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ANTIVIRAL ACTIVITY OF SOME *C*$_3$-SYMMETRICAL *N*-METHYL BENZYLAMINE-SUBSTITUTED 1,3,5-TRIAZINES AND RELATED COMPOUNDS

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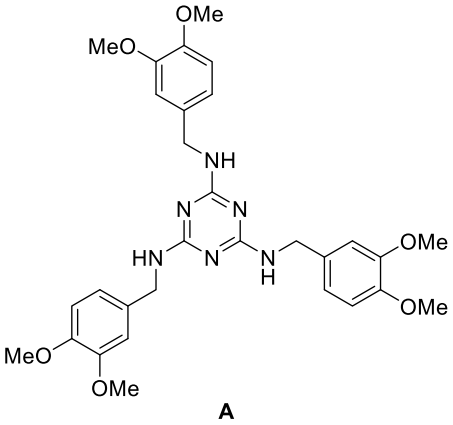
Abstract – We report a few new *C*$_3$-symmetrical 1,3,5-triazine (TAZ) derivatives and the results of evaluation of their anti-herpes simplex virus type 1 (anti-HSV-1) activity and cytotoxic activity against Vero cells. Among the tested TAZ derivatives **3a~3f**, a new *C*$_3$-symmetrical trisubstituted TAZ molecule (**3d-Me**) showed a considerably high level of anti-HSV-1 activity (EC_{50} = 4.2 μM) with low cytotoxicity (CC_{50} => 200 μM) against Vero cells, but its activity was lower than that of original *N*-demethylated compound **3d-H** (**A**). The results for *N*-methylated *C*$_3$-symmetrical multivalent molecules (**3c-Me**~**3e-Me**) seem to provide interesting information for a derivatization in the search for new *C*$_3$-type symmetrical antiviral TAZ derivatives.

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.[1,2] 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.[3-14] 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.[5,11] Among previously targeted *C*$_3$-symmetrical TAZ derivatives, we found that *C*$_3$-symmetrical tri-substituted TAZ derivative **3d-H** (**A**) showed a high level of anti-HSV-1 activity (EC_{50} = 0.98 μM) and a considerably low level of cytotoxic activity (CC_{50} => 200 μM) against Vero cells.[10] Regarding the carbohydrate recognition property of TAZ derivative **3d-H** (**A**), the results of our thermodynamic

experiments indicated that the C_3-type TAZ derivative **3d-H** (**A**) is a potential new lead having a carbohydrate recognition property in the search for antiviral active molecules (Figure 1).[12]

As an extension of molecular modification of these compounds, we further synthesized some new C_3-symmetrical TAZ derivatives having three *N*-methylated benzylamine groups on a symmetrical TAZ framework. In this paper, we describe the results of a few additional syntheses of such geometrical TAZ derivatives and evaluation of their anti-HSV-1 activities and structure-activity relationships (SARs).

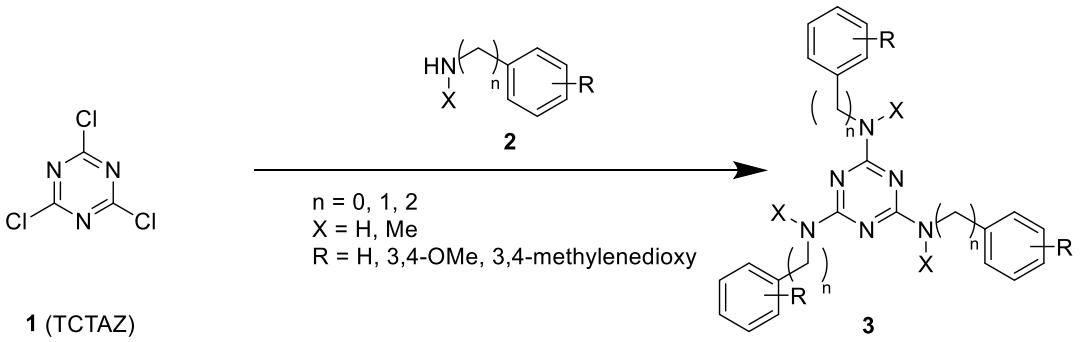


A

Figure 1. Antiviral lead compound (**A**)

