM). It is noteworthy that all of the C_S-type compounds (**4**) having three benzylamines in the TAZ template listed in Table 4, except for compound (**4bc**), showed considerably high anti-HSV-1 activities (EC_{50} = 1.77 ~ 7.86 μM) and low cytotoxicity (CC_{50} > 200 μM). In contrast,

most of the *Cs*-symmetrical TAZ derivatives (**7**) having an isopropoxy group and two substituted phenylethyllamino groups showed no anti-HSV-1 activity (EC_{50} > 100 μM). Two compounds (**7s** and **7t)** including phenolic hydroxy groups or indole groups showed anti-HSV-1 activity (EC_{50} = 6.9 ~ > 25 μM) with high cytotoxicity (CC_{50} = 25.8 ~ 35.6 μM). The results obtained indicated that the presence of three benzylamino groups as substituents seems to be a profitable structure for the expression of a high level of anti-HSV-1 activity. The reason for no activity of compound **4bc** (EC_{50} > 100 and CC_{50} > 200 μM) is not clear.

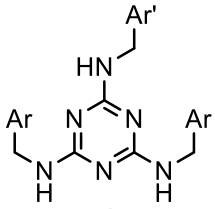
Table 3. Yields of C_3- and C_S-symmetrical multivalent hybrid-type TAZ derivatives shown in Schemes 2 and 3 and reaction conditions of target C_3- and C_S-symmetrical multivalent hybrid-type TAZ derivatives

Entry	Starting compound (**S**)	Reactant (**R**)	Base[a] (Additive) [**B**/(**A**)]	Ratio of **S** : **R** : **B** (: **A**)	Reaction conditions[b]	Products (yield %)
12	**3a**	TAEA	K_2CO_3	5 : 1 : 10	reflux 5.5 h, DMF	**8a** (41)
13	**3b**	TAEA	K_2CO_3	5 : 1 : 10	reflux 6.5 h, DMF	**8b** (57)
14	**3a**	**9q**	K_2CO_3	3 : 1 : 6	reflux 3 h, DMF	**10aq** (12)
15	**3a**	**9s**	DIPEA	2.2 : 1 : 2.2	reflux 7 d, THF	**10as** (36)
16	**5**	**2b**	DIPEA	1 : 1 : 1	rt 1 h, THF	**11b** (79)
17[c]	**5**	**2e**	DIPEA	1 : 1 : 1	0 °C 2 h, THF	**11e** (97)
18	**11b**	TAEA	Et_3N/NaI	3 : 1 : 6 : 3	MW 70 °C (90 W) 2 h, MW 100 °C (100 W) 1 h, THF	**12b** (51)
19	**11e**	TAEA	Et_3N	3 : 1 : 12	50 °C 19 h, MeCN-THF	**12e** (49)
20	**13**	TAEA	DIPEA	3.3 : 1 : 3.3	reflux 4 h, THF	**14** (60)
21	**15**	TAEA	DIPEA	3 : 1 : 3	reflux 22 h, THF, N_2	**16** (19), **17** (37)
22	**1**	THEA	collidine	3 : 1 : 3	0 °C to rt 10 min, reflux 12 h, acetone	[**18**]
23	[**18**]	2-$PrNH_2$	DIPEA	1 : 12 : 6	reflux 12 h, THF	**19** (13)

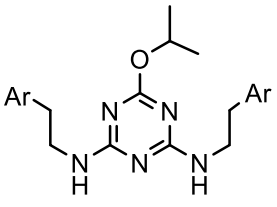
a) DIPEA stands for *N*,*N*-diisopropylethylamine. *b)*MW means microwave irradiation. *c*) Data were taken from ref. 12.

Regarding the multivalent symmetrical molecules and for the purpose of comparison of the biological activities of *Cs*-type TAZ derivatives (**4** and **7**), we further prepared new hybrid-type TAZ derivatives (**8** and **10**) constructed on tris-aminoethylamine (TAEA) and diaminoalkane frameworks. The structures of target hybrid-type compounds obtained in this study are shown in Table 5. The results of biological evaluation of these hybrid-type compounds and the data for acyclovir[17] are also shown in Table 5. Only new linear methylene linker mode multivalent C_2-symmetrical TAZ derivative **10aq** showed a high level of anti-HSV-1 activity (EC_{50} = 19.1 μM) with low cytotoxicity (CC_{50} > 200 μM), but its anti-HSV-1

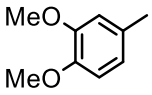
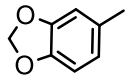
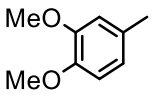
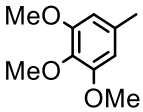
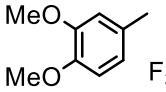
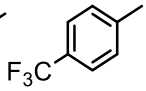
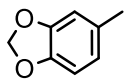
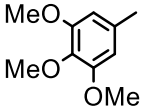
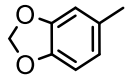
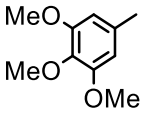
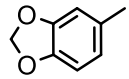
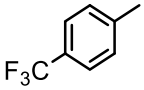
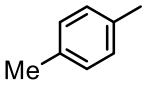
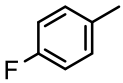
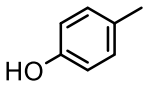
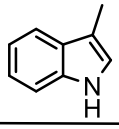
Table 4. Anti-HSV-1 activity (EC_{50}) and cytotoxicity (CC_{50}) of C_S-symmetrical TAZ derivatives against Vero cells and calculated log *P* values of target TAZ derivatives (**4** and **7**)



4

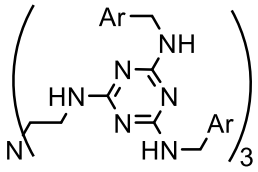
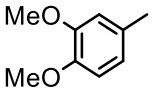
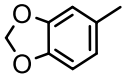
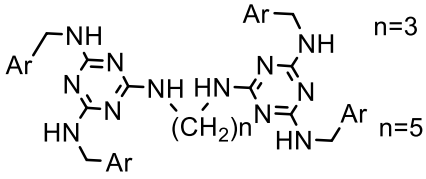
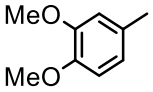
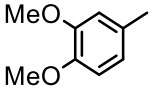
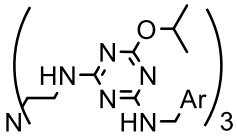
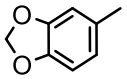
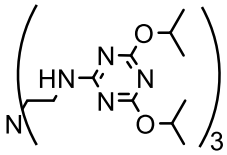
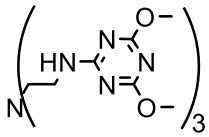
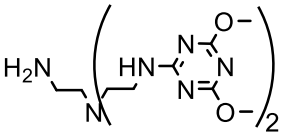
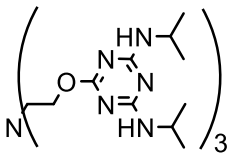
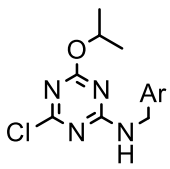
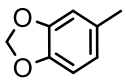


7

Compound	Ar	Ar'	EC_{50} (μM)	CC_{50} (μM)	Log $P^{a)}$
4ab			1.77	>200	4.00
4ac			5.58	>200	4.16
4ad			6.6	>400	5.55
4ba			3.49	>200	3.84
4bc			> 100	>200	3.59
4bd			7.86	>200	5.23
7p			> 100	>200	5.33
7q			>100	>200	6.27
7r			>100	>200	5.61
7s			>25	25.8	4.76
7t			6.9	35.6	3.95

a) All log *P* values were calculated by using SCIGRESS v.2.8.1.

Table 5. Anti-HSV-1 activity (EC_{50}), cytotoxicity (CC_{50}) against Vero cells, and calculated log *P* values of target hybrid type TAZ derivatives (**8**, **10**, **12**, **14**, **16**, **19**) and related compounds (**11** and**17**)

Compound		Ar	EC_{50} (μM)	CC_{50} (μM)	Log $P^{a)}$
8a			>100	>200	8.29
8b			>100	>200	7.33
10aq	 n=3		19.1	>200	5.65
10as	n=5		>100	>200	6.50
12b			>100	>200	6.78
12e			>100	>200	8.78
14			>100	>200	6.23
16			>100	>200	1.7
17			>100	>200	0.395
19			>100	>200	5.71
11b			>100	53.0	3.00
11e			>100	>200	3.67
aciclovir[b)]			1.1	> 444	

a) All log *P* values were calculated by using SCIGRESS v.2.8.1. *b*) Data were taken from reference 17.

activity was slightly lower than that of the C_3-type trivalent original molecules (**A** and **B**). The results for other hybrid-type compounds are also shown in Table 5. The hybrid-type C_3-symmetrical derivatives (**14, 16** and **19**) and a byproduct C_2-symmetrical derivative **17** having two aliphatic isopropylamino, two isopropoxy or two methoxy groups on the TAZ ring showed no anti-HSV-1 activity (EC_{50} > 100 μM) and showed low cytotoxicity (CC_{50} > 200 μM). The C_3-symmetrical hybrid-type compounds (**12b** and **12e**) also showed no anti-HSV-1 activity (EC_{50} > 100 μM). Regarding synthetic intermediates **11b** and **11e,** notable anti-HSV-1 activity was not observed. Regarding calculated log *P* values[16] for the compounds, there were few distinct correlations between log *P* values and anti-HSV-1 activity (EC_{50}) values shown in Tables 4 and 5.

From these results, we consider that the hybrid-type new C_2-symmetrical multivalent mid-size molecule[18,19] (**10aq**) is a useful lead in the search for new multivalent antiviral compounds. We hope that we will encounter a new promising mid-size molecule, though we need further structural transformation.

On the basis of the information obtained by the evaluation of biological activities of the tri-substituted TAZ derivatives and hybrid-type multivalent mid-size series together with recent information on the C_3-type TAZ series,[12,13] we are now investigating further molecular modifications of these TAZ derivatives (**4ab** and **10aq**) with the aim of developing new synthetic compounds with anti-HSV-1 activity.

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. MicromATR Vision [an apparatus of attenuated total reflectance (ATR)] was used for a neat sample operation. 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 were expressed in δ ppm downfield from an internal TMS signal for ^{1}H-NMR and the carbon signal of the corresponding solvent [$CDCl_3$ (77.00 ppm), DMSO-d_6 (39.50 ppm)] 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). Detection of products was accomplished with UV light and iodine. Microwave irradiation experiments were carried out in a CEM Discover Focused Microwave System. Open column, flash column, and centrifugal chromatography separations of the reaction products were performed on silica gel (Kanto 60N or Able-Biott) with a UV detector.

Commercially available starting materials were used without further purification, and dry solvents were used in all reactions.

General Procedure for C_S-Symmetrical Tribenzylamino-substituted TAZ Derivatives (4) (Table 1): Example: Synthesis of N^2-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-N^4,N^6-bis(3,4-dimethoxybenzyl)-1,3,5-triazine-2,4,6-triamine (4ab) (Entry 1): To a suspension mixture of dibenzylamino-TAZ intermediate **3a** (669 mg, 1.50 mmol) in dioxane (4 mL) was added piperonylamine (**2b**, 567 mg, 3.75 mmol) at room temperature with stirring, and then the mixture was subjected to microwave irradiation (MW) at 100 °C (100 W) for 45 min with stirring. After addition of saturated aq. NH_4Cl (20 mL), the mixture was extracted with CH_2Cl_2 (30 mL×3). The combined organic layer was washed with brine (20 mL) and dried over $MgSO_4$. After evaporation of the solvent, the crude compound **4ab** (636.6 mg, 1.14 mmol, 76%) was obtained as a white solid. An analytically pure sample was obtained as colorless crystals after recrystallization from EtOH. Mp 57-61 °C. IR (KBr) cm^{-1}: 3403 (NH), 1562, 1513 (C=N), 1259, 1234, 1138, 1028 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ : 3.82 (6H, s, OCH_3 on C3'), 3.85 (6H, s, OCH_3 on C4'), 4.49 (6H, br s, Hα', α), *ca*. 5.3 (1H, br s, NH), 5.44 (2H, br s, NH), 5.91 (2H, s, H2"), 6.70 (2H, br s, H6", 7"), 6.76, 6.77 (3H, br s, H4", 5'), 6.81 (2H, br s, H6'), 6.82 (2H, br s, H2'). ^{13}C-NMR ($CDCl_3$) δ: 44.36, 44.49 (Cα, α'), 55.78 (OCH_3 on C4'), 55.87 (OCH_3 on C3'), 100.91 (C2"), 108.08 (C4", 7"), 110.84 (C2'), 110.06 (C5'), 119.71 (C6'), 120.58 (C6"), 131.81 (C1'), 133.26 (C5"), 146.62 (C3a"), 147.70 (C7a"), 148.16 (C4'), 148.98 (C3'), 165.91 (C2, 4, 6). Positive-ion FAB-MS *m/z*: 561 $(M+H)^+$. HR-FAB-MS *m/z*: 561.2465 (Calcd for $C_{29}H_{33}N_6O_6$: 561.2462). Anal. Calcd for $C_{29}H_{32}N_6O_6\cdot H_2O$: C, 60.19; H, 5.92; N, 14.53. Found: C, 60.23; H, 5.66; N, 14.42.

N^2,N^4-Bis(3,4-dimethoxybenzyl)-N^6-(3,4,5-trimethoxybenzyl)-1,3,5-triazine-2,4,6-triamine (4ac) (Entry 2): Colorless solid. Mp 67-70 °C. IR (KBr) cm^{-1}: 3386 (NH), 1562, 1508 (C=N), 1262, 1234, 1126, 1027 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ : 3.79 (6H, s, OCH_3 on C3", 5"), 3.82 (9H, s, OCH_3 on C4", 3'), 3.85 (6H, s, OCH_3 on C4'), *ca*. 4.45 (2 H, br s, Hα'), 4.50 (4H, br s, Hα), 5.35, 5.44 (3H, br s, NH), 6.52 (2H, br s, H2", 6"), 6.76 (2H, d, *J* = 7.6 Hz, H5'), 6.81 (2H, br s, H6'), 6.82 (2H, br s, H2'). ^{13}C-NMR ($CDCl_3$) δ : 44.46 (Cα), 44.95 (Cα'), 55.76 (C4"), 55.85 (C3'), 56.01 (OCH_3 on C3", 5"), 60.75 (OCH_3 on C4"), 104.43 (C2", 6"), 110.84 (C2'), 111.06 (C5'), 119.69 (C6'), 131.72 (C1'), 134.99 (C1"), 137.00 (C4"), 148.16 (C4'), 148.96 (C3'), 153.25 (C3", 5"), 166.12 (C2, 4, 6). Positive-ion FAB-MS *m/z*: 607 $(M+H)^+$. HR-FAB-MS *m/z*: 607.2871 (Calcd for $C_{31}H_{39}N_6O_7$: 607.2880). Anal. Calcd for $C_{31}H_{38}N_6O_7\cdot 0.7H_2O$: C, 60.12; H, 6.41; N, 13.57. Found: C, 60.12; H, 6.27; N, 13.46.

