Note

Preparation and Antiviral Activity of Some New C₃- and C_s-Symmetrical Tri-Substituted Triazine Derivatives Having Benzylamine Substituents

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We report the preparation of new C₃- and C_s-symmetrical molecules constructed on a triazine (TAZ) template. Anti-herpes simplex virus type 1 (anti-HSV-1) and cytotoxic activities against Vero cells of synthesized TAZ derivatives were evaluated. The results suggested that the presence of an electron-donating group(s) on the benzene ring in benzylamine groups on the TAZ template is an important structural factor for expressing a high level of anti-HSV-1 activity and low cytotoxicity for these C₃ types of TAZ derivatives. Among the tested TAZ derivatives, compounds **4f** and **7h** showed the highest anti HSV-1 activities (EC₅₀=0.98 and 1.23 μM, respectively) and low cytotoxic activities to Vero cells (50% cytotoxic concentration (CC₅₀)=292.2 and >200 μM, respectively).

Key words 1,3,5-triazine; benzylamine-substituent; C₃-symmetry; anti-herpes simplex virus type 1; hydrogen bond donor; structure–activity relationship

In the search for new types of antiviral active compounds, extensive efforts have been made to find promising new antiviral candidates.¹⁾ It is well known that many types of receptors or functionalized proteins on membranes in a native state often have a high order of symmetrical interfaces.²⁾ C₃- or C₂-geometric symmetrical molecules have frequently been found in various synthetic biologically active compounds.³⁾ Aiming to develop new synthetic bioactive compounds, we targeted such geometrical symmetric molecules constructed on a symmetrical template.

In our previous studies on antiviral compounds in the tri-substituted 1,3,5-triazine (TAZ) series, we found that many of the new C₃- and C_s-symmetrical TAZ derivatives synthesized previously showed a wide range of bioactivities against herpes simplex virus type 1 (HSV-1) or cytotoxic activities to Vero cells.⁴⁾ Regarding tri-substituted TAZ derivatives, we have reported that some symmetrical TAZ derivatives having alkoxy and/or alkylamino substituents show a high level of anti-HSV-1 activity⁵⁾ (Fig. 1). Notably, we found that

some TAZ derivatives that have benzylamine substituents on a TAZ template such as compound **4h** show a high level of anti-HSV-1 activity (EC₅₀=5.4 μM) and low cytotoxicity (50% cytotoxic concentration (CC₅₀)=291.9 μM). In terms of a structure–activity relationship (SAR) study and finding new types of antiviral active leads, molecular modification by the introduction of benzylamine functionalities into a TAZ template seems to be interesting.

Here, we describe the synthesis of new types of symmetrical TAZ derivatives that have various benzylamine substituents on symmetrical TAZ templates and the results of their biological evaluations.

Results

Synthesis of New Target Derivatives of Symmetrical Tri-Substituted TAZ Derivatives Our strategies for the synthesis of target TAZ derivatives by using 2,4,6-trichlorotriazine (TCTAZ: **1**) as a starting material are summarized in Chart 1.

The pathway for the synthesis of C₃- and C_s-type symmetrical TAZ derivatives (**4** and **7**) together with intermediates of TAZ derivatives is shown in Chart 1. All of the substitution reactions of the starting TCTAZ (**1**) or monoalkoxy-dichlorotriazine (**5**)⁵⁾ with various benzylamines (**2a–k**) were performed in a one-pot reaction and the desired new TAZ derivatives (**4** and **7**) were obtained. All of the target C₃-type TAZ derivatives (**4**) were obtained in moderate to good yields (42–85%) as shown in Table 1, and C_s-type symmetrical TAZ derivatives (**7**) were also obtained in moderate yields (Table 2). For the synthesis of these new targeted C₃- and C_s-symmetrical tri-substituted TAZ derivatives, we used the same procedure as that described for the preparation of symmetrical TAZ derivatives (see Experimental).

All of the structures of the synthesized C₃- and C_s-sym-

Fig. 1. Symmetrical Target Molecules Constructed on Tri-Substituted TAZ Derivatives

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Chart 1. Synthesis of C_3 - and C_5 -Symmetrical TAZ DerivativesTable 1. Synthesis of C_3 -Symmetrical Benzylamine-Type TAZ Derivatives (4)

Entry	ArCH ₂ NH ₂ (2)	Reaction time of MW (min) ^{a)}	Products (yield %)
1	2a	60	4a (85)
2	2b	60	4b (53)
3	2b	40 ^{b)}	3b (46) ^{c)} , 4b (5) ^{c)}
4	2c	60	4c (75)
5	2d	60	4d (42)
6	2e	30	4e (66)
7	2f	50	4f (80)
8	2g	20	4g (57)
9	2i	20	4i (63)

a) In the all reactions except for Entry 3, stirring of the reaction mixtures (ratio of 1:2=1:10) in dioxane were conducted at 0°C for 30min, at room temperature for 1h, and then irradiation of microwave (100 W, 100°C) for a proper shown time. b) Stirring the reaction mixture (ratio of 1:2b=1:6) in THF was conducted at room temperature for 10 min, and then irradiation of microwave (90 W, 70°C) for 20 min. c) Yields after recrystallization.

metrical TAZ derivatives (4 and 7) and a few intermediates (3, 6) were confirmed by spectroscopic and analytical data. The geometries of the obtained symmetrical TAZ derivatives described above were confirmed from ¹³C-NMR spectroscopic data⁶⁾ (see Experimental for details).

Biological Activity and Discussion In many synthetic receptor-type molecules mimicking the supramolecular interaction of biomolecules, it is expected that the ability to form multiple hydrogen bonds plays an important role in guest molecule recognition. Considering the hydrogen bonded interaction in a supramolecular host-guest system, it is also expected that a convergent orientation of incorporated functional groups is an effective array to produce multiple hydrogen bonding interactions between host and guest molecules.^{7,8)} From this point of view, title C_3 - and C_5 -geometrical molecules that have donors or acceptors for hydrogen bonds on a symmetrical TAZ template are thought to offer new biologically active molecules.

From biological evaluations of anti-HSV-1 activities (EC_{50}) by plaque reduction assays⁹⁾ and cytotoxic activities (CC_{50}) against Vero cells of synthesized TAZ derivatives (Table 3), most of the C_3 -symmetrical benzylamine-type TAZ derivatives (4) presented hydrogen bond donor protons of a benzylamine (–NH–) functionality. Many of the C_3 -symmetrical benzylamine-type TAZ derivatives (4) showed a significantly high level of anti-HSV-1 activity, and compound 4f showed

a high level of anti-HSV-1 activity (EC_{50} =0.98 μ M) and a low level of cytotoxic activity (CC_{50} =292.2 μ M) as did compound 4h⁵⁾ (EC_{50} =5.4 μ M and CC_{50} =291.9 μ M) reported previously. All of the compounds that have electron-withdrawing substituents (4c and 4d) including non-substituted compound 4a showed considerably high levels of anti-HSV-1 activity (EC_{50} =7.4–13.2 μ M) and cytotoxic activity (CC_{50} =5.5–94.9 μ M). Regarding the two biological activities (anti-HSV-1 activity and cytotoxic activity), the opposite order in electron-withdrawing (attracting) effects between the two activities was observed (4a<4c<4d for anti-HSV-1 activity and 4a>4c>4d for cytotoxic activity). Lower levels of cytotoxic activity (CC_{50} =13.0–94.9 μ M) were observed for compounds 4c and 4d than for non-substituted compound 4a.

Considerably high levels of anti-HSV-1 activity (EC_{50} =0.98–38.7 μ M) were observed for C_3 -type compounds (4b, 4f, 4h⁵⁾ and 4i) that have electron-donating substituents such as methyl or methoxy groups on the benzene rings except for compounds 4g and 4e (see Table 3), and these compounds showed cytotoxic activities over 200 μ M. The obtained biological results indicated that the nature of substituents on the benzene rings prefers electron-donating substituents for expressing a high level of anti-HSV-1 activity and low level of cytotoxicity for these C_3 types of TAZ derivatives. We also consider that benzylamine groups in C_3 -type molecules may act as hydrogen-bond donors to receptor binding sites.