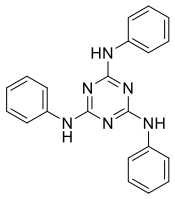
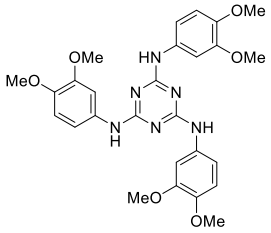
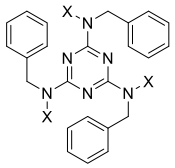
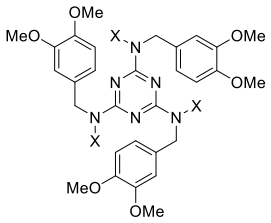
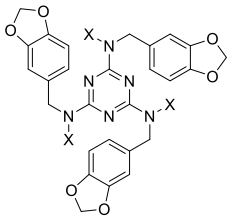
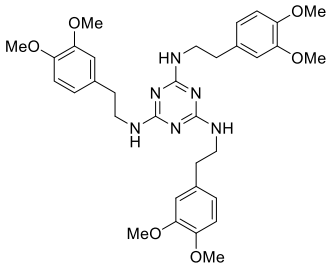
RESULTS AND DISCUSSION

A few additional C_3-symmetrical TAZ derivatives (**3**) were newly synthesized from 2,4,6-trichloro-1,3,5-triazine (TCTAZ, **1**) as a starting material using a substitution reaction by nucleophiles such as arylalkylamine or arylamine derivatives (**2**) (**Scheme 1**). The details for the preparation of these C_3-symmetrical TAZ derivatives (**3**) are given in EXPERIMENTAL.



Scheme 1. Synthetic pathway of target C_3-symmetrical TAZ derivatives (**3**)

Table 1. Anti-HSV-1 activities of C_3-symmetrical triamino-substituted TAZ derivatives (**3a~3f**)

Compound	Structure	EC_{50} (μ M)	CC_{50} (μ M)
3a		>100	>200
3b		>100	>200
3c-H a) X=H		13.2	5.5
3c-Me X=Me		>100	>200
3d-H (A) a) X=H		0.98	292.2
3d-Me X=Me		4.2	>200
3e-H b) X=H		5.4	291.8
3e-Me X=Me		>100	>200
3f		>100	>200
aciclovir c)		1.1	>444

a) Data were taken from reference 10. b) Data were taken from reference 14.
c) Data were taken from reference 16.

As can be seen in EXPERIMENTAL, the yields in the procedure for C_3-symmetrical TAZ derivatives (**3a~3f**) with the starting TCTAZ (**1**) were good, and this method for synthesis of TAZ derivatives[10] was reconfirmed to be useful as a general procedure for the synthesis of *N*-methylated C_3-type TAZ derivatives. The presence of a phenylethylamino functionality in the C_3-type TAZ molecules (**3f**) also gave a good result. The structures of the obtained new C_3-symmetrical TAZ derivatives were established by spectroscopic methods and elemental analysis. Correct molecular ion peaks were observed in high-resolution positive FAB-MS spectra of all TAZ derivatives (**3a~3f**). The geometries of the obtained symmetrical TAZ derivatives were confirmed from ^{13}C-NMR spectroscopic data.

The anti-HSV-1 activities (EC_{50}) determined by plaque reduction assays[15] and cytotoxicity (CC_{50}) of C_3-type TAZ derivatives (**3a~3f**) against Vero cells are summarized in Table 1. Among the tri-substituted symmetrical TAZ derivatives tested (**3a~3f**), the C_3-symmetrical derivative **3d-Me** having three substituted *N*-methylated benzylamino groups showed the highest anti-HSV-1 activity (EC_{50} = 4.2 μM) and low cytotoxicity (CC_{50} => 200 μM). It is noteworthy that the C_3-type compounds **3c-Me** and **3e-Me**, but not compound **3d-M**, having three *N*-methylated benzylamines in the TAZ template (listed in Table 1) showed no anti-HSV-1 activities (EC_{50} => 200 μM) and low cytotoxicity (CC_{50} => 200 μM). In contrast, we previously observed that all of the C_3-symmetrical TAZ derivatives (**3c-H**[10], **3d-H** (**A**)[10] and **3e-H**[14]) corresponded to the compounds **3c-Me**, **3d-Me** and **3e-Me** that have three benzylamino groups with free NH functionality showed considerably high anti-HSV-1 activities (EC_{50} = 0.98~13.2 μM). Non-*N*-methylated compound **3d-H** (**A**) corresponding to (**3d-Me**) showed a high level of anti-HSV-1 activity (EC_{50} = 0.98 μM) with a low level of cytotoxicity (CC_{50} = 292.2 μM).[10] The results obtained indicated that the presence of three *N*-methylated benzylamino groups as substituents seems to be an undesirable structure for the expression of anti-HSV-1 activity. The reason for decreased activity of *N*-methylated compounds may the lack of a hydrogen bonding donor property of the -NH- functionalities in these molecules.

In connection with the trivalent C_3-type symmetrical TAZ derivatives and the purpose of comparison of the biological activities of TAZ derivatives, we further prepared C_3-type TAZ derivatives (**3a, 3b** and **3f**). The structures of target compounds obtained in this study are shown in Table 1. The results of biological evaluation of these compounds and data for aciclovir[16] are also shown in Table 1. The arylamine-substituted TAZ derivatives (**3a** and **3b**) unfortunately showed no anti-HSV-1 activity (EC_{50} => 100 μM) and showed low cytotoxicity (CC_{50} => 200 μM). The arylethylamine-substituted C_3-symmetrical derivative (**3f**) also showed no anti-HSV-1 activity (EC_{50} => 100 μM).

On the basis of the information obtained by evaluation of biological activities of newly synthesized C_3-type tri-substituted TAZ derivatives in Table 1 together with previous information on the C_3-type TAZ

series,[10-14] we are considering *N*-non-methylated benzylamine-substituted TAZ derivative is a favorable modification for new C_3-type antiviral TAZ molecules. Further molecular modifications of these related TAZ derivatives with the aim of developing new antiviral compounds are under way.

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 for 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. ^{l}H- and ^{13}C-NMR spectra were obtained by ECG600R. Chemical shifts were expressed in δ ppm downfield from an internal TMS signal for ^{l}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: ^{l}H-^{l}H 2D correlation spectroscopy (COSY), ^{l}H-^{l3}C heteronuclear multiple-quantum coherence (HMQC), and ^{l}H-^{l3}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.

Procedure for Preparation of C_3-Symmetrical Tribenzylamino-substituted TAZ Derivatives (3a~3f) (Table 1):

N^2,N^4,N^6-Triphenyl-1,3,5-triazine-2,4,6-triamine (3a)[17]

To a solution of TCTAZ (184 mg, 1.0 mmol) in 1,4-dioxane (2.0 mL) was added a solution of aniline (0.911 mL, 10 mmol) in 1,4-dioxane (2.0 mL) dropwise at 0 °C, and the mixture was continuously stirred for 30 min at 0 °C and then for another 60 min 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 (20 mL), the resulting mixture was extracted with CH_2Cl_2 (30 mL×3). The combined organic layer was washed with brine (10 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residual solid was purified by silica gel column chromatography with *n*-hexane/AcOEt as an eluent to give the desired product **(3a)** (289 mg, 82% yield) as a white solid. Mp 233-234 °C (Lit.[17] mp 236-237 °C); FAB-MS (positive) *m*/*z* 355 $(M+H)^+$. HRMS (FAB) Calcd for $C_{21}H_{19}N_6^+$: *m*/*z* 355.1666 $(M+H)^+$. Found: 355.1674; ^{1}H-NMR (DMSO-d_6) δ 7.00 (3H, t,

J = 8.0 Hz, Ar H-4 in C_6H_5), 7.29 (6H, dd, *J* = 6.9, 8.0 Hz, Ar H-3 in C_6H_5), 7.81 (6H, d, *J* = 6.9 Hz, Ar H-2 in C_6H_5), 9.24 (3H, br s, NH); ^{13}C-NMR (DMSO-d_6) δ 120.3 (Ar C-3 in C_6H_5), 122.0 (Ar C-4 in C_6H_5), 128.3 (Ar C-2 in C_6H_5), 139.9 (Ar C-1 in C_6H_5), 164.1 (Ar C-1,3,5 in triazine). *Anal*. Calcd for $C_{21}H_{18}N_6$: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.20; H, 5.09; N, 23.76.