N^2,N^4-Bis(3,4-dimethoxybenzyl)-N^6-(4-(trifluoromethyl)benzyl)-1,3,5-triazine-2,4,6-triamine (4ad) (Entry 3): Colorless solid. Mp 55-60 °C. IR (KBr) cm^{-1}: 3282 (NH), 1563, 1513 (C=N), 1325 ($ArCF_3$), 1262, 1235, 1161, 1138, 1120 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ : 3.79 (3H, s, OCH_3 on C3'), 3.82

(3H, s, OCH_3 on C4'), 4.42, 4.48, 4.57 (6H, br s, Hα, α'), 5.49, 5.65* (3H, br s, NH), 6.64-6.82 (6H, m, H5', 6', 2'), 7.23-7.41 (2H, m, H2", 6"), 7.49* (1.95H, br d, *J* = 6.9 Hz, H3", 5"), 7.58 (0.05H, br d, *J* = 6.9 Hz, H3", 5"). (The observed ^{1}H-signals assignable to the predominant tautomer are asterisked.) ^{13}C-NMR ($CDCl_3$) δ : 41.51, 44.00, 44.34 (C α, α'), 55.71, 55.78 (OCH_3), 110.75 (C2'), 111.00 (C5'), 119.62 (C6'), 124.10 (q, *J* = 271.6 Hz, CF_3), 125.24 (C3", 5"), 127.41 (C2", 6"), 129.13 (q, *J* = 31.8 Hz, C4"), 131.66 (C1'), 143.75 (C1"), 148.13 (C4'), 148.94 (C3'), 166.08 (C2, 4, 6). Positive-ion FAB-MS *m/z*: 585 $(M+H)^+$. HR-FAB-MS *m/z*: 585.2446 (Calcd for $C_{29}H_{32}F_3N_6O_4$: 585.2437). Anal. Calcd for $C_{29}H_{31}F_3N_6O_4 \cdot 0.7H_2O$: C, 58.32; H, 5.47; N, 14.07. Found: C, 58.41; H, 5.40; N, 13.84.

***N*^{2},*N*^{4}-Bis(benzo[*d*][1,3]dioxol-5-ylmethyl)-*N*^{6}-(3,4-dimethoxybenzyl)-1,3,5-triazine-2,4,6-triamine (4ba) (Entry 4):** Colorless solid. Mp 53-55 °C. IR (KBr) cm^{-1}: 3408 (NH), 1563, 1512 (C=N), 1250, 1038 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ : 3.81 (3H, br s, OCH_3 on C3"), 3.84 (3H, br s, OCH_3 on C4"), *ca*. 4.38, 4.44*, *ca*. 4.47 (6H, br s, Hα, α'), 5.45 (3H, br s, NH), 5.90 (4H, s, H2'), 6.69 (4H, br s, H6', 7'), 6.73-6.85 (5H, m, H4', 5", 6", 2"). (The observed ^{1}H-signals assignable to the predominant tautomer are asterisked.) ^{13}C-NMR ($CDCl_3$) δ: 44.31 (Cα, α'), 55.75, 55.84 (OCH_3 on C3', 4'), 100.88 (C2'), 108.04 (C4', 7'), 110.75 (C2"), 111.03 (C5"), 119.64 (C6"), 120.53 (C6'), 131.95 (C1"), 133.45 (C5'), 146.55 (C3a'), 147.66 (C7a'), 148.09 (C4"), 148.95 (C3"), 166.12 (C2, 4, 6). Positive-ion FAB-MS *m/z*: 545 $(M+H)^+$. HR-FAB-MS *m/z*: 545.2137 (Calcd for $C_{28}H_{29}N_6O_6$: 545.2149). Anal. Calcd for $C_{28}H_{28}N_6O_6$: C, 61.50; H, 5.20; N, 15.37. Found: C, 61.50; H, 5.20; N, 15.37.

***N*^{2},*N*^{4}-Bis(benzo[*d*][1,3]dioxol-5-ylmethyl)-*N*^{6}-(3,4,5-trimethoxybenzyl)-1,3,5-triazine-2,4,6-triamine (4bc) (Entry 5):** Colorless solid. Mp 55-60 °C. IR (KBr) cm^{-1}: 3408 (NH), 1566, 1503 (C=N), 1234, 1126, 1038 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ : 3.78 (6H, br s, OCH_3 on C3", 5"), 3.81 (3H, br s, OCH_3 on C4"), *ca.* 3.9 (0.5H, br s, NH), 4.43 (6H, br s, Hα, α'), 5.56* (2.5H, br s, NH), 5.89 (4H, br s, H2'), 6.50 (2H, br s, H2", 6"), 6.68 (4H, br s, H6',7'), 6.74 (2H, br s, H4'). (The observed ^{1}H-signals assignable to the predominant tautomer are asterisked.) ^{13}C-NMR ($CDCl_3$) δ: 44.27 (Cα), 44.88 (Cα'), 55.96 (OCH_3 on C3", 5"), 60.72 (OCH_3 on C4"), 100.86 (C2'), 104.34 (C2", 6"), 108.00 (C4', 7'), 120.48 (C6'), 133.38 (C5'), 135.13 (C1"), 136.91 (C4"), 146.54 (C3a'), 147.65 (C7a'), 153.20 (C3", 5"), 166.05 (C2, 4, 6). Positive-ion FAB-MS *m/z*: 575 $(M+H)^+$. HR-FAB-MS *m/z*: 575.2257 (Calcd for $C_{29}H_{31}N_6O_7$: 575.2254). Anal. Calcd for $C_{29}H_{30}N_6O_7$: C, 60.62; H, 5.26; N, 14.63. Found: C, 60.50; H, 5.30; N, 14.45.

***N*^{2},*N*^{4}-Bis(benzo[*d*][1,3]dioxol-5-ylmethyl)-*N*^{6}-[4-(trifluoromethyl)benzyl]-1,3,5-triazine-2,4,6-triamine (4bd) (Entry 6):** Colorless crystals. Mp 120-124 °C (from EtOH). IR (KBr, tab) cm^{-1}: 3447 (NH), 1577, 1531, 1506 (C=N), 1327 ($ArCF_3$), 1250, 1110, 1039 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ : 4.43 (4H, br s, Hα), 4.61 (2H, br s, Hα'), 5.09, 5.15, 5.23*, 5.34 (3H, br s, NH), 5.92*, 5.93 (4H, s, H2'), 6.72 (4H, br s, H6', 7'), 6.79 (2H, br s, H4'), 7.38 (2H, br d, *J* = 7.3 Hz, H2", 6"), 7.54 (2H, br d, *J* = 7.3 Hz,

H3”, 5”). ^{13}C-NMR ($CDCl_3$) δ : 44.11 (Cα’), 44.43 (Cα), 100.95 (C2’), 108.15 (C7’), 108.30, 109.39* (C4’), 120.59 (C6’), 124.19 (q, *J* = 271.7 Hz, CF_3) 125.38 (q, *J* = 2.9 Hz, C3”, 5”), 127.49 (C2”, 6”), 129.27 (q, *J* = 33.2 Hz, C4”), 133.16, 133.33* (C5’), 143.72, 143.77* (C1”), 146.70 (C3a’), 147.76 (C7a’), 166.08 (C2, 4, 6). (The observed ^{1}H- and ^{13}C-signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS *m/z*: 553 $(M+H)^+$. HR-FAB-MS *m/z*: 553.1799 (Calcd for $C_{27}H_{24}F_3N_6O_4$: 553.1811). Anal. Calcd for $C_{27}H_{23}F_3N_6O_4$: C, 58.69; H, 4.20; N, 15.21. Found: C, 58.62; H, 4.20; N, 15.21.

General Procedure for *C*$_S$-Symmetrical Isopropoxy-diarylalkylamino-TAZ Derivatives (7) (Table 2): Example: Synthesis of 6-Isopropoxy-*N*^{2},*N*^{4}-diphenethyl-1,3,5-triazine-2,4-diamine (7p) (Entry 7): To a solution of 2,4-dichloro-6-isopropoxy-1,3,5-triazine (**5**, 416 mg, 2.00 mmol) in dioxane (4 mL) was added phenethylamine (**6p**, 1.21 g, 10.0 mmol) at 0 ºC with stirring, and the reaction mixture was continuously stirred for 10 min at 0 ºC and then for another 20 min at room temperature. Then the mixture was subjected to microwave irradiation (MW) at 100 ºC (100 W) for 30 min with stirring. After addition of water (50 mL), the mixture was extracted with CH_2Cl_2 (30 mL×3). The combined organic layer was washed with saturated aq. NH_4Cl (90 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residue was recrystallized by MeCN to give compound **7p** (0.646 g, 1.71 mmol, 86%) as colorless crystals. Mp 136-140 ºC (from MeCN). IR (KBr) cm^{-1}: 3344 (NH), 1624, 1521 (C=N), 1314, 1165, 1102 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.29, 1.35* (6H, s, H2”, 3”), 2.85, 2.91* (4H, br s, Hβ), 3.58, 3.68* (4H, br s, Hα), 5.12, 5.24* (1H, br s, H1”), *ca*. 5.10, *ca*. 5.15, 5.31* (2H, br s, NH), 7.17-7.25 (5H, m, H2’, 4’, 6’), 7.25-7.33 (2H, m, H3’, 5’). ^{13}C-NMR ($CDCl_3$) δ: 21.98 (C2”, 3”), 35.97 (Cβ), 41.89*, 42.26 (Cα), 68.89*, 69.27, 69.35 (C1”), 126.36 (C2’, 6’), 128.54 (C3’, 5’), 128.77 (C4’), 139.04 (C1’), 166.94, 167.29* (C2, 4), 169.82*, 171.11 (C6). (The observed ^{1}H- and ^{13}C-signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS *m/z*: 378 $(M+H)^+$. HR-FAB-MS *m/z*: 378.2294 (Calcd for $C_{22}H_{28}N_5O$: 378.2292). Anal. Calcd for $C_{22}H_{27}N_5O$: C, 70.00; H, 7.21; N, 18.55. Found: C, 70.00; H, 7.29; N, 18.55.

6-Isopropoxy-*N*^{2},*N*^{4}-bis(4-methylphenethyl)-1,3,5-triazine-2,4-diamine (7q) (Entry 8): Colorless crystals. Mp 126-128 ºC (from MeCN). IR (KBr) cm^{-1}: 3339, 3255, 3107 (NH), 1623, 1515 (C=N), 1316, 1102 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.28, 1.34* (6H, br s, H2”, 3”), 2.32 (6H, s, CH_3 on C4’), 2.80*, 2.86 (4H, br s, Hβ), 3.55, 3.56, 3.64* (4H, br s, Hα), 5.12, 5.23* (1H, br s, H1”), *ca*. 5.16, 5.29 (2H, br s, NH), 7.10 (8H, br s, H2’, 3’, 5’, 6’). ^{13}C-NMR ($CDCl_3$) δ: 20.97 (CH_3 on C4’), 21.96 (C2”, 3”), 35.47 (Cβ), 41.96*, 42.33 (Cα), 68.83*, 69.23 (C1”), 128.62 (C2’, 6’), 129.20 (C3’, 5’), 135.83, 135.89 (C1’, 4’), 166.96, 167.24*, 167.47 (C2, 4), 169.79*, 169.82 (C6). (The observed ^{1}H- and ^{13}C-signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS *m/z*: 406 $(M+H)^+$. HR-FAB-MS *m/z*: 406.2608 (Calcd for $C_{24}H_{32}N_5O$: 406.2607). Anal. Calcd for $C_{24}H_{31}N_5O$: C, 71.08 H,

7.70; N, 17.27. Found: C, 71.26; H, 7.76; N, 17.11.

6-Isopropoxy-*N*^{2},*N*^{4}-bis(4-fluorophenethyl)-1,3,5-triazine-2,4-diamine (7r) (Entry 9): Colorless crystals. Mp 138-140 °C (from MeCN). IR (KBr) cm^{-1}: 3345 (NH), 1622, 1509 (C=N), 1314, 1230, 1149, 1098 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.29¶, 1.35¶ (6H, br s, H2", 3"), 2.83¶, 2.86¶ (4H, br s, Hβ), 3.56¶, 3.64¶ (4H, br s, H*α*), 4.96, 5.07 (1.5H, br s, NH), [5.12 (0.2H), 5.23 (0.8H)] (br s, H1"), 5.24 (0.5H, br s, NH), 6.98 (4H, t, *J* = 8.3 Hz, H3', 5'), 7.15 (4H, br s, H2', 6'). ^{13}C-NMR ($CDCl_3$) δ: 21.97 (C2", 3"), 35.16 (C*β*), 41.96¶, 42.28¶ (C*α*), 69.39¶, 69.45¶ (C1"), 115.33 (d, *J* = 2.1 Hz, C3', 5'), 130.15 (d, *J* = 8.6 Hz, C2', 6'), 134.64 (C1'), 161.59 (d, *J* = 244.2 Hz, C4'), 166.97¶, 167.27¶ (C2, 4), 169.49¶, 169.86¶ (C6). [Signals that appeared in ^{1}H- and ^{13}C-NMR spectra are consistent with the tautomeric mixture of two isomers with the ratio of *ca.* 1 : 1. The signals assignable to each tautomer are marked with a superscript ¶.] Positive-ion FAB-MS *m/z*: 414 $(M+H)^+$. HR-FAB-MS *m/z*: 414.2100 (Calcd for $C_{22}H_{26}F_2N_5O$: 414.2105). Anal. Calcd for $C_{22}H_{25}F_2N_5O$: C, 63.91; H, 6.09; N, 16.94. Found: C, 63.87; H, 6.14; N, 16.86.

6-Isopropoxy-*N*^{2},*N*^{4}-diphenethyl-1,3,5-triazine-2,4-diamine (7s) (Entry 10): White solid. Mp 88-90 °C. IR (KBr) cm^{-1}: 3410 (NH), 1577, 1514 (C=N), 1317, 1240, 1103 (C-N and/or C-O). ^{1}H-NMR (DMSO-d_6) δ: [1.21*(*J* = 5.5 Hz), 1.25 (*J* = 6.4 Hz), 1.29 (*J* = 6.9 Hz)] (6H, d, H2", 3"), 2.68-2.78 (4H, m, Hβ), 3.41,* 3.46 (4H, m, Hα), 5.11-5.23 (1H, m, H1"), 6.72 (4H, dd, *J* = 8.2, 2.2 Hz, H3', 5'), 6.93, 6.98 (0.7H, br s, NH), 7.02-7.08 (4H, m, H2', 6'), 7.14-7.22 (1.3H, m, NH), 9.29,* 9.31 (2H, br s, OH). ^{13}C-NMR (DMSO-d_6) δ: 22.08 (C2", 3"), 34.45, 34.78,* 34.89 (Cβ), 42.29,* 42.54 (Cα), 67.78,* 68.19, 68.60 (C1"), 115.33 (C3', 5'), 129.68 (C2', 6'), 129.92 (C1'), 155.73 (C4'), 166.65, 166.84, 166.94,* 167.15 (C2, 4), 169.52,* 169.69, 170.05 (C6). (The observed ^{1}H- and ^{13}C-signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS *m/z*: 410 $(M+H)^+$. HR-FAB-MS *m/z*: 410.2192 (Calcd for $C_{22}H_{27}N_5O_3$: 410.2192). Anal. Calcd for $C_{22}H_{27}N_5O_3 \cdot 0.4H_2O$: C, 63.41; H, 6.72; N, 16.81. Found: C, 63.43; H, 6.64; N, 16.76.

6-Isopropoxy-*N*^{2},*N*^{4}-bis[2-(1*H*-indol-3-yl)ethyl]-1,3,5-triazine-2,4-diamine (7t) (Entry 11): White solid. Mp 70-73 °C. IR (KBr) cm^{-1}: 3410 (NH), 1573, 1516 (C=N), 1338, 1317, 1157, 1104 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.24, 1.31 (6H, br s, H2", 3"), 2.92, 3.00 (4H, br s, Hβ), 3.62, 3.72 (4H, br s, Hα), 5.11, 5.23* (1H, br s, H1"), 5.31*, 5.43 (2H, br s, NH), 6.74*, 6.83 (2H, br s, H2'), 7.06 (2H, br s, H6'), 7.14 (2H, br s, H5'), 7.25 (2H, br s, H7'), 7.55*, 7.60 (2H, br s, H4'), 8.40*, 8.48 (2H, br s, NH of indole). ^{13}C-NMR ($CDCl_3$) δ: 21.91 (C2", 3"), 25.34 (Cβ), 40.71*, 40.97 (Cα), 68.90, 69.34* (C1"), 111.21 (C7'), 112.51*, 112.74 (C3'), 118.55 (C4'), 119.08 (C6'), 121.80 (C5'), 122.11 (C2'), 127.16 (C3a'), 136.31 (C7a'), 166.70*, 167.15 (C2, 4), 169.63, 170.03* (C6). (The observed ^{1}H- and ^{13}C-signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS *m/z*: 456 $(M+H)^+$. HR-FAB-MS *m/z*: 456.2512 (Calcd for $C_{26}H_{30}N_7O$: 456.2513). Anal. Calcd for $C_{26}H_{29}N_7O \cdot 1/3EtOAc \cdot$

1/3H_2O: C, 66.87; H, 6.66; N, 19.97. Found: C, 67.10; H, 6.67; N, 20.04.

General Procedure for *C*$_3$- and *C*$_2$-Symmetrical Multivalent Hybrid-type TAZ Derivatives (8, 10): Example: Synthesis of *N*^{2}-[2-[Bis[2-[[4,6-bis[(3,4-dimethoxybenzyl)amino]-1,3,5-triazin-2-yl]amino]-ethyl]amino]ethyl]-*N*^{4},*N*^{6}-bis(3,4-dimethoxybenzyl)-1,3,5-triazine-2,4,6-triamine (8a) (Entry 12): To a suspension of intermediate **3a** (1.411 g, 2.55 mmol) in DMF (2.5 mL) was added TAEA (74.6 mg, 0.510 mmol) and K_2CO_3 (705 mg, 5.10 mmol) at room temperature with stirring. The reaction mixture was refluxed for 5.5 h. After evaporation of the solvent and addition of 1M HCl (20 mL), the brown residue was extracted with CH_2Cl_2 (20 mL×3). The combined organic layer was washed with 1M aq. $NaHCO_3$ (50 mL) and dried over $MgSO_4$. After evaporation of the solvent, the brown oily residue was purified by flush column chromatography (CH_2Cl_2 : EtOH = 95 : 5 → 90 : 10) to obtain compound **8a** (305 mg, 0.222 mmol, 41%) as a white solid. Mp 103-110 ºC. IR (KBr) cm^{-1}: 3389 (NH), 2833 ($ArOCH_3$) 1565, 1516 (C=N), 1262, 1234, 1138, 1026 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ: 2.61 (6H, br s, H2’’), 2.73* (5.6H, br s, NH), 3.38 (6H, br s, H1”), 3.77 (18H, br s, OCH_3 on C3’), 3.81 (18H, br s, OCH_3 on C4'), 4.35, 4.47* (12H, br s, Hα), [4.88 (1.8H), 5.12 (1.2H), 5.97 (0.15H), 6.32 (0.25H)] (br s, NH), 6.60-6.90 (18H, m, H2’, 5’, 6’). ^{13}C-NMR ($CDCl_3$) δ: 38.68 (C1”), 44.29 (Cα), 55.74 (OCH_3 on C3’ or 4’), 55.83 (OCH_3 on C4’ or 3’, C2”), 110.74 (C5’), 110.98 (C2’), 119.54 (C6’), 132.03 (C1’), 148.05 (OCH_3 on C4’), 148.92 (OCH_3 on C3’), 166.17 (C2, 4, 6). (The observed ^{1}H- and ^{13}C-signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS *m/z*: 1374 $(M+H)^+$. HR-FAB-MS *m/z*: 1374.6868 (Calcd for $C_{69}H_{88}N_{19}O_{12}$: 1374.6860). Anal. Calcd for $C_{69}H_{87}N_{19}O_{12}\cdot EtOH\cdot 1.5H_2O$: C, 58.91; H, 6.68; N, 18.38. Found: C, 58.88; H, 6.58; N, 18.38.

***N*^{2},*N*^{4}-Bis(benzo[*d*][1,3]dioxol-5-ylmethyl)-*N*^{6}-[2-[bis[2-[[4,6-bis[(benzo[*d*][1,3]dioxol-5-ylmethyl)-amino]-1,3,5-triazin-2-yl]amino]ethyl]amino]ethyl]-1,3,5-triazine-2,4,6-triamine (8b) (Entry 13):** Colorless solid. Mp 90-93 ºC. IR (KBr) cm^{-1}: 3410 (NH), 1567, 1501 (C=N), 1249, 1038 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ: 2.55 (6H, br s, H2”), ca. 3.2* (3.8H, br s, NH), 3.31 (6H, br s, H1”), 4.29, 4.40* (12H, br s, Hα), 5.19, 5.38 (3.5H, br s, NH), 5.86 (12H, br s, H2’), *ca*. 6.25 (1.7H, br s, NH), 6.50-6.90 (18H, br s, H4’, 6’, 7’). ^{13}C-NMR ($CDCl_3$) δ: 39.09 (C1”), 44.21 (Cα), 54.27 (C2”), 100.84 (C2’), 108.00, 108.11 (C4’, 7’), 120.47 (C6’), 133.62 (C5’), 146.47, 147.60 (C3’α, 7’α), 165.52, 165.72, 165.92 (C2, 4, 6). (The observed ^{1}H- and ^{13}C-signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS *m/z*: 1278 $(M+H)^+$. HR-FAB-MS *m/z*: 1278.4091 (Calcd for $C_{63}H_{64}N_{19}O_{12}$: 1278.4982). Anal. Calcd for $C_{63}H_{63}N_{19}O_{12}\cdot EtOH\cdot 0.5H_2O$: C, 58.55; H, 5.29; N, 19.96. Found: C, 58.32; H, 5.12; N, 20.10.

***N*^{2},*N*$^{2'}$-(Propane-1,3-diyl)bis(*N*^{4},*N*^{6}-bis(3,4-dimethoxybenzyl)-1,3,5-triazine-2,4,6-triamine (10aq) (Entry 14):** White solid. mp 71-74 ºC. IR (NaCl) cm^{-1}: 3377(NH), 1671, 1558 (C=N), 1262, 1235, 1139, 1027 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.73 (2H, br s, H2’’), 2.22 (5H, br s, NH), 3.39 (4H, br s,

H1'', 3''), 3.81, 3.835, 3.84, 3.85 (24H, br s, OCH_3), 4.40, 4.52 (8H, br s, Hα), 5.13 (0.4H, br s, NH), 5.28 (0.6H, br s, NH), 6.65-6.9 (12H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 30.07 (C2''), 37.44 (br s, C1'', 3"), 44.41 (br s, Cα), 55.76, 55.84 (OCH_3), 110.80 (C5'), 111.02 (C2'), 119.55 (C6'), 131.99 (br s, C1'), 148.09 (C4'), 148.95 (C3'), 165.95 (br s, C2, 4, 6). Positive-ion FAB-MS *m/z*: 893 $(M+H)^+$. HR-FAB-MS *m/z*: 893.4423 (Calcd for $C_{45}H_{57}N_{12}O_8$: 893.4422). Anal. Calcd for $C_{45}H_{56}N_{12}O_8 \cdot 1.5H_2O$: C, 58.75; H, 6.46; N, 18.27. Found: C, 58.83; H, 6.72; N, 18.15.

Synthesis of N^2,$N^{2'}$-(Pentane-1,5-diyl)bis[N^4,N^6-bis(3,4-dimethoxybenzyl)-1,3,5-triazine-2,4,6-triamine] (10as) (Entry 15): To a suspension of intermediate **3a** (981 mg, 2.20 mmol) in THF (10 mL) was added 1,5-diaminopentane (**9s**, 102 mg, 1.00 mmol) and *N*,*N*-diisopropylethylamine (DIPEA, 284 mg, 2.20 mmol) at room temperature with stirring. The reaction mixture was refluxed for 7 d. After addition of water (20 mL), the mixture was extracted with CH_2Cl_2 (20 mL×3). The combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residual yellow oil was purified by centrifugal chromatography (CH_2Cl_2 : EtOH = 97 : 3) to give compound **10as** (330 mg, 358 mmol, 36%) as a white solid. Mp 75-77 ºC. IR (KBr) cm^{-1}: 3403 (NH), 1557, 1506 (C=N), 1262, 1234, 1137, 1027 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.29 (2H, br s, H3"), 1.47 (4H, br s, H2", 4"), 2.66 (1.7H, br s, NH), 3.21, 3.30 (4H, br s, H1", 5"), 3.79, 3.82 (24H, OCH_3), 4.47 (8H, br s, Hα), 5.17 (0.7H, br s, NH), 5.60 (3.6H, br s, NH), 6.70-6.85 (12H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 24.01 (C3"), 29.30 (C2", 4"), 40.32 (C1", 5"), 44.29 (Cα), 55.67, 55.76 (OCH_3), 110.75 (C5'), 110.97 (C2'), 119.56 (C6'), 131.98 (br s, C1'), 148.01 (C4'), 148.87 (C3'), 166.00 (br s, C2, 4, 6). Positive-ion FAB-MS *m/z*: 921 $(M+H)^+$. HR-FAB-MS *m/z*: 921.4763 (Calcd for $C_{47}H_{61}N_{12}O_8$: 921.4735). Anal. Calcd for $C_{47}H_{60}N_{12}O_8 \cdot 1.2H_2O$: C, 59.88; H, 6.67; N, 17.83. Found: C, 59.89; H, 6.61; N, 17.68.

Synthesis of *N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-chloro-6-isopropoxy-1,3,5-triazin-2-amine (11b) (Entry 16): Compound **11b** was prepared from the reaction of **5** with piperonylamine **2b** under the conditions shown in Table 3 in a manner similar to that for the preparation of compound **11e** reported before.[12] Colorless crystals. Mp 148-150 ºC (from MeCN). IR (KBr) cm^{-1}: 3260, 3121 (NH), 1645, 1564, 1530 (C=N), 1298, 1248, 1234, 1038, (C-N and/or C-O), 806 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ: 1.32 (2H, d, *J* = 6.2 Hz, H2", H3"), 1.36* (4H, d, *J* = 6.2 Hz, H2", H3"), 4.55 (1.3H, d, *J* = 6.2 Hz, Hα), 4.56* (0.7H, d, *J* = 6.2 Hz, Hα), 5.24 (0.3H, qu, *J* = 6.2 Hz, H1"), 5.29* (0.7H, qu, *J* = 6.2 Hz, H1"), 5.95* (1.3H, s, H2'), 5.95 (0.7H, s, H2'), 6.28 (0.3H, br s, NH), 6.73* (0.7H, br s, NH), 6.75-6.83, m, H4', 6', 7'). ^{13}C-NMR ($CDCl_3$) δ: 21.66*, 21.69 (C2", 3"), 44.80*, 44.89 (Cα), 71.67, 72.01* (C1"), 101.10 (C2'), 108.01 (C4'), 108.32 (C7'), 120.79*, 121.11 (C6'), 131.25*, 131.28 (C5'), 147.15 (C7a'), 147.92 (C3a'), 166.93 (C2), 169.79 (C4), 170.31 (C4 or 6), 170.38 (C6 or 4), 171.45 (C6). (The observed ^{1}H- and ^{13}C-signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS *m/z*: 323 $(M+H)^+$. HR-FAB-MS *m/z*: 323.0914 (Calcd for $C_{14}H_{16}ClN_4O_3$: 323.0911). Anal. Calcd for $C_{14}H_{15}ClN_4O_3 \cdot$

0.2H_2O: C, 51.52; H, 4.76; N, 17.17. Found: C, 51.56; H, 4.76; N, 17.04.

***N*-Benzyl-4-chloro-6-isopropoxy-1,3,5-triazin-2-amine (11e) (Entry 17):** See reference 12.

Synthesis of N^2-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-N^4-[2-[bis[2-[[4-[(benzo[*d*][1,3]dioxol-5-ylmethyl)-amino]-6-isopropoxy-1,3,5-triazin-2-yl]amino]ethyl]amino]ethyl]-6-isopropoxy-1,3,5-triazine-2,4-diamine (12b) (Entry 18): To a solution of compound **4c** (485 mg, 1.50 mmol) in THF was added TAEA (73.1 mg, 0.500 mmol), Et_3N (304 mg, 3.00 mmol) and NaI (229 mg, 1.50 mmol) at room temperature with stirring. The reaction mixture was subjected to MW at 70 °C (90 W) for 2 h and at 100 °C (100 W) for 1 h with stirring. After addition of water (35 mL) to the resulting mixture, the mixture was extracted with CH_2Cl_2 (25 mL×3). The combined organic layer was washed with saturated aq. NH_4Cl (50 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by centrifugal chromatography (CH_2Cl_2 : EtOH = 95 : 5) to give compound **5c** (257 mg, 0.256 mmol, 51%) as a white solid. Mp 97-100 °C. IR (KBr) cm^{-1}: 3409 (NH), 1575, 1514 (C=N), 1317, 1249, 1105, 1039 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.20, 1.30 (18H, br s, H2”, H3”), 2.64 (6H, br s, H2’”), 3.42 (6H, br s, H1’”), 4.35, 4.48 (6H, br s, Hα), *ca*. 5.1 (0.8H, br s, NH), 5.11, 5.18 (3H, br s, H1”), 5.45 (0.4H, br s, NH), 5.90 (6H, br s, H2’), *ca*. 5.9 (0.8H, br s, NH), 6.15 (0.4H, br s, NH), *ca*. 6.3 (0.4H, br s, NH), 6.6-6.85 (9H, m, ArH), *ca*. 8.5 (0.2H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 21.89 (C2’’, 3”), 38.69, 38.96* (br s, C1’’’), 44.27, 44.43* (br s, Cα), 53.38, 55.65*, 56.22 (br s, C2”’), 68.95, 69.24* (br s, C1”), 100.87 (C2’), 108.00 (C4’, 7’), 120.53 (C6’), 133.15 (br s, C5’), 146.55, (C7a’), 147.64 (C3a’), 167.07 (br s, C2, 4), 167.46 (br s, C6). (The observed ^{1}H- and ^{13}C-signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS *m/z*: 1005 $(M+H)^+$. HR-FAB-MS *m/z*: 1005.4813 (Calcd for $C_{48}H_{61}N_{16}O_9$: 1005.4807). Anal. Calcd for $C_{48}H_{60}N_{16}O_9 \cdot 2H_2O$: C, 55.37; H, 6.20; N, 21.53. Found: C, 55.44; H, 5.94; N, 21.31.

Synthesis of N^2-Benzyl-N^4-[2-[bis[2-[[4-(benzylamino)-6-isopropoxy-1,3,5-triazin-2-yl]amino]ethyl]-amino]ethyl]-6-isopropoxy-1,3,5-triazine-2,4-diamine (12e) (Entry 19): To a suspension of compound **11e** (585 mg, 2.10 mmol) in MeCN (15 mL) and THF (10 mL) was added TAEA (102 mg, 0.700 mmol) and Et_3N (850 mg, 8.40 mmol) at room temperature. The reaction mixture was stirred at 50 °C for 19 h with stirring. After addition of water (75 mL) to the resulting mixture, the mixture was extracted with EtOAc (40 mL×3). The combined organic layer was washed with brine (40 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by centrifugal chromatography (CH_2Cl_2 : EtOH = 95 : 5) to afford compound **12e** (299 mg, 0.343 mmol, 49%) as a colorless solid. **12e**: Mp 85-88 °C. IR (ATR, neat) cm^{-1}: 3254 (NH), 1564, 1508 (C=N), 1144, 1104 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.17, 1.29* (18H, br s, H2’’, 3”), 2.60, 2.64* (6H, br s, H2”’), 3.24 (1.9H, br s, NH), 3.38, 3.42* (6H, br s, H1’’’), 4.46, 4.58* (6H, br s, Hα), *ca.* 5.1 (0.2H, br s, NH), 5.09, 5.19* (3H, br s, H1”), 5.48 (0.5H, br s, NH), *ca.* 6.35 (3.4H, br s, NH), 7.10-7.35 (15H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 21.87 (C2’’, 3”), 38.93*,

39.58 (br s, C1''), 44.53*, 44.57 (Cα), 53.60*, 55.99 (br s, C2'''), 68.94*, 69.29 (br s, C1''), 127.01 (C4'), 127.30 (C2', 6'), 128.41 (C3', 5'), 139.27 (br s, C1'), 167.05 (br s, C2, 4), 169.63 (br s, C6). (The observed ^{1}H- and ^{13}C-signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS *m/z*: 873 $(M+H)^+$. HR-FAB-MS *m/z*: 873.5108 (Calcd for $C_{45}H_{61}N_{16}O_3$: 873.5113). Anal. Calcd for $C_{45}H_{60}N_{16}O_3 \cdot 0.4H_2O$: C, 61.40; H, 6.96; N, 25.46. Found: C, 61.56; H, 6.97; N, 25.36.

Synthesis of *N*^{1}-(4,6-Diisopropoxy-1,3,5-triazin-2-yl)-*N*^{2},*N*^{2}-bis[2-[(4,6-diisopropoxy-1,3,5-triazin-2-yl)amino]ethyl]ethane-1,2-diamine (14) (Entry 20): To a solution of compound **13** (765 mg, 3.30 mmol) in THF (10 mL) was added TAEA (146 mg, 1.00 mmol) and DIPEA (427 mg, 3.30 mmol) at room temperature. The reaction mixture was refluxed for 4 h. After addition of water (15 mL) to the resulting mixture, the mixture was extracted with CH_2Cl_2 (20 mL×3). The combined organic layer was washed with brine (15 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by centrifugal chromatography (CH_2Cl_2 : EtOH = 97 : 3) to give compound **14** (438 mg, 0.598 mmol, 60%) as a colorless solid. Mp 155-158 °C. IR (KBr) cm^{-1}: 3261, 3144 (N-H), 1621, 1575 (C=N), 1178, 1124, 1099 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, d, *J* = 6.2 Hz, H2', 3' on C4), 1.35 (3H, d, *J* = 6.2 Hz, H2', 3' on C6), 2.67-2.74 (6H, m, H2''), 3.44-3.50 (6H, m, H1''), 5.22 (3H, qu, *J* = 6.2 Hz, H1' on C4), 5.30 (3H, qu, *J* = 6.2 Hz, H1' on C6), 6.44 (3H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 21.86 (C2', 3'), 38.54 (C1''), 53.42 (C2''), 70.17 (C1' on C4), 70.40 (C1' on C6), 167.95 (C2), 171.85 (C4), 171.55 (C6). Positive-ion FAB-MS *m/z*: 732 $(M+H)^+$. HR-FAB-MS *m/z*: 732.4631 (Calcd for $C_{33}H_{58}N_{13}O_6$: 732.4633). Anal. Calcd for $C_{33}H_{57}N_{13}O_6 \cdot EtOH \cdot H_2O$: C, 52.81; H, 8.23; N, 22.88. Found: C, 52.98; H, 7.87; N, 22.54.

Synthesis of *N*^{1}-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-*N*^{2},*N*^{2}-bis[2-[(4,6-dimethoxy-1,3,5-triazin-2-yl)-amino]ethyl]ethane-1,2-diamine (16) and *N*^{1}-(2-Aminoethyl)-*N*^{2}-(4,6-dimethoxy-1,3,5-triazin-2-yl)-*N*^{1}-[2-[(4,6-dimethoxy-1,3,5-triazin-2-yl)amino]ethyl]ethane-1,2-diamine (17) (Entry 21): To a solution of TAEA (292 mg, 2.00 mmol) in THF (20 mL) was added a solution of compound **13** (1.09 g, 6.20 mmol) in THF (5 mL) and DIPEA (775 mg, 6.00 mmol) with stirring at room temperature under an N_2 atmosphere. The reaction mixture was refluxed for 22 h. After addition of water (30 mL) to the resulting mixture, the mixture was extracted with CH_2Cl_2 (40 mL×3). The combined organic layer was washed with brine (25 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by centrifugal chromatography (CH_2Cl_2 : 95% EtOH : 28% NH_3 = 70 : 27.5 : 2.5) to give compounds **16** (219 mg, 0.389 mmol, 19%) and **17** (316 mg, 0.744 mmol, 37%).

16: White solid. Mp 62-64 °C. IR (KBr) cm^{-1}: 3264, 3153 (N-H), 1571, 1544 (C=N), 1345, 1254, 1105 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ: 2.75 (6H, t, *J* = 5.5 Hz, H2'), 3.47 (6H, dt, *J* = 5.5, 5.2 Hz, H1'), 3.90 (9H, s, OMe on C4), 3.94 (9H, s, OMe on C6), 6.44 (3H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 38.71 (C1'), 52.98 (C2'), 54.42 (OMe on C4), 54.51 (OMe on C6), 167.95 (C2), 171.82 (C4), 172.41 (C6).

Positive-ion FAB-MS *m/z*: 564 $(M+H)^+$. HR-FAB-MS *m/z*: 565.2750 (Calcd for $C_{21}H_{34}N_{13}O_6$: 564.2755). Anal. Calcd for $C_{21}H_{33}N_{13}O_6 \cdot 5/6EtOH$: C, 45.23; H, 6.36; N, 30.25. Found: C, 44.97; H, 5.91; N, 30.10.

17: Colorless solid. Mp 117-118 °C. IR (ATR) cm^{-1}: 3015, 2970 (N-H), 1577, 1550 (C=N), 1362, 1229, 1217 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ: 2.40 (2H, br s, NH), 2.61 (2H, t, *J* = 5.5 Hz, H2"), 2.72 (4H, t, *J* = 5.5, Hz, H2'), 2.80 (2H, t, *J* = 5.5 Hz, H1"), 3.49 (4H, t, *J* = 5.5 Hz, H1'), 3.95 (6H, s, OMe on C4), 4.02 (6H, s, OMe on C6), 6.71 (2H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 39.01 (C1'), 39.56 (C1"), 53.26 (C2'), 54.39 (OMe on C4), 54.47 (OMe on C6), 56.28 (C2"), 167.95 (C2), 171.88 (C4), 172.42 (C6). Positive-ion FAB-MS *m/z*: 425 $(M+H^+)$. HR-FAB-MS *m/z*: 425.2370 (Calcd for $C_{21}H_{34}N_{13}O_6$: 425.2373). Anal. Calcd for $C_{16}H_{28}N_{10}O_4 \cdot 0.4H_2O$: C, 44.52; H, 6.72; N, 32.45. Found: C, 44.76; H, 6.62; N, 32.18.

Synthesis of 6-[2-[Bis[2-[[4,6-bis(isopropylamino)-1,3,5-triazin-2-yl]oxy]ethyl]amino]ethoxy]-*N*^{2},*N*^{4}-diisopropyl-1,3,5-triazine-2,4-diamine (19) (Entry 22 and 23): (Step 1): To a solution of TCTAZ (**1**, 5.53 g, 30.0 mmol) in acetone (20 mL) was added a solution of THEA (1.49 g, 10.0 mmol) and collidine (3.64 g, 30.0 mmol) in acetone (30 mL) drop by drop for 20 min with stirring at 0 °C under an N_2 atmosphere. The reaction mixture was refluxed for 12 h. After filtration of white solids (collidine·HCl salt), ice water (50 mL) was added to the filtrate. The resulting mixture was extracted with CH_2Cl_2 (40 mL×3). The combined organic layer was washed with brine (10 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residue was solidified to give the crude intermediate **18** by addition of a solvent (*n*-hexane : EtOAc = 7 : 3, *ca.* 5 mL). **(Step 2):** To a solution of the crude intermediate **18** in THF (200 mL) was added 2-propylamine and DIPEA (7.75 g, 60.0 mmol) at room temperature. The reaction mixture was refluxed for 12 h. After filtration of white solids (DIPEA·HCl salt) and evaporation of the solvent, the residue was purified by flash column chromatography (CH_2Cl_2 : 95% EtOH : 28% NH_3 = 95 : 4.7 : 0.3) to afford compound **19** (936 mg, 1.28 mmol, 13%) as a pale yellow solid. Mp 97-99 °C. IR (ATR) cm^{-1}: 3255 (NH), 1565 (C=N), 1325, 1181 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.18 (36H, br s, H2', 3'), 3.00 (6H, br s, H2''), 4.08, 4.16* (6H, br s, H1'), 4.29, 4.35* (6H, br s, H1''), 4.85, 4.92* (6H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 22.78, 22.95* (C2', 3'), 42.27*, 42.47 (C1'), 53.59 (C2''), 64.32 (C1''), 166.48 (C2, 4), 170.52 (C6). (The observed ^{1}H- and ^{13}C-signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS *m/z*: 729 $(M+H)^+$. HR-FAB-MS *m/z*: 729.5123 (Calcd for $C_{33}H_{61}N_{16}O_3$: 729.5113). Anal. Calcd for $C_{33}H_{60}N_{16}O_3 \cdot 0.25EtOH \cdot 0.5H_2O$: C, 53.69; H, 8.41; N, 29.90. Found: C, 53.89; H, 8.59; N, 29.68.

Antiviral Activity Assay and Cytotoxicity

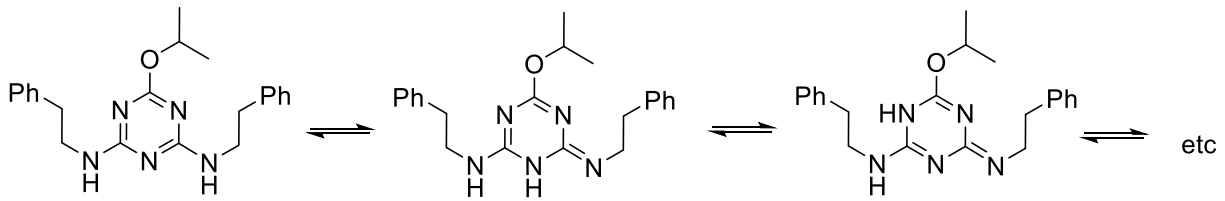
The anti-HSV-1 activities (EC_{50}) of the synthesized TAZ derivatives were measured by using a plaque reduction assay,[15] and their cytotoxicity against Vero cells (CC_{50}) was also evaluated as we described previously. The results are summarized in Tables 4 and 5 together with data for acyclovir.[17] Calculated

log *P* values for the compounds are also shown in the tables. There were few distinct correlations between log *P* values and anti-HSV-1 activity (EC_{50}).

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. N. Mibu, K. Yokomizo, W. Uchida, S. Takemura, J. Zhou, H. Aki, T. Miyata, and K. Sumoto, *Chem. Pharm. Bull.*, 2012, **60**, 408.
6. 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.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. N. Mibu, T. Ohata, M. Sano, J.-R. Zhou, K. Yokomizo, H. Aki, and K. Sumoto, *J. Therm. Anal. Calorim.*, 2019, **135**, 2807 (DOI 10.1007/s10973-018-7573-4).
14. 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.
15. R. F. Schinazi, J. Peters, C. C. Williams, D. Chance, and A. J. Nahmias, *Antimicrob. Agents Chemother.*, 1982, **22**, 499.

16. Log *P* values were calculated by using SCIGRESS v.2.8.1.
17. T. Ikeda, K. Yokomizo, M. Okawa, R. Tsuchihashi, J. Kinjo, T. Nohara, and M. Uyeda, *Biol. Pharm. Bull*., 2005, **28**, 1779.
18. M. Belema, Van N. Nguyen, C. Bachand, D. H. Deon, J. T. Goodrich, C. A. James, R. Lavoie, O. D. Lopez, A. Martel, J. L. Romine, E. H. Ruediger, L. B. Snyder, D. R. St. Laurent, F. Yang, J. Zhu, H. S. Wong, D. R. Langley, S. P. Adams, G. H. Cantor, A. Chimalakonda, A. Fura, B. M. Johnson, J. O. Knipe, D. D. Parker, K. S. Santone, R. A. Fridell, J. A.Lemm, D. R. II O'Boyle, R. J. Colonno, M. Gao, N. A. Meanwell, and L. G. Hamann, *J. Med. Chem*., 2014, **57**, 2013.
19. D. A. DeGoey, J. T. Randolph, D. Liu, J. Pratt, C. Hutchins, P. Donner, A. C. Krueger, M. Matulenko, S. Patel, C. E. Motter, L. Nelson, R. Keddy, M. Tufano, D. D. Caspi, P. Krishnan, N. Mistry, G. Koev, T. J. Reisch, R. Mondal, T. Pilot-Matias, Y. Gao, D. W. A. Beno, C. J. Maring, A. Molla, E. Dumas, A. Campbell, L. Williams, C. Collins, R. Wagner, and W. M. Kati, *J. Med. Chem.*, 2014, **57**, 2047.
20. Some of the tri-substituted TAZ derivatives described in this paper showed a complicated ^{13}C-NMR signal pattern because of their keto-enol tautomeric isomers in solutions. Compounds (**4ad**, **4ba**, **4bc**, **4bd**, **7p-t**, **8a**, **8b**, **11b**, **11e**, **12b**, **12e**, **19**) that have a *sec*-alkylamino groups on a TAZ template are examples of TAZ derivatives with such a signal pattern. These compounds showed the presence of a few tautomeric isomers in solution. For example, signals that appeared in the ^{13}C-NMR spectrum of compound **7p** seem to be consistent with the tautomeric mixture of a few isomers shown below (**T**$_1$, **T**$_2$, **T**$_3$ etc.).



T$_1$ **T**$_2$ **T**$_3$

7p

Tautomeric Isomerism of TAZ Derivative **7p**