The exceptional anti-HSV-1 activity for compound 4g may be due to intramolecular hydrogen bond formation between the basic benzylamine moiety and the *ortho*-methoxy group in the molecule 4g that weakens such intermolecular hydrogen-bonding interaction of the TAZ molecule 4g to receptor binding sites (see Fig. 2). This exceptional result for compound 4g also indicates the importance of intermolecular hydrogen bond formation ability of C_3 -type TAZ molecules in the supramolecular interaction with its binding site for expressing a high level of anti-HSV-1 activity.

Despite the considerably high level of cytotoxic activity (CC_{50} =22.6 μ M) of compound 4e, the reason for exceptionally low level of anti-HSV-1 activity (EC_{50} >100 μ M) for this compound is still unclear at present. The positional effect of methoxy groups on benzene rings in these TAZ derivatives may be required for expression of anti-HSV-1 activity.

Among the C_5 -symmetrical benzylamine-type TAZ derivatives (7a, 7b, 7e–k) as shown in Table 3, a C_5 -symmetrical benzylamine-type TAZ derivative (7h) that has two benzyl-

Table 2. Synthesis of C_3 -Symmetrical Benzylamine-Type TAZ Derivatives (7)

Entry	ArCH ₂ NH ₂ (2)	Ratio of 1:2 (: DIPEA) ^{a)}	Reaction conditions ^{a)}	Product (yield %)
1	2a	1:1:1 (DIPEA)	0°C 2 h	6a (97)
2	2a	1:5	MW 60 min	7a (79)
3	2b	1:5	MW 45 min	7b (82) ^{b)}
4	2e	1:5	MW 60 min	7e (75) ^{b)}
5	2f	1:6	MW 30 min	7f (75) ^{b)}
6	2g	1:5	MW 30 min	7g (72)
7	2h	1:3	MW 30 min	7h (34) ^{b)}
8	2i	1:5	MW 30 min	7i (89)
9	2j	1:5	MW 30 min	7j (84) ^{b)}
10	2k	1:5	MW 45 min	7k (78)

^{a)} In the all reactions except for Entry 1, the reaction mixtures were subjected to microwave irradiation (100 W, 100°C) in dioxane. In the reaction of Entry 1, the reaction mixture with *N,N*-diisopropylethylamine (DIPEA) was used in THF. ^{b)} Yields after recrystallization.

Table 3. Anti-HSV-1 Activity (EC₅₀) and Cytotoxicity (CC₅₀) against Vero Cells of Synthesized New C_3 - and C_5 -Symmetrical Benzylamine-Type TAZ Derivatives (4, 7) and Intermediates (3, 6)

Compound	Ar	EC ₅₀ (μM)	CC ₅₀ (μM)	Compound	Ar	EC ₅₀ (μM)	CC ₅₀ (μM)
3b		> 100	188.8	6a		> 100	> 200
3f		> 100	102.5	7a		> 100	192.4
3h		> 100	> 200	7b		> 100	75.4
4a		13.2	5.5	7e		> 100	> 200
4b		38.7	>200	7f		> 100	> 200
4c		11.0	13.0	7g		> 100	20.6
4d		7.4	94.9	7h		1.23	328
4e		> 100	22.6	7i		72.1	162.3
4f		0.98	292.2	7j		12.6	81.1
4g		> 100	> 200	7k		> 100	14.6
4h^{a)}		5.4	291.9	aciclovir ^{b)}		1.1	> 444
4i		28.0	> 200				

^{a)} Data were taken from ref. 5). ^{b)} Data were taken from ref. 15).

Fig. 2. Intramolecular Hydrogen Bond Formation in Compound **4g**

amine groups with electron-donating substituents and an isopropoxy group showed a considerably high level of anti-HSV-1 activity ($EC_{50}=1.23\ \mu\text{M}$); however, many structurally related C_3 -symmetrical derivatives (**7a**, **7b**, **7e**, **7f**, **7g** and **7k**) showed low levels of anti-HSV-1 activity ($EC_{50}>100\ \mu\text{M}$) compared to that of compound **7h**. Compounds **7i** and **7j** showed moderate levels of anti-HSV-1 activity ($EC_{50}=72.1$ and $12.6\ \mu\text{M}$, respectively). Interestingly, many compounds in this series (**7a**, **7b**, **7g**, **7i**, **7j** and **7k**) showed moderate levels of cytotoxic activity ($CC_{50}=14.6\text{--}192.4\ \mu\text{M}$, see Table 3). Intermediates **3** and **6** listed in Table 3 showed almost no anti-HSV-1 or cytotoxic activity (see Table 3).

Regarding calculated $\log P$ values¹⁰⁾ for the compounds (see Supplementary Materials), there were few distinct correlations between $\log P$ values and anti-HSV-1 activity (EC_{50}) values shown in Table 3.

The results showing high levels of anti-HSV-1 activity for C_3 - or C_5 -symmetrical compounds (**4f** and **7h**) strongly suggest that at least the presence of two hydrogen bond donor benzylamine protons in the target TAZ derivatives is required as an important structural factor for the expression of a high level of anti-HSV-1 activity. A similar assumption is also substantiated by our previous observation of the disappearance of anti-HSV-1 activity by *N*-acetylated C_3 -symmetrical amine-type molecules.¹¹⁾

In the comparison with the anti-HSV-1 activity of acyclovir, it was found that the mode of action of acyclovir is different from the modes of action of TAZ derivatives described in this paper; however, it is noteworthy that some new symmetrical TAZ derivatives such as **4f** and **7h** showed similar levels of anti-HSV-1 activity with a large safety index value.

The results of calorimetric experiments¹²⁾ showed sugar recognition properties of highly active compounds with good SI values (CC_{50}/EC_{50}) such as compound **4f** (SI=298). From the point of the view of substituents as hydrogen-bond donors or acceptors, ITC experiments suggested that the reaction of compound **4f** with sugars showed a thermodynamic signature different from that of the entropically driven reaction of triisopropoxy-substituted TAZ derivative. Thus, we consider that such an enthalpic C_3 -type TAZ derivative having benzylamine functionalities may act as a hydrogen-bond donor to proposed receptor binding sites. On the basis of the obtained structural information on biological activities in this series, we are further investigating chemical modifications to new TAZ framework molecules in order to find new promising leads.

Experimental

Melting points were determined using a micro melting point apparatus (Yanaco MP-S3) without correction. IR spectra were measured by a JASCO FTIR-4100 IR spectrophotom-

eter. 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. ^1H - and ^{13}C -NMR spectra were obtained by ECG600R. Chemical shifts were expressed in δ ppm downfield from an internal tetramethylsilane (TMS) signal for ^1H -NMR and the carbon signal of the corresponding solvent [CDCl_3 (77.00 ppm), dimethyl sulfoxide (DMSO)- d_6 (39.50 ppm), THF - d_8 (67.20 ppm)] for ^{13}C -NMR. The signal assignments were confirmed by two-dimensional (2D)-NMR analyses: ^1H - ^1H 2D correlation spectroscopy (COSY), ^1H - ^{13}C heteronuclear multiple-quantum coherence (HMOC), and ^1H - ^{13}C heteronuclear multiple-bond connectivity (HMBC). Microanalyses were performed with a Yanaco MT-6 CHN coder. Routine monitoring of reactions was carried out using precoated Kieselgel 60F₂₅₄ plates (E. Merck). Microwave irradiation experiments were carried out in a CEM Discover Focused Microwave System. For the separation of crude products in small experimental scales (below 2 mmol), we applied Centrifugal chromatography separation of the reaction products 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 the Preparation of C_3 -Symmetrical Benzylamine-Type TAZ Derivatives (4**) (Table 1): Example: Synthesis of N^2,N^4,N^6 -Tribenzyl-1,3,5-triazine-2,4,6-triamine (**4a**) (Entry 1)** To a solution of TCTAZ (**1**, 277 mg, 1.50 mmol) in dioxane (2.5 mL), a solution of benzylamine (**2a**, 1.61 g, 15.0 mmol) in dioxane (1.5 mL) was added dropwise at 0°C , and the mixture was continuously stirred for 30 min at room temperature and then for another 1 h at room temperature. Then the mixture was subjected to microwave irradiation (MW) at 100°C (100 W) for 60 min with stirring. After addition of water (30 mL), the mixture was extracted with EtOAc ($2\times 25\ \text{mL}$). The combined organic layer was dried over MgSO_4 . After evaporation of the solvent, the residual solid was purified by centrifugal chromatography (*n*-hexane–EtOAc=50:50) to give an analytically pure **4a** (507 mg, 1.28 mmol, 85%) as a pale yellow solid.

4a: mp $103.0\text{--}104.5^\circ\text{C}$ (from 2-PrOH). IR cm^{-1} : 3405, 3249 (NH), 1536, 1500 (C=N), 1163 (C–N). ^1H -NMR (CDCl_3) δ : 4.53 (6H, brs, CH_2), 5.39 (3H, brs, NH), 7.18–7.32 (15H, m, H, C2', 3', 4', 5', 6'), ^{13}C -NMR (CDCl_3) δ : 44.56 (ArCH_2), 127.02 (C4'), 127.51 (C2', 6'), 128.44 (C3', 5'), 139.45 (C1'), 166.27 (C2, 4, 6). Positive-ion FAB-MS m/z : 397 ($\text{M}+\text{H}^+$). HR-FAB-MS m/z : 397.2147 (Calcd for $\text{C}_{24}\text{H}_{25}\text{N}_6$: 397.2147). Anal. Calcd for $\text{C}_{24}\text{H}_{24}\text{N}_6$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.70; H, 6.19; N, 21.05.

N^2,N^4,N^6 -Tris(4-methylbenzyl)-1,3,5-triazine-2,4,6-triamine (4b**) (Entry 2)** Compound **4b** was prepared from the reaction of **1** with 4-methylbenzylamine (**2b**) under the conditions shown in Table 1. Purification by centrifugal chromatography (CH_2Cl_2 –EtOH=97:3) afforded **4b** (53%) as a white solid. An analytical sample of **4b** was obtained as white crystals by concentration of the filtrate.

4b: mp $116\text{--}117^\circ\text{C}$ (from 2-PrOH). IR cm^{-1} : 3440 (NH), 1575, 1504 (C=N), 1346, 1245 (C–N), 808 (1,4-disubstituted benzene). ^1H -NMR (CDCl_3) δ : 1.83 (1.6H, brs, NH), 2.31 (9H, s, CH_3), 4.50 (6H, brs, H_α), 5.17 (0.6H, brs, NH), 5.27

(0.8H, brs, NH), 7.08 (6H, d, $J=7.3$ Hz, H3', 5'), 7.16 (6H, d, $J=7.3$ Hz, H2', 6'). ^{13}C -NMR (CDCl_3) δ : 21.06 (CH_3), 44.40 (Ca), 127.54 (C2', 6'), 129.13 (C3', 5'), 136.40 (C1'), 136.62 (C4'), 166.28 (C2, 4, 6). Positive-ion FAB-MS m/z : 439 ($\text{M}+\text{H}$) $^+$. HR-FAB-MS m/z : 439.2603 (Calcd for $\text{C}_{27}\text{H}_{31}\text{N}_6$: 439.2610). *Anal.* Calcd for $\text{C}_{27}\text{H}_{30}\text{N}_6$: C, 73.94; H, 6.89; N, 19.16. Found: C, 73.91; H, 6.98; N, 19.07.

6-Chloro- N^2,N^4 -bis(4-methylbenzyl)-1,3,5-triazine-2,4-diamine (3b) (Entry 3) Compound **3b** was obtained from the reaction of **1** and **2b** in THF (ratio of **1**:**2b**=1:6) under the conditions shown in Table 1 in 46% yield after recrystallization from 2-PrOH as a white solid together with **4b** (5%) obtained by concentration of the filtrate.

3b: mp 235–237°C (from 2-PrOH). IR cm^{-1} : 3248 (NH), 1541, 1511 (C=N), 1343, 1091 (C–N and/or C–O), 796, 582 (C–Cl). ^1H -NMR ($\text{THF}-d_8$) δ : 2.27, 2.28* (6H, s, CH_3), 4.44–4.49 (4H, m, CH_2), 4.71 (0.4H, brs, NH), 7.01–7.09 (4H, m, H3', 5'), 7.11–7.19 (4H, m, H2', 6'), 7.29 (0.8H, brs, NH), 7.40 (0.8H, brs, NH). ^{13}C -NMR ($\text{THF}-d_8$, 67.20) δ : 20.93 (CH_3), 44.58, 44.75, 44.80* (CH_2), 127.85, 128.14*, 128.27 (C2', C6') 129.47 (C3', 5'), 136.84*, 136.90, 136.98, 137.02 (C4'), 137.13, 137.16* (C1'), 166.93, 167.08*, 167.24 (C2, 4), 169.58*, 170.10* (C6). (The observed ^1H - and ^{13}C -signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS m/z : 354 ($\text{M}+\text{H}$) $^+$. HR-FAB-MS m/z : 354.1482 (Calcd for $\text{C}_{19}\text{H}_{21}\text{ClN}_5$: 354.1485). *Anal.* Calcd for $\text{C}_{19}\text{H}_{20}\text{ClN}_5$: C, 64.49; H, 5.70; N, 19.79. Found: C, 64.47; H, 5.76; N, 19.72.

N^2,N^4,N^6 -Tris(4-chlorobenzyl)-1,3,5-triazine-2,4,6-triamine (4c) [112484-31-8] (Entry 4) Compound **4c** was prepared from the reaction of **1** with 4-chlorobenzylamine (**2c**) under the conditions shown in Table 1. Separation of the products by centrifugal chromatography (CH_2Cl_2 –EtOH=97:3) gave **4c** (75%) as a white solid. An analytical sample of **4c** was obtained as colorless crystals by recrystallization from propionitrile (EtCN).

4c: mp 156–158°C (from EtCN). IR cm^{-1} : 3396, 3246 (NH), 1526 (C=N), 1330, 1161 (C–N). ^1H -NMR ($\text{DMSO}-d_6$) δ : 4.31 (3.3H, brs, Ha of tautomer **B**), 4.40 (2.7H, d, $J=5.5$ Hz, Ha of tautomer **A**), 7.05 (0.6H, brs, NH of **A**), 7.15 (3.3H, brs, H2', 6' of **B**), 7.19 (1.2H, brs, NH of **A** and **B**), 7.23 (3.3H, brs, H3', 5' of **B**), 7.28 (2.7H, d, $J=7.6$ Hz, H2', 6' of **A**), ca. 7.32 (1.2H, brs, NH of **B**), 7.34 (2.7H, d, $J=7.6$ Hz, H3', 5' of **A**). (The integral values of the peaks at δ_{H} 7.15–7.34 were calculated from the spectral data after addition of D_2O .) ^{13}C -NMR ($\text{DMSO}-d_6$) δ : 42.37 (Ca of **A**), 42.66 (Ca of **B**), 127.88 (C3', C5' of **B**), 127.98 (C3', C5' of **A**), 128.80 (C2', 6' of **A**), 128.96 (C2', 6' of **B**), 130.82 (C4' of **A** and **B**), 139.86 (C1' of **A** and **B**), 165.72 (C2, 4, 6 of **A**), 165.89 (C2, 4, 6 of **B**). Positive-ion FAB-MS m/z : 499 ($\text{M}+\text{H}$) $^+$. HR-FAB-MS m/z : 499.0975 (Calcd for $\text{C}_{24}\text{H}_{22}\text{Cl}_3\text{N}_6$: 499.0972). *Anal.* Calcd for $\text{C}_{24}\text{H}_{21}\text{Cl}_3\text{N}_6$: C, 57.67; H, 4.23; N, 16.81. Found: C, 57.63; H, 3.97; N, 16.81.

N^2,N^4,N^6 -Tris[4-(trifluoromethyl)benzyl]-1,3,5-triazine-2,4,6-triamine (4d) (Entry 5) Compound **4d** was prepared from the reaction of **1** with 4-(trifluoromethyl)benzylamine (**2d**) under the conditions shown in Table 1. Separation of the products by centrifugal chromatography (*n*-hexane–EtOAc=30:70) gave **4d** (42%) as a white solid. An analytical sample of **4d** was obtained as a white solid by recrystallization from 2-PrOH.

4d: mp 128–130°C (from 2-PrOH). IR cm^{-1} : 3462, (NH), 1530, 1502 (C=N), 1323, 1105, 1066 (C–N and/or C–O). ^1H -NMR ($\text{DMSO}-d_6$) δ : 4.39, 4.42*, 4.51, 4.52 (6H, brs, Ca), 7.19*, 7.42 (3H, brs, NH), 7.31, 7.48* (6H, brs, C2', 6'), 7.49, 7.66* (6H, d, $J=8.2$ Hz, C3', 5'). ^{13}C -NMR ($\text{DMSO}-d_6$) δ : 42.74, 42.97* (Ca), 124.27* (q, $J=273.1$ Hz, CF_3) 124.39 (q, $J=271.7$ Hz, CF_3), 124.74*, 124.96 (C3', 5'), 127.02*, 127.11 (q, $J=31.8$ Hz, C4'), 127.55, 127.67* (C2', C6'), 145.66, 145.77* (C1'), 165.80, 166.00* (C2, 4, 6). (The observed signals of the predominant tautomer are asterisked.) Positive-ion FAB-MS m/z : 601 ($\text{M}+\text{H}$) $^+$. HR-FAB-MS m/z : 601.1763 (Calcd for $\text{C}_{27}\text{H}_{22}\text{F}_9\text{N}_6$: 601.1762). *Anal.* Calcd for $\text{C}_{27}\text{H}_{21}\text{F}_9\text{N}_6 \cdot 0.7\text{H}_2\text{O}$: C, 52.89; H, 3.68; N, 13.71. Found: C, 53.06; H, 3.38; N, 13.69.

N^2,N^4,N^6 -Tris(4-methoxybenzyl)-1,3,5-triazine-2,4,6-triamine (4e) (Entry 6) Compound **4e** was prepared from the reaction of **1** with 4-methoxybenzylamine (**2e**) under the conditions shown in Table 1. Separation of the products by centrifugal chromatography (CH_2Cl_2 –EtOH=97:3) gave **4e** (66%) as a white solid. An analytical sample of **4e** was obtained as a white solid by recrystallization from EtOH.

4e: mp 135–136°C (from EtOH). IR cm^{-1} : 3439, 3367 (NH), 1556, 1499 (C=N), 1345, 1246, 1171, 1030 (C–N or C–O), 810 (1,4-disubstituted benzene). ^1H -NMR ($\text{DMSO}-d_6$) δ : 3.70 (9H, s, OCH_3), 4.33 (6H, brs, Ha), 6.77 (3H, brs, H3', 5' of **B**), 6.81–6.87 † (1H, NH), 6.83 (3H, d, $J=6.9$ Hz, H3', 5' of **A**), 7.01 (1.6H, brs, NH), 7.13 (3H, brs, H2', 6' of **B**), 7.18 (3H, d, $J=6.9$ Hz, H2', 6' of **A**), 7.16–7.23 † (0.4H, NH). (The peaks with the mark † attached are assumed to be overlapped with the peaks of NH.) ^{13}C -NMR ($\text{DMSO}-d_6$) δ : 42.40, 42.67* (Ca) 54.93 (OCH_3), 113.37 (C3', 5'), 128.21 (C2', 6' of **A**), 128.51* (C2', 6' of **B**), 132.80*, 132.90 (C1'), 157.86 (C4'), 165.74*, 165.86 (C2, 4, 6). (Signals for only the predominant tautomer **B** are asterisked.) Positive-ion FAB-MS m/z : 487 ($\text{M}+\text{H}$) $^+$. HR-FAB-MS m/z : 487.2460 (Calcd for $\text{C}_{27}\text{H}_{31}\text{N}_6\text{O}_3$: 487.2458). *Anal.* Calcd for $\text{C}_{27}\text{H}_{30}\text{N}_6\text{O}_3$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.47; H, 6.15; N, 17.19.

N^2,N^4,N^6 -Tris(3,4-dimethoxybenzyl)-1,3,5-triazine-2,4,6-triamine (4f) (Entry 7) Compound **4f** was prepared from the reaction of **1** with 3,4-dimethoxybenzylamine (**2f**) under the conditions shown in Table 1. Separation of the products by centrifugal chromatography (CH_2Cl_2 –EtOH=95:5) gave **4f** (80%) as a white solid. An analytical sample of **4f** was obtained as a colorless solid by recrystallization from 2-PrOH. Compound **4f** was converted into hydrochloride (**4f**·HCl) as colorless crystals by a routine procedure.

4f: mp 47°C (from 2-PrOH). IR cm^{-1} : 3378 (NH), 1501 (C=N), 1257, 1230, 1134, 1023 (C–N and/or C–O). ^1H -NMR (CDCl_3) δ : 1.80 (1.8H, brs, NH), 3.85 (9H, s, OCH_3 on C3'), 3.87 (9H, s, OCH_3 on C4'), 4.53 (6H, brs, ArCH_2), 5.19 (0.5H, brs, NH), 5.33 (0.7H, brs, NH), 6.80 (3H, d, $J=7.6$ Hz, H5'), 6.85 (3H, d, $J=7.6$ Hz, H6'), 6.86 (3H, s, H2'). ^{13}C -NMR (CDCl_3) δ : 44.54 (ArCH_2), 55.82, 55.90 (OCH_3), 110.90 (C2'), 111.09 (C5'), 119.77 (C6'), 131.86 (C1'), 148.20 (C4'), 149.01 (C3'), 166.17 (C2, 4, 6). ^1H -NMR ($\text{DMSO}-d_6$) δ : 3.65, 3.70* (18H, brs, OCH_3 on C3', 4'), ca. 3.7 (1H, brs, NH), 4.34, 4.35* (6H, brs, ArCH_2), 6.72–6.97 (9H, m, ArH), [7.02 (1.6H), 7.17 (0.4H)] (brs, NH). ^{13}C -NMR ($\text{DMSO}-d_6$) δ : 42.87, 43.13* (ArCH_2), 55.35, 55.49 (OCH_3 on C3', 4'), 111.50 (C2', 5'), 119.11, 119.49* (C6'), 133.29 (C1'), 147.48, 148.48 (C3', 4'), 165.81 (C2, 4, 6). (The observed ^1H - and ^{13}C -signals assignable to the predominant tautomer are asterisked.)

Positive-ion FAB-MS m/z : 577 (M+H)⁺. HR-FAB-MS m/z : 577.2784 (Calcd for C₃₀H₃₇N₆O₆: 577.2775). *Anal.* Calcd for C₃₀H₃₆N₆O₆·*i*-PrOH: C, 62.25; H, 6.97; N, 13.26. Found: C, 62.35; H, 6.89; N, 13.22.

4f: HCl: mp 128–131°C (from 2-PrOH–H₂O). IR cm^{-1} : 3254 (br, NH⁺), 1625 (NH₂⁺), 1567, 1515 (C=N), 1263, 1234, 1137, 1023 (C–N and/or C–O). ¹H-NMR (DMSO-*d*₆) δ : 3.69*, 3.73*, 3.75 (18H, brs, OCH₃ on C3', 4'), *ca.* 3.7 (1H, brs, NH), 4.46*, 4.48 (6H, brs, ArCH₂), 6.75–7.15 (9H, m, ArH), 8.82*, 8.88, 9.03 (3H, brs, NH). ¹³C-NMR (DMSO-*d*₆) δ : 43.23*, 43.45, 43.76 (ArCH₂), 55.39, 55.48*, 55.52*, 55.54 (OCH₃), 111.60*, 111.71*, 111.83 (C2', 5'), 119.81 (C6'), 130.10*, 130.48, 131.03 (C1'), 147.96, 148.03, 148.13*, 148.64* (C3', 4'), 154.54* (C2, 4, 6). (The observed ¹H- and ¹³C-signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS m/z : 577 (M+H)⁺. HR-FAB-MS m/z : 577.2766 (Calcd for C₃₀H₃₇N₆O₆: 577.2775). *Anal.* Calcd for C₃₀H₃₆N₆O₆·HCl·1.6H₂O: C, 56.13; H, 6.31; N, 13.09. Found: C, 56.13; H, 6.26; N, 13.05.

N²,N⁴,N⁶-Tris(2,4-dimethoxybenzyl)-1,3,5-triazine-2,4,6-triamine (4g) (Entry 8) Compound **4g** was prepared from the reaction of **1** with 2,4-dimethoxybenzylamine (**2g**) under the conditions shown in Table 1. Separation of the products by centrifugal chromatography (CH₂Cl₂–EtOH=96:4) gave **4g** (57%) as a white solid. An analytical sample of **4g** was obtained as colorless crystals by recrystallization from EtOH.

4g: mp 137–138°C (from EtOH). IR cm^{-1} : 3444, 3421 (NH), 1556, 1499 (C=N), 1206, 1157, 1115, 1031 (C–N or C–O), 924, 810 (1,2,4-trisubstituted benzene). ¹H-NMR (CDCl₃) δ : 3.78 (9H, s, OCH₃ on C4' or C2'), 3.80 (9H, s, OCH₃ on C2' or C4') 4.42, 4.52* (6H, brs, H α), 5.05 (1H, brs, NH), 5.30 (2H, brs, NH), 6.36 (3H, brs, H5'), 6.43 (3H, brs, H3'), 7.16 (3H, d, *J*=8.3 Hz, H6'). ¹³C-NMR (CDCl₃) δ : 39.72 (C α), 55.23 (OCH₃ on C2' or C4'), 55.31 (OCH₃ on C4' or C2'), 98.32 (C3'), 103.65 (C5'), 120.16 (C1'), 130.08 (C6'), 158.45 (C4' or C2'), 160.07 (C2' or C4'), 166.15 (C2, 4, 6). Positive-ion FAB-MS m/z : 577 (M+H)⁺. HR-FAB-MS m/z : 577.2789 (Calcd for C₃₀H₃₇N₆O₆: 577.2775). *Anal.* Calcd for C₃₀H₃₆N₆O₆: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.57; H, 6.29; N, 14.58.

N²,N⁴,N⁶-Tris(benzo[d][1,3]dioxol-5-ylmethyl)-1,3,5-triazine-2,4,6-triamine (4h)⁵⁾ Compound **4h** was prepared from the reaction of **1** with piperonylamine (**2h**) (see ref. 5).

N²,N⁴,N⁶-Tris(3,4,5-trimethoxybenzyl)-1,3,5-triazine-2,4,6-triamine (4i) (Entry 10) Compound **4i** was prepared from the reaction of **1** with 3,4,5-trimethoxybenzylamine (**2i**) under the conditions shown in Table 1. Separation of the products by centrifugal chromatography (CH₂Cl₂–EtOH=96:4) gave **4i** (63%) as a white solid. An analytical sample of **4i** was obtained as colorless crystals by recrystallization from 2-PrOH.

4i: mp 64–65°C (from 2-PrOH). IR cm^{-1} : 3363 (NH), 1590, 1560, 1498 (C=N), 1328, 1230, 1119 (C–N or C–O), 1003 (C–O), 811 (1,2,3,5-tetrasubstituted benzene). ¹H-NMR (CDCl₃) δ : 3.79 (18H, s, OCH₃ on C3', 5'), 3.82 (9H, s, OCH₃ on C4'), 4.50 (6H, brs, H α), 5.44, 5.50 (3H, brs, NH), 6.52 (6H, s, H2', 6'). ¹³C-NMR (CDCl₃) δ : 44.93 (C α), 55.99 (OCH₃ on C3, 5'), 60.72 (OCH₃ on C4'), 104.44 (C2', 6'), 134.88 (C1'), 137.03 (C4'), 153.25 (C3', 5'), 166.13 (C2, 4, 6). Positive-ion FAB-MS m/z : 667 (M+H)⁺. HR-FAB-MS m/z : 667.3086 (Calcd for C₃₃H₄₃N₆O₉: 667.3092). *Anal.* Calcd for

C₃₃H₄₂N₆O₉·0.5 2-PrOH·0.5H₂O: C, 58.71; H, 6.71; N, 11.91. Found: C, 58.57; H, 6.74; N, 11.78.

Preparation of Intermediate Di-benzylamino-Substituted TAZ Derivatives (3)

6-Chloro-N²,N⁴-bis(3,4-dimethoxybenzyl)-1,3,5-triazine-2,4-diamine (3f)

This compound was prepared in a manner similar to that for the preparation of **3h** described by Vidal-Mosquera *et al.*¹³⁾ To a solution of **1** (922 mg, 5.0 mmol) in THF (100 mL), **2f** (3.34 g, 20.0 mmol) was added dropwise at room temperature, and then the mixture was refluxed for 1.2 h. Then the white solids were filtered, and water (200 mL) was added. After the mixture had been stirred at 60°C for 10 min, the solid was filtered and washed with EtOH (50 mL) to give analytically pure compound **3f** (1.51 g, 4.29 mmol, 86%) as a white solid.

3f: mp 193–194. IR cm^{-1} : 3250 (NH), 1555, 1514 (C=N), 1240, 1137, 1021 (C–N and/or C–O), 799, 736 (C–Cl). ¹H-NMR (DMSO-*d*₆) δ : 3.67* (3.3H, s, OCH₃ on C3'), 3.71* (3.3H, s, OCH₃ on C4'), 3.72 (3.6H, brs, OCH₃), 3.73 (1.8H, s, OCH₃), 4.33–4.40 [4H, m, C α : including 4.38* (d, *J*=6.2 Hz)], 6.72–6.96 [6H, m, ArH: including 6.73* (1.1H, dd, *J*=8.3, 1.4 Hz, H6'), 6.79* (*ca.* 1.1H, d, *J*=8.3 Hz, H5'), 6.89* (*ca.* 1.1H, d, *J*=1.4 Hz, H2')], [8.05 (0.3H), 8.19 (0.3H), 8.23 (0.3H), 8.31* (1.1H)] (t, *J*=6.2 Hz, NH). ¹³C-NMR (DMSO-*d*₆) δ : 43.19, 43.28, 43.41* (C α), [55.29* (on C3'), 55.35, 55.42* (on 5'), 55.51] (OCH₃), 111.38*, 111.51 (C2'), 111.67* (C5'), 119.22, 119.29, 119.36* (C6'), 131.43, 131.61* (C1'), 147.73*, 147.78 (C4'), 148.55*, 148.59 (C3'), 165.23, 165.36*, 165.61 (C2, 4), 167.77*, 168.30 (C6). (The observed ¹H- and ¹³C-signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS m/z : 446 (M+H)⁺. HR-FAB-MS m/z : 446.1586 (Calcd for C₂₁H₂₅ClN₅O₄: 446.1595). *Anal.* Calcd for C₂₁H₂₄ClN₅O₄: C, 56.57; H, 5.43; N, 15.71. Found: C, 56.35; H, 5.42; N, 15.68.

6-Chloro-N²,N⁴-bis(benzo[d][1,3]dioxol-5-ylmethyl)-1,3,5-triazine-2,4-diamine (3h)¹³⁾

In a manner similar to that for the preparation of **3f**, the reaction of **1** and **2f** only by stirring for 30 min at room temperature, product **3h** was obtained in 96% yield as a white solid.

3h: mp 225–226. IR cm^{-1} : 3244 (NH), 1558 (C=N), 1280, 1038 (C–N and/or C–O), 796 (C–Cl). ¹H-NMR (DMSO-*d*₆) δ : 4.31–4.35 [4H, m, C α : including 4.33* (d, *J*=6.2 Hz)], 5.96*, 5.97, 5.98 (4H, s, H2'), 6.68–6.70 [1.1H, m, ArH: including 6.69* (brd, *J*=8.3 Hz, H6')], 6.72–6.78 [3H, m, ArH: including 6.77* (d, *J*=8.3 Hz, H7')], 6.83–6.88 [1.9H, m, ArH: including 6.85* (brs, H4')], [8.08 (0.5H), 8.21 (1.1H), 8.24 (1.1H), 8.33 (3.3H)] (t, *J*=6.2 Hz, NH). ¹³C-NMR (DMSO-*d*₆) δ : 43.14, 43.23, 43.36* (C α), 100.76 (C2'), 107.82, 107.86* (C7'), 107.90, 108.00* (C4'), 120.26, 120.37, 120.46* (C6'), 132.92, 133.07, 133.13* (C5'), 146.03 (C3a'), 146.15 (C7a'), 165.20, 165.30*, 165.56 (C2, 4), 167.81*, 168.33 (C6). (The observed ¹H- and ¹³C-signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS m/z : 414 (M+H)⁺. HR-FAB-MS m/z : 414.0974 (Calcd for C₁₉H₁₇ClN₅O₄: 414.0969). *Anal.* Calcd for C₁₉H₁₆ClN₅O₄·0.2H₂O: C, 54.67 H, 3.96; N, 16.78. Found: C, 54.63; H, 3.90; N, 16.84.

Preparation of N-Benzyl-4-chloro-6-isopropoxy-1,3,5-triazin-2-amine (6a) (Table 2, Entry 1) Compound **6a** was obtained from the reaction of **5b** with **2a** under the conditions shown in Table 2. Thus, to a solution of intermediate **5b** (2.08 g, 10.0 mmol) in THF (150 mL), benzylamine **2a** (1.07 g, 8.00 mmol) and diisopropylethylamine (DIPEA,

1.29 g, 10.0 mmol) were added and the reaction mixture was stirred for 2 h at 0°C. After removal of the precipitated solids (DIPEA·HCl salt), evaporation of the solvent gave crude compound **6a** (2.71 g, 9.74 mmol, 97%) as a white powder. An analytically pure sample of **6a** was obtained as a white powder by recrystallization from acetonitrile (MeCN).

6a: mp 127–128°C (from MeCN). IR cm^{-1} : 3262, 3110 (NH), 1638, 1527 (C=N), 1294, 1231, 1105 (C–N and/or C–O), 803 (C–Cl). $^1\text{H-NMR}$ (CDCl_3) δ : [1.31 (2H), 1.34* (4H)] (d, $J=6.2$ Hz, H_2'' , 3''), [4.65 (0.7H), 4.67* (1.3H)] (d, $J=6.2$ Hz, H_α), 5.20–5.30 (1H, m, H_1''), [6.33 (0.3H), 6.78* (0.7H)] (brs, NH), 7.26–7.37 (5H, m, $\text{H}_2'-6'$). $^{13}\text{C-NMR}$ (CDCl_3) δ : 21.63*, 21.67 (C2'', 3''), 44.99*, 45.07 (C α), 71.66, 72.02* (C1''), 127.33, 127.62 (C2', 6'), 127.66*, 127.72 (C4'), 128.70*, 128.74 (C3', C5'), 137.45 (C1'), 167.07 (C2), 169.81, 170.33, 170.40, 171.47 (C4, 6). (The observed ^1H - and ^{13}C -signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS m/z : 279 (M+H) $^+$. HR-FAB-MS m/z : 279.0981 (Calcd for $\text{C}_{13}\text{H}_{16}\text{ClN}_4\text{O}$: 279.1013). *Anal.* Calcd for $\text{C}_{13}\text{H}_{15}\text{ClN}_4\text{O}$: C, 56.02; H, 5.42; N, 20.10. Found: C, 55.96; H, 5.43; N, 19.93.

General Procedure for the Preparation of C_S -Symmetrical Benzylamine-Type TAZ Derivatives (7) (Table 2): Example 1 (No Base by MW): Synthesis of 6-Isopropoxy- N^2,N^4 -bis(4-methylbenzyl)-1,3,5-triazine-2,4-diamine (7b) (Entry 3) To a solution of intermediate **5b**⁽⁴⁾ (416 mg, 2.0 mmol) in dioxane (4 mL) was added **2b** (1.21 g, 10.0 mmol) at room temperature. Then the mixture was subjected to MW at 100°C (100 W) for 45 min with stirring. After addition of water (50 mL), the mixture was extracted with EtOAc (2×50 mL). The combined organic layer was washed with saturated aqueous NH_4Cl solution and dried over MgSO_4 . After evaporation of the solvent, the residue was recrystallized from 2-PrOH to obtain analytically pure compound **7b** as a colorless solid.

7b: mp 142–143°C (from 2-PrOH). IR cm^{-1} : 3347, 3239 (NH), 1609, 1579 (C=N), 1158, 1104 (C–N and/or C–O). $^1\text{H-NMR}$ (CDCl_3) δ : [1.27 (brs), 1.31* (d, $J=6.2$ Hz)] (6H, H_2'' , 3''), 2.32 (6H, brs, CH_3), 4.51, 4.55* (4H, brs, H_α), [5.13 (0.3H), 5.23 (0.7H)] (brs, H_1''), [5.38, 5.45 (0.6H), 5.61 (1.4H)] (brs, NH), 7.11 (4H, d, $J=6.9$ Hz) (H_3' , 5'), 7.17 (4H, d, $J=6.9$ Hz) (H_2' , 6'). $^{13}\text{C-NMR}$ (CDCl_3) δ : 21.06 (CH_3), 21.94 (C2'', 3''), 44.40, 44.50* (C α), 69.02*, 69.43 (C1''), 127.38, 127.53* (C2', 6'), 129.18 (C3', 5'), 135.83*, 136.10 (C1'), 136.82 (C4'), 167.07, 167.35* (C2, 4), 169.93*, 170.30 (C6). (The observed ^1H - 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 : 378.2284 (Calcd for $\text{C}_{22}\text{H}_{28}\text{N}_5\text{O}_4$: 378.2294). *Anal.* Calcd for $\text{C}_{22}\text{H}_{28}\text{N}_5\text{O}_4$: C, 70.00; H, 7.21; N, 18.55. Found: C, 70.04; H, 7.22; N, 18.56.

N^2,N^4 -Dibenzyl-6-isopropoxy-1,3,5-triazine-2,4-diamine (7a) (Entry 2) Compound **7a** was prepared from the reaction of **5b** with **2a** under the conditions shown in Table 2 using the above method. After the workup, separation of the products by centrifugal chromatography (CH_2Cl_2 –EtOH=98:2) gave **7a** (79%) as a white solid. An analytically pure sample of **7a** was obtained as colorless crystals by recrystallization from diisopropylether (2-Pr $_2$ O).

7a: mp 117–119°C (from 2-Pr $_2$ O). IR cm^{-1} : 3336, 3246 (NH), 1615, 1508 (C=N), 1160, 1104 (C–N and/or C–O). $^1\text{H-NMR}$ (CDCl_3) δ : [1.24 (2H, brs), 1.28* (4H, d, $J=5.5$ Hz)] (H_2'' , 3''), 4.55, 4.59* (4H, brs, H_α), [5.12 (0.3H), 5.21* (0.7H)]

(brs, H_1''), [5.53 (0.5H), 5.73 (0.2H), 5.84 (0.3H), 5.97* (1H)] (brs, NH), 7.20–7.35 (10H, m, $\text{H}_2'-6'$). $^{13}\text{C-NMR}$ (CDCl_3) δ : 21.89 (C2'', 3''), 44.53, 44.67* (C α), 69.01, 69.48* (C1''), 127.11, 127.31, 127.49 (C2', 6', 4'), 128.46 (C3', C5'), 138.96*, 139.21 (C1'), 167.15, 167.36* (C2, 4), 169.87, 170.21* (C6). (The observed ^1H - and ^{13}C -signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS m/z : 350 (M+H) $^+$. HR-FAB-MS m/z : 350.1989 (Calcd for $\text{C}_{20}\text{H}_{24}\text{N}_5\text{O}$: 350.1981). *Anal.* Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_5\text{O}$: C, 68.74; H, 6.63; N, 20.04. Found: C, 68.73; H, 6.74; N, 20.00.

6-Isopropoxy- N^2,N^4 -bis(4-methoxybenzyl)-1,3,5-triazine-2,4-diamine (7e) (Entry 4) Colorless needles. mp 132–134°C (from EtOH). IR cm^{-1} : 3392, 3261, 3101 (NH), 1583, 1530 (C=N), 1238, 1170, 1108, 1030 (C–N and/or C–O). $^1\text{H-NMR}$ (CDCl_3) δ : [1.26 (2H, brs), 1.32* (4H, d, $J=5.5$ Hz)] (H_2'' , 3''), 3.78 (6H, brs, OCH_3 on C4'), 4.48, 4.53* (4H, brs, H_α), [5.13 (0.3H), 5.24* (0.7H)] (brs, H_1''), [5.42 (0.3H), 5.55* (1.0H), 5.73 (0.7H)] (brs, NH), 6.83 (4H, d, $J=7.6$ Hz, H_3' , 5'), 7.20 (4H, d, $J=7.6$ Hz, H_2' , 6'). $^{13}\text{C-NMR}$ (CDCl_3) δ : 21.93 (C2'', 3''), 44.07, 44.15* (C α), 55.22 (OCH_3), 68.97*, 69.38 (C1''), 113.87 (C3', 5'), 128.96, 128.79* (C2', 6'), 130.93*, 131.27 (C1'), 158.79 (C4'), 166.97, 167.26* (C2, 4), 169.89*, 170.30 (C6). (The observed ^1H - 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 : 410.2180 (Calcd for $\text{C}_{22}\text{H}_{28}\text{N}_5\text{O}_3$: 410.2192). *Anal.* Calcd for $\text{C}_{22}\text{H}_{27}\text{N}_5\text{O}_3$: C, 64.53; H, 6.65; N, 17.10. Found: C, 64.51; H, 6.67; N, 17.04.

N^2,N^4 -Bis(3,4-dimethoxybenzyl)-6-isopropoxy-1,3,5-triazine-2,4-diamine (7f) (Entry 5) Colorless crystals. mp 146–147°C (from MeCN). IR cm^{-1} : 3397, 3248 (NH), 1553, 1516 (C=N), 1262, 1162, 1136, 1026 (C–N and/or C–O). $^1\text{H-NMR}$ (CDCl_3) δ : [1.28 (2H, brs), 1.33 (4H, d, $J=4.8$ Hz)] (H_2'' , 3''), 3.80–3.90 (12H, m, OCH_3 on C3',4'), 4.56 (4H, brs, H_α), [5.15 (0.3H), 5.26 (0.7H)] (brs, H_1''), [5.42 (1.4H), 5.59 (0.6H)] (brs, NH), 6.76–6.90 (6H, m, H_2' , 5', 6'). $^{13}\text{C-NMR}$ (CDCl_3) δ : 21.94 (C2'', 3''), 44.62 (C α), 55.82, 55.90* (OCH_3), 69.11*, 69.59 (C1''), 110.78 (C2'), 111.12 (C5'), 119.64, 119.74* (C6'), 131.34*, 131.57 (C1'), 148.28 (C4'), 149.04 (C3'), 167.02, 167.33* (C2, 4), 170.28*, 170.31 (C6). (The observed ^1H - and ^{13}C -signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS m/z : 470 (M+H) $^+$. HR-FAB-MS m/z : 470.2397 (Calcd for $\text{C}_{24}\text{H}_{32}\text{N}_5\text{O}_5$: 470.2403). *Anal.* Calcd for $\text{C}_{24}\text{H}_{31}\text{N}_5\text{O}_5$: C, 61.39; H, 6.65; N, 14.92. Found: C, 61.25; H, 6.79; N, 14.91.

N^2,N^4 -Bis(2,4-dimethoxybenzyl)-6-isopropoxy-1,3,5-triazine-2,4-diamine (7g) (Entry 6) Colorless crystals. mp 134–136°C (from 2-PrOH). IR cm^{-1} : 3417, 3248 (NH), 1612, 1592, 1526 (C=N), 1228, 1206, (C–N and/or C–O). $^1\text{H-NMR}$ (CDCl_3) δ : [1.22–1.29 (2H), 1.29–1.40 (4H)] (brs, H_2'' , 3''), [3.79 (8H), 3.82 (4H)] (s, OCH_3), [4.55, 4.51 (brs), 4.56* (d, $J=5.5$ Hz)] (4H, H_α), 5.11*, 5.26, 5.35 (1H, brs, H_1''), 5.34, 5.39, 5.50* (2H, brs, NH), 6.34–6.47 (4H, m, H_3' , 5'), 7.13–7.22 (2H, m, H_6'). $^{13}\text{C-NMR}$ (CDCl_3) δ : 21.99 (C2'', 3''), 40.03 (C α), 55.25, 55.33 (OCH_3), 68.69*, 69.06 (C1''), 98.43 (C3'), 103.67 (C5'), 119.49*, 119.70 (C1'), 129.81, 130.10*, 130.25 (C6'), 158.50 (C2'), 160.29 (C4'), 166.95, 167.20* (C2, 4), 169.88*, 170.13 (C6). (The observed ^1H - and ^{13}C -signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS m/z : 470 (M+H) $^+$. HR-FAB-MS m/z : 470.2402 (Calcd for $\text{C}_{24}\text{H}_{32}\text{N}_5\text{O}_5$: 470.2403). *Anal.* Calcd for $\text{C}_{24}\text{H}_{31}\text{N}_5\text{O}_5$: C, 61.39; H, 6.65; N, 14.92. Found: C, 61.21; H, 6.72; N, 14.68.

***N*²,*N*⁴-Bis(benzo[*d*][1,3]dioxol-5-ylmethyl)-6-isopropoxy-1,3,5-triazine-2,4-diamine (7h) (Entry 7)** White solid. mp 143–145°C (from EtOAc). IR cm^{-1} : 3338, 3239, 3097 (NH), 1612, 1521 (C=N), 1246, 1232, 1102, 1038 (C–N and/or C–O). ¹H-NMR (CDCl_3) δ : 1.28, 1.32* (6H, d, $J=6.2\text{ Hz}$, H2'', 3''), 4.46, 4.50*, 4.51 (4H, brs, Ha), 5.14, 5.24* (1H, brs, H1''), 5.36, 5.42*, 5.58 (2H, brs, NH), 5.93 (4H, s, H2'), 6.70–6.85 (6H, m, H4', 6', 7'). ¹³C-NMR (CDCl_3) δ : 21.96 (C2'', 3''), 44.46, 44.58* (Ca), 69.14, 69.54* (C1''), 100.98 (C2'), 108.19 (C4', 7'), 120.64 (C6'), 132.79*, 133.10 (C5'), 146.76 (C3a'), 147.79 (C7a'), 166.99*, 167.05 (C2, 4 or C6), 167.30 (C6 or C2, 4). (The observed ¹H- and ¹³C-signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS m/z : 438 (M+H)⁺. HR-FAB-MS m/z : 438.1779 (Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_5\text{O}_5$: 438.1777). Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_5\text{O}_5$: C, 60.40; H, 5.30; N, 16.01. Found: C, 60.42; H, 5.27; N, 16.00.

6-Isopropoxy-*N*²,*N*⁴-bis(3,4,5-trimethoxybenzyl)-1,3,5-triazine-2,4-diamine (7i) (Entry 8) Colorless crystals. mp 148–150°C (from 2-PrOH). IR cm^{-1} : 3315, 3246 (NH), 1586, 1542 (C=N), 1225, 1159, 1334, 1099 (C–N and/or C–O). ¹H-NMR (CDCl_3) δ : [1.29 (brs), 1.33 (d, $J=4.8\text{ Hz}$)] (6H, H2'', 3''), 3.82 (18H, brs, OCH₃), 4.53*, 4.56 (4H, m, Ha), [5.16 (0.25H, brs), 5.26* (0.75H, brs)] (H1''), [5.45*, 5.52 (1.5H), 5.67 (0.5H)] (brs, NH), 6.54 (4H, brs, H2', 6'). ¹³C-NMR (CDCl_3) δ : 21.91 (C2'', 3''), 40.91, 44.93, 44.98, 45.09* (Ca), 56.07 (OCH₃ on C3', 5'), 60.79 (OCH₃ on C4'), 69.24*, 69.60 (C1''), 104.39*, 104.70 (C2', 6'), 134.48*, 134.66 (C1'), 137.16 (C3', 5'), 153.34 (C4'), 167.11, 167.37* (C2, 4), 169.98*, 170.27 (C6). (The observed ¹H- and ¹³C-signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS m/z : 530 (M+H)⁺. HR-FAB-MS m/z : 530.2621 (Calcd for $\text{C}_{26}\text{H}_{36}\text{N}_5\text{O}_7$: 530.2615). Anal. Calcd for $\text{C}_{26}\text{H}_{36}\text{N}_5\text{O}_7$: C, 58.97; H, 6.66; N, 13.22. Found: C, 58.94; H, 6.74; N, 13.20.

***N*²,*N*⁴-Bis(3,4-dimethylbenzyl)-6-isopropoxy-1,3,5-triazine-2,4-diamine (7j) (Entry 9)** Colorless solid. mp 119–123°C (from EtOH). IR cm^{-1} : 3397, 3247, 3105 (NH), 1614, 1577, 1523 (C=N), 1166, 1146, 1104 (C–N and/or C–O). ¹H-NMR (CDCl_3) δ : [1.28 (2H, brs), 1.32* (4H, d, $J=5.5\text{ Hz}$)] (H2'', 3''), 2.23 (12H, brs, CH₃), 4.49, 4.54* (4H, brs, Ha), [5.14 (0.3H), 5.25* (0.7H)] (brs, H1''), [5.38* (1.4H), 5.52 (0.6H)] (brs, NH), 7.02–7.12 (6H, m, H2', 5', 6'). ¹³C-NMR (CDCl_3) δ : 19.36 (CH₃ on C4'), 19.69 (CH₃ on C3'), 21.95 (C2'', 3''), 44.41, 44.52* (Ca), 68.99, 69.42* (C1''), 124.86, 125.04* (C6'), 128.74, 128.92* (C2'), 129.73 (C5'), 135.47 (C4'), 136.22*, 136.48 (C1'), 136.71 (C3'), 167.03, 167.33* (C2, 4), 169.93, 170.21* (C6). (The observed ¹H- and ¹³C-signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS m/z : 406 (M+H)⁺. HR-FAB-MS m/z : 406.2594 (Calcd for $\text{C}_{24}\text{H}_{32}\text{N}_5\text{O}$: 406.2607). Anal. Calcd for $\text{C}_{24}\text{H}_{31}\text{N}_5\text{O}$: C, 71.08; H, 7.70; N, 17.27. Found: C, 71.03; H, 7.70; N, 17.27.

6-Isopropoxy-*N*²,*N*⁴-bis(2,4,6-trimethylbenzyl)-1,3,5-triazine-2,4-diamine (7k) (Entry 10) Colorless crystals. mp 146–147°C (from EtOH). IR cm^{-1} : 3252, 3105, 2975 (NH), 1619, 1577, 1519 (C=N), 1172, 1017 (C–N and/or C–O). ¹H-NMR (CDCl_3) δ : [1.26 (d, $J=5.5\text{ Hz}$), 1.35*, 1.43 (brs)] (6H, H2'', 3''), 2.26, 2.27, 2.31* (6H, brs, CH₃ on C4'), 2.36, 2.37 (12H, brs, CH₃ on C2', 6'), 4.42, 4.55, 4.58*, 4.66 (4H, brs, Ha), 4.68, 4.86* (2H, brs, NH), [5.09 (0.25H), 5.24* (0.6H), 5.43 (0.15H)] (brs, H1''), 6.86, 6.88 (4H, brs, H3', 5'). ¹³C-NMR (CDCl_3) δ : 19.56 (CH₃ on C2', 6'), 20.87 (CH₃ on C4'), 21.96 (C2'', 3''), 39.31*, 39.43 (Ca), 68.95, 69.38*, 69.79

(C1''), 129.06 (C3', 5'), 131.16*, 131.41 (C1'), 137.35 (C2', 4', 6'), 166.48, 166.76, 167.10, 167.32* (C2, 4), 169.79, 170.17*, 170.70 (C6). (The observed ¹H- and ¹³C-signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS m/z : 434 (M+H)⁺. HR-FAB-MS m/z : 434.2905 (Calcd for $\text{C}_{26}\text{H}_{36}\text{N}_5\text{O}$: 434.2920). Anal. Calcd for $\text{C}_{26}\text{H}_{35}\text{N}_5\text{O}$: C, 72.02; H, 8.14; N, 16.15. Found: C, 71.81; H, 8.34; N, 16.00.

Antiviral Activity Assay and Cytotoxicity Assay of Synthesized TAZ Derivatives The anti-HSV-1 activities (EC_{50}) of the synthesized TAZ derivatives were measured by using a plaque reduction assay⁹⁾ and their cytotoxicity against Vero cells (CC_{50}) was also evaluated as our previous description.⁵⁾ The results are summarized in Table 3 together with data for aciclovir.¹⁵⁾ Calculated $\log P$ values¹⁰⁾ for the compounds are also shown in Supplementary Materials (Fig. S1). There were few distinct correlations between $\log P$ values by using ChemBioDraw Ultra v.14.0 and anti-HSV-1 activity (EC_{50}).

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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- 6) Some of the tri-substituted TAZ derivatives described in this paper showed a complicated ¹³C-NMR signal pattern because of their keto-enol tautomeric isomers in solutions. Compounds (**3b**, **4c–e**, **6a**, **7a**, **7b**, **7e–k**) that have *sec*-benzylamino groups on a TAZ template are examples of TAZ derivatives with such a signal pattern. These compounds showed the presence of two tautomeric isomers in solution. Thus, signals that appeared in the ¹³C-NMR spectra of C₃-type compounds (**4c–e**) are fully consistent with the tautomeric mixture of two isomers shown below (**A** and **B**). We showed examples of ¹H- and ¹³C-NMR spectra of some tri-substituted TAZ derivatives (**3–7**) in Supplementary Materials (Fig. S2) for readers' convenience.

Tautomeric Isomerism of TAZ derivatives **4c–e**

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