N^2,*N*^{4},*N*^{6}-Tris(3,4-dimethoxyphenyl)-1,3,5-triazine-2,4,6-triamine (3b)[18]

To a solution of TCTAZ (184 mg, 1.0 mmol) in 1,4-dioxane (2.0 mL) was added a solution of 3,4-dimethoxyaniline (1.53 g, 10 mmol) in 1,4-dioxane (2.0 mL) dropwise at 0 °C, and the mixture was continuously stirred for 30 min at 0 °C and then for another 60 min 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 (20 mL), the resulting mixture was extracted with CH_2Cl_2 (30 mL×3). The combined organic layer was washed with brine (10 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residual solid was purified by silica gel column chromatography with *n*-hexane/AcOEt as an eluent to give the desired product **(3b)**[18] (483 mg, 90% yield) as a brown solid. Mp 111-119 °C; FAB-MS (positive) *m*/*z* 535 $(M+H)^+$. HRMS (FAB) Calcd for $C_{27}H_{31}N_6O_6^+$: *m*/*z* 535.2300 $(M+H)^+$. Found: 535.2300; ^{1}H-NMR (DMSO-d_6) δ 3.42-3.92 (18H, m, OCH$_3$ on Ar C-3, Ar C-4 in C_6H_3), 6.84 (3H, d, *J* = 8.4 Hz, Ar H-5 or Ar H-6 in C_6H_3), 7.03-7.55 (6H, m, Ar H-2, Ar H-5 or Ar H-6 in C_6H_3), 8.92 (3H, br s, NH); ^{13}C-NMR (DMSO-d_6) δ 55.4 (OCH$_3$ on Ar C-3 or Ar C-4 in C_6H_3), 55.9 (OCH$_3$ on Ar C-3 or Ar C-4 in C_6H_3), 106.3, 112.0, 112.6 (Ar C-2, Ar C-5, Ar C-6 in C_6H_3), 133.5, 144.3, 148.5 (Ar C-1, Ar C-3, Ar C-4 in C_6H_3), 164.1 (Ar C-1,3,5 in triazine). *Anal*. Calcd for $C_{27}H_{30}N_6O_6 \bullet 0.3H_2O$: C, 60.06; H, 5.71; N, 15.56. Found: C, 60.07; H, 5.59; N, 15.55.

N^2,*N*^{4},*N*^{6}-Tribenzyl-*N*^{2},*N*^{4},*N*^{6}-trimethyl-1,3,5-triazine-2,4,6-triamine (3c-Me)

To a solution of TCTAZ (184 mg, 1.0 mmol) in 1,4-dioxane (4.0 mL) was added *N*-methyl-1-phenylmethanamine (1.29 mL, 10 mmol) dropwise at 0 °C, and the mixture was continuously stirred for 30 min at 0 °C and then for another 60 min 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 (20 mL), the resulting mixture was extracted with CH_2Cl_2 (30 mL×3). The combined organic layer was washed with brine (10 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residual solid was purified by silica gel column chromatography with CH_2Cl_2 as an eluent to give the desired product **(3c-Me)** (413 mg, 94% yield) as a white solid. Mp 69-71 °C; FAB-MS (positive) *m*/*z* 439 $(M+H)^+$. HRMS (FAB) Calcd for $C_{27}H_{31}N_6^+$: *m*/*z* 439.2605 $(M+H)^+$. Found: 439.2623; ^{1}H-NMR (DMSO-d_6) (125 °C) δ 3.04 (9H, s, N-CH$_3$), 4.78 (6H, s, N-CH$_2$-C_6H_5), 7.16-7.32 (15H, m, Ar H-2,3,4 in C_6H_5); ^{13}C-NMR (DMSO-d_6) (125 °C) δ 33.1 (N-CH$_3$), 50.6 (N-CH$_2$-C_6H_5), 126.0, 126.8, 127.5 (Ar C-2, Ar C-3, Ar C-4 in C_6H_5), 138.3 (Ar C-1 in C_6H_5), 165.1

(Ar C-1,3,5 in triazine). *Anal*. Calcd for $C_{27}H_{30}N_6$: C, 73.94; H, 6.89; N, 19.16. Found: C, 73.83; H, 6.88; N, 19.13.

N^2,N^4,N^6-Tris(3,4-dimethoxybenzyl)-N^2,N^4,N^6-trimethyl-1,3,5-triazine-2,4,6-triamine (3d-Me)

To a solution of TCTAZ (184 mg, 1.0 mmol) in 1,4-dioxane (2.0 mL) was added a solution of 1-(3,4-dimethoxyphenyl)-*N*-methylmethanamine (1.91 mL, 10 mmol) in 1,4-dioxane (2.0 mL) dropwise at 0 °C, and the mixture was continuously stirred for 30 min at 0 °C and then for another 60 min 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 (20 mL), the resulting mixture was extracted with CH_2Cl_2 (30 mL×3). The combined organic layer was washed with brine (10 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residual solid was purified by silica gel column chromatography with *n*-hexane/AcOEt as an eluent to give the desired product **(3d-Me)** (543 mg, 88% yield) as a white solid. Mp 113-114 °C; FAB-MS (positive) *m*/*z* 619 $(M+H)^+$. HRMS (FAB) Calcd for $C_{33}H_{43}N_6O_6^+$: *m*/*z* 619.3239 $(M+H)^+$. Found: 619.3254; ^{1}H-NMR (DMSO-d_6) (125 °C) δ 3.04 (9H, s, N-C<u>H</u>$_3$), 3.70 (9H, s, OC<u>H</u>$_3$ on Ar C-3 in C_6H_3), 3.75 (9H, s, OC<u>H</u>$_3$ on Ar C-4 in C_6H_3), 4.71 (6H, s, N-C<u>H</u>$_2$-C_6H_3), 6.79 (3H, d, J = 7.8 Hz, Ar <u>H</u>-6 in C_6H_3), 6.86 (3H, d, J = 7.8 Hz, Ar <u>H</u>-5 in C_6H_3), 6.90 (3H, s, Ar <u>H</u>-2 in C_6H_3); ^{13}C-NMR (DMSO-d_6) (125 °C) δ 33.0 (N-<u>C</u>H$_3$), 50.3 (N-<u>C</u>H$_2$-C_6H_3), 55.5 (O<u>C</u>H$_3$ on Ar C-3 in C_6H_3), 55.7 (O<u>C</u>H$_3$ on Ar C-4 in C_6H_3), 112.8 (Ar <u>C</u>-2 or Ar <u>C</u>-5 in C_6H_3), 112.9 (Ar <u>C</u>-2 or Ar <u>C</u>-5 in C_6H_3), 119.7 (Ar <u>C</u>-6 in C_6H_3), 131.4 (Ar <u>C</u>-1 in C_6H_3), 148.0 (Ar <u>C</u>-4 in C_6H_3), 148.9 (Ar <u>C</u>-3 in C_6H_3), 165.1 (Ar <u>C</u>-1,3,5 in triazine). *Anal*. Calcd for $C_{33}H_{42}N_6O_6$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.05; H, 6.82; N, 13.50.

N^2,N^4,N^6-Tris(benzo[*d*][1,3]dioxol-5-ylmethyl)-N^2,N^4,N^6-trimethyl-1,3,5-triazine-2,4,6-triamine (3e-Me)

To a solid of 1-(benzo[*d*][1,3]dioxol-5-yl)-*N*-methylmethanamine hydrochloride (2.02 g, 10 mmol) were successively added a solution of TCTAZ (184.4 mg, 1.0 mmol) in 1,4-dioxane (4.0 mL) dropwise and triethylamine (1.39 mL, 10 mmol) at 0 °C, and the mixture was continuously stirred for 30 min at 0 °C and then for another 60 min 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 (20 mL), the resulting mixture was extracted with CH_2Cl_2 (30 mL×3). The combined organic layer was washed with brine (10 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residual solid was purified by silica gel column chromatography with *n*-hexane/AcOEt as an eluent to give the desired product **(3e-Me)** (99 mg, 17% yield) as a yellow solid. Mp 106-109 °C; FAB-MS (positive) *m*/*z* 571 $(M+H)^+$. HRMS (FAB) Calcd for $C_{30}H_{31}N_6O_6^+$: *m*/*z* 571.2300 $(M+H)^+$. Found: 571.2301; ^{1}H-NMR (DMSO-d_6) (125 °C) δ 3.02 (9H, s, N-C<u>H</u>$_3$), 4.68 (6H, s, N-C<u>H</u>$_2$-C_6H_3), 5.93 (6H, s, O-C<u>H</u>$_2$-O), 6.69-6.83 (9H, m, Ar <u>H</u>-2, Ar <u>H</u>-5, Ar <u>H</u>-6 in

C_6H_3); ^{13}C-NMR (DMSO-d_6) (125 °C) δ 33.0 (N-C$\underline{H}_3$), 50.4 (N-C$\underline{H}_2$-C_6H_3), 100.1 (O-$\underline{C}H_2$-O), 107.3, 107.3, 120.1 (Ar $\underline{C}$-2, Ar $\underline{C}$-5, Ar $\underline{C}$-6 in C_6H_3), 132.3 (Ar $\underline{C}$-1 in C_6H_3), 145.7 (Ar $\underline{C}$-3 or Ar $\underline{C}$-4 in C_6H_3), 146.8 (Ar $\underline{C}$-3 or Ar $\underline{C}$-4 in C_6H_3), 165.0 (Ar $\underline{C}$-1,3,5 in triazine). *Anal*. Calcd for $C_{30}H_{30}N_6O_6$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.16; H, 5.36; N, 14.62.

N^2,*N*^{4},*N*^{6}-Tris(3,4-dimethoxyphenethyl)-1,3,5-triazine-2,4,6-triamine (3f)[19]

To a solution of TCTAZ (184 mg, 1.0 mmol) in 1,4-dioxane (2.0 mL) was added a solution of 2-(3,4-dimethoxyphenyl)ethan-1-amine (1.81 g, 10 mmol) in 1,4-dioxane (2.0 mL) dropwise at 0 °C, and the mixture was continuously stirred for 30 min at 0 °C and then for another 60 min 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 (20 mL), the resulting mixture was extracted with CH_2Cl_2 (30 mL×3). The combined organic layer was washed with brine (10 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residual solid was purified by silica gel column chromatography with *n*-hexane/AcOEt as an eluent to give the desired product **(3f)** (540 mg, 87% yield) as a white solid.[19] Mp 125-130 °C; FAB-MS (positive) *m*/*z* 619 $(M+H)^+$. HRMS (FAB) Calcd for $C_{33}H_{43}N_6O_6^+$: *m*/*z* 619.3239 $(M+H)^+$. Found: 619.3246; ^{1}H-NMR ($CDCl_3$) δ 2.58-2.96 (6H, m, NH-CH_2-C$\underline{H}_2$-C_6H_3), 3.38-3.70 (6H, m, NH-C$\underline{H}_2$-CH_2-C_6H_3), 3.84 (9H, s, OC$\underline{H}_3$ on Ar C-3 or Ar C-4 in C_6H_3), 3.85 (9H, s, OC$\underline{H}_3$ on Ar C-3 or Ar C-4 in C_6H_3), 4.30-5.40 (3H, m, N$\underline{H}$), 6.72 (3H, s, Ar $\underline{H}$-2 in C_6H_3), 6.74 (3H, d, J = 8.1 Hz Ar $\underline{H}$-6 in C_6H_3), 6.79 (3H, d, J = 8.1 Hz Ar $\underline{H}$-5 in C_6H_3); ^{13}C-NMR ($CDCl_3$) δ 35.7 (NH-CH_2-$\underline{C}H_2$-C_6H_3), 42.2 (NH-$\underline{C}H_2$-CH_2-C_6H_3), 55.9 (O$\underline{C}H_3$ on Ar C-3 or Ar C-4 in C_6H_3), 56.1 (O$\underline{C}H_3$ on Ar C-3 or Ar C-4 in C_6H_3), 111.5 (Ar $\underline{C}$-5 in C_6H_3), 112.2 (Ar $\underline{C}$-2 in C_6H_3), 120.8 (Ar $\underline{C}$-6 in C_6H_3), 131.9 (Ar $\underline{C}$-1 in C_6H_3), 147.7 (Ar $\underline{C}$-3 or Ar $\underline{C}$-4 in C_6H_3), 149.1 (Ar $\underline{C}$-3 or Ar $\underline{C}$-4 in C_6H_3), 166.3 (Ar $\underline{C}$-1,3,5 in triazine). *Anal*. Calcd for $C_{33}H_{42}N_6O_6$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.92; H, 6.79; N, 13.49.

Antiviral Activity Assay and Cytotoxicity

The anti-HSV-1 activities (EC_{50} values) of the synthesized TAZ derivatives (**3a**~**3f**) 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 Table 1 together with data for aciclovir.[16]

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