

SOME NEW C_3 - AND C_S -SYMMETRICAL TRIALKYLAMINO-SUBSTITUTED 1,3,5-TRIAZINES AND THEIR BIOLOGICAL EVALUATION

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Abstract – We report the preparation of some new additionally synthesized symmetrical 1,3,5-triazines (TAZ) and the results of biological evaluation of their anti-herpes simplex virus type 1 (anti-HSV-1) activity and cytotoxic activity against Vero cells. All of the new trisubstituted TAZ derivatives **3a-3e** showed considerable levels of anti-HSV-1 activity ($EC_{50} = 4.4 \sim 30.3 \mu\text{M}$). Among the tested compounds, two compounds (**3c-2** and **3d**) that have three 3,4-methylenedioxyphenylalkylamino groups showed low levels of cytotoxicity ($CC_{50} > 200 \mu\text{M}$) against Vero cells. On the other hand, the C_3 -symmetrical TAZ derivatives **3a-2**, **3b-2** and **3e** showed considerably high levels of cytotoxicity ($CC_{50} = 8.91 \sim 15.2 \mu\text{M}$). The structure-activity relationships for anti-HSV-1 activity and cytotoxicity of synthesized single-drug type 2,4,6-trisubstituted TAZ derivatives are also discussed.

Supramolecular interaction by macromolecules with symmetrical features such as two-fold (C_2) or three-fold (C_3) geometry is one of the common interactions in many crucial biological responses.^{1,2} To develop new bioactive molecules, we have recently designed and synthesized many new compounds with such symmetrical geometry and evaluated their bioactivities in order to find new types of bioactive leads.²⁻⁶ In connection with these projects, we have recently reported the preparation of various new types of C_3 -, C_2 - and C_S -symmetrical oligovalent 1,3,5-triazine (TAZ) derivatives and the results of biological evaluation of the synthesized symmetrical TAZ derivatives.^{3,7-11}

Among previously targeted C_3 - and C_5 -type symmetrical TAZ derivatives, we found that a few 2,4,6-trisubstituted symmetrical TAZ derivatives including C_3 -type **A (3f)** and C_5 -type **B (3g)** compounds showed high levels of anti-HSV-1 activity and considerably low levels of cytotoxic activity ($CC_{50} > 200 \mu\text{M}$) against Vero cells^{7,12} (see Figure 1), and we also found that some highly active C_3 -symmetrical TAZ derivatives showed a carbohydrate recognition property.^{4,13} As an extension of molecular modification of TAZ derivatives, we further synthesized a few trivalent symmetrical TAZ derivatives in which arylalkylamino groups were introduced in the molecules. In this paper, we describe the results of evaluation of their biological activities and the structure-activity relationships (SARs) of these unique trivalent symmetrical TAZ derivatives.

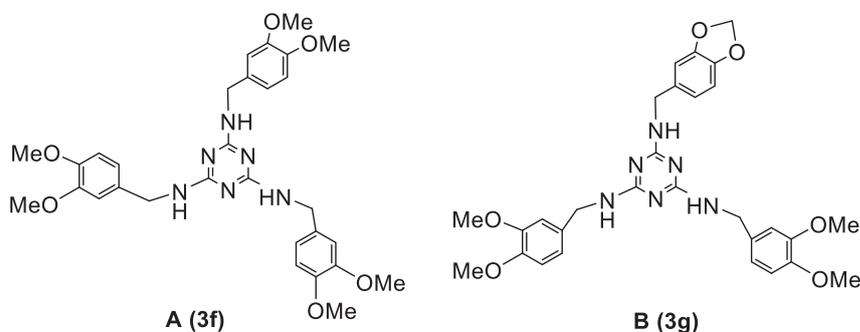
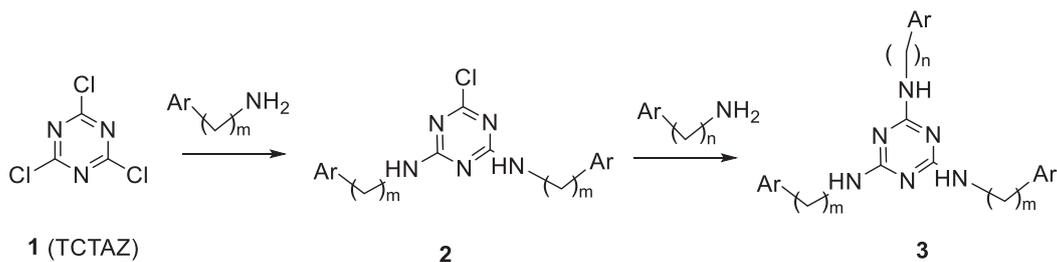


Figure 1. Anti-HSV-1 active C_3 - and C_5 -symmetrical TAZ derivatives (**A** and **B**)

Trisubstituted symmetrical TAZ derivatives (**3a-3e**) 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 or phenethylamine derivatives. C_5 -symmetrical TAZ derivative **3d** was prepared from intermediate TAZ derivative **2c-1**⁷ and the corresponding homopiperonylamine (see Scheme 1 and Figure 2). The details for the stepwise preparation of these symmetrical TAZ derivatives (**3**) are given in EXPERIMENTAL.

The structures of the obtained new symmetrical trivalent TAZ derivatives (**3a-2**, **3b-2**, **3c-2**, **3d** and **3e**) were established by spectroscopic methods and elemental analysis. Correct molecular ion peaks were observed in high-resolution positive FAB-MS spectra of all symmetrical TAZ derivatives (**3a-3e**). The structures and results of biological assays of these compounds are summarized in Table 1.

The yields obtained by the procedure using TCTAZ (**1**) as a starting material to target new symmetrical trivalent TAZ derivatives (**3a-3e**) were good to excellent (43~85%), and this stepwise method for the synthesis of TAZ derivatives was confirmed to be a useful procedure for the synthesis of these single-drug type trivalent TAZ derivatives (see EXPERIMENTAL).



Scheme 1. Stepwise synthesis of C_3 - and C_5 -symmetrical trivalent TAZ derivatives from TCTAZ (**1**)

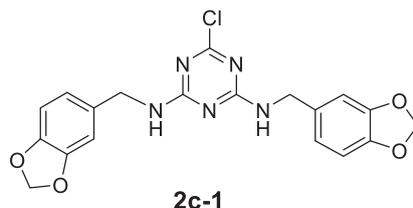


Figure 2. Structure of intermediate **2c-1** for the preparation of compound **3d**

The results of biological evaluation of these new trivalent derivatives [anti-HSV-1 activity (EC_{50}) and cytotoxicity (CC_{50})] together with data for previously reported highly active compounds and data for aciclovir¹⁴ are summarized in Table 1.

All of the new trivalent C_3 - and C_5 -symmetrical TAZ derivatives **3a-3e** showed considerably high levels of anti-HSV-1 activity ($EC_{50} = 4.4 \sim 30.3 \mu\text{M}$).

It is noteworthy that all of the symmetrical TAZ derivatives (**3a-2**, **3b-2**, **3c-2**, **3d** and **3e**) having new arylethylamine groups in the molecules showed high levels of anti-HSV-1 activity comparable to those of previously reported highly active compounds **3c-1**, **3f** (A) and **3g** (B) (see Table 1). Among the tested trivalent TAZ derivatives, C_3 -symmetrical derivatives **3a-1** and **3a-2** having simple non-substituted benzyl or phenylethyl groups showed considerable levels of anti-HSV-1 activity ($EC_{50} = 13.2$ and $18.7 \mu\text{M}$, respectively) and cytotoxicity ($CC_{50} = 5.5$ and $15.2 \mu\text{M}$). The same tendencies for EC_{50} and CC_{50} values were observed for C_3 -type compound **3b-2** having 4-methoxyphenylethyl groups in the TAZ template ($EC_{50} = >6.3$ and $CC_{50} = 8.91 \mu\text{M}$). The C_3 -symmetrical derivative (**3e**) having indole-3-ethyl groups in the TAZ template also showed high levels of anti-HSV-1 activity ($EC_{50} = 4.4 \mu\text{M}$) and cytotoxicity ($CC_{50} = 11.4 \mu\text{M}$). The C_3 - and C_5 -symmetrical trivalent TAZ derivatives (**3c-2** and **3d**) having three 2,4-methylenedioxyarylethyl groups in the TAZ rings also showed high levels of anti-HSV-1 activity ($EC_{50} = 30.3$ and $10.2 \mu\text{M}$, respectively), but both compounds showed low levels of cytotoxicity ($CC_{50} = >200 \mu\text{M}$). We previously observed that the C_3 -type benzylamine TAZ derivative (**3c-1**) shows a high level of anti-HSV-1 activity ($EC_{50} = 5.4 \mu\text{M}$) and low level of cytotoxicity ($CC_{50} = 291.9 \mu\text{M}$).¹¹

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

Compound	Structure	EC_{50} (μM)	CC_{50} (μM)	Compound	Structure	EC_{50} (μM)	CC_{50} (μM)
3a-1 ^a		n = 1	13.2	5.5		4.4	11.4
3a-2		n = 2	18.7	15.2			
3b-1 ^a		n = 1	38.7	>200		0.98	292.2
3b-2		n = 2	>6.3	8.91			
3c-1 ^b		n = 1	5.4	291.9		1.77	>200
3c-2		n = 2	30.3	>200			
3d		10.2	>200	aciclovir ^d		1.1	>444

^a Data were taken from reference 7. ^b Data were taken from reference 11. ^c Data were taken from reference 12. ^d Data were taken from reference 14.

These findings indicate that the methylene length (C1 or C2) is not crucial for the expression of anti-HSV-1 activities and that probably hydrogen bonding acceptor groups such as alkoxy groups on the phenyl rings in compounds **3c-1**, **3c-2** and **3d** are generally favorable for the low level of cytotoxicity in this series (see Table 1).

In fact, we have already found that C_3 -type compound **A (3f)** having three 3,4-dimethoxyphenyl groups, which corresponded to compound **3c-1**, showed a high level of activity ($EC_{50} = 0.98 \mu M$) and low level of

cytotoxicity ($CC_{50} = 292.2 \mu\text{M}$). We have also found that C_S -symmetrical TAZ derivative **B (3g)** having two kinds of hydrogen bonding acceptor groups on the phenyl ring also showed a high level of anti-HSV-1 activity ($EC_{50} = 1.77 \mu\text{M}$) and low level of cytotoxicity ($CC_{50} = >200 \mu\text{M}$).

Taking these previous results into consideration, we consider that the nature of aryl groups in the molecule may be one of the important factors for the expression of anti-HSV-1 activity and cytotoxicity in addition to the type of substituents on aryl rings.^{7,12} The molecular geometry of trisubstituted symmetrical TAZ molecules also seems to be an important factor for the expression of anti-HSV-1 activity, i.e., both C_3 - and C_s -geometric dimensional features are generally favorable.

The results obtained suggest that the symmetrical trivalent TAZ molecule (**3**) is a useful lead in the search for new single-drug type antiviral TAZ derivatives. We are now investigating further chemical modifications of these TAZ derivatives with the aim of developing new oligovalent anti-HSV-1 active leads.

EXPERIMENTAL

Melting points were determined using a micro melting point apparatus (Yanaco MP-S3) without correction. IR spectra were measured by a Shimadzu FTIR-8100 IR spectrophotometer. Low- and high-resolution mass spectra (LR-MS and HR-MS) were obtained by a JEOL JMS HX-110 double-focusing model equipped with an FAB ion source interfaced with a JEOL JMA-DA 7000 data system. ^1H - and ^{13}C -NMR spectra were obtained by ECG600R. Chemical shifts were expressed in δ ppm downfield from an internal TMS signal for ^1H -NMR and the carbon signal of the corresponding solvent [CDCl_3 (77.00 ppm), $\text{DMSO}-d_6$ (39.50 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 (HMQC), and ^1H - ^{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 60F₂₅₄ 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. Centrifugal chromatography separations of the reaction products were performed on silica gel (Kanto 60N or Able-Biott) with a UV detector. Commercially available materials were used without further purification, and dry solvents were used in all reactions.

Symmetrical TAZ derivatives (**3a-1**, **3c-1**, **3f** and **3g**) were prepared from TCTAZ (**1**) and the corresponding benzylamines by previously reported procedures.^{7,11,12}

N^2, N^4, N^6 -Triphenethyl-1,3,5-triazine-2,4,6-triamine (**3a-2**)

To a solution of TCTAZ (**1**, 277 mg, 1.50 mmol) in dioxane (2.5 mL) was added phenethylamine (1.82 g, 15.0 mmol) in dioxane (1.5 mL) at room temperature with stirring. Then the mixture was subjected to

microwave irradiation (MW) (100 W) at 100 °C for 80 min with stirring. After addition of water (20 mL), the mixture was extracted with CH₂Cl₂ (30 mL×3). The combined organic layer was washed with brine (10 mL) and dried over MgSO₄. After evaporation of the solvent, the obtained material was purified by centrifugal chromatography (CH₂Cl₂ : EtOH = 98 : 2) to give compound **3a-2** (557 mg, 1.27 mmol, 85%) as a colorless solid. Mp 133-135 °C. IR cm⁻¹: 3402, 3248 (NH), 1561, 1531, 1497 (C=N), 1206, 1162 (C-N). ¹H-NMR (CDCl₃) δ: 2.87 (6H, br s, Hβ), 3.64 (6H, br s, Hα), 4.77, 4.96* (3H, br s, NH), 7.2-7.4 (15H, m, ArH). ¹³C-NMR (CDCl₃) δ: 36.11 (Cβ), 42.07 (br s, Cα), 126.28 (C2', 6'), 128.51, 128.79 (C3', 4', 5'), 139.31 (C1'), 166.05 (br s, C2, 4, 6). (The observed ¹³C-signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS *m/z*: 439 (M+H)⁺. HR-FAB-MS *m/z*: 439.2609 (Calcd for C₂₇H₃₁N₆: 439.2610). *Anal.* Calcd for C₂₇H₃₀N₆·0.35H₂O: C, 72.89; H, 6.96; N, 18.89. Found: C, 72.89; H, 6.98; N, 18.66.

***N*²,*N*⁴,*N*⁶-Tris(4-methylphenethyl)-1,3,5-triazine-2,4,6-triamine (3b-2)**

To a solution of TCTAZ (**1**, 277 mg, 1.50 mmol) in dioxane (2.5 mL) was added 4-methylphenethylamine (2.03 g, 15.0 mmol) in dioxane (1.5 mL) at room temperature with stirring. Then the mixture was subjected to MW (100 W) at 100 °C for 20 min with stirring. After addition of water (20 mL), the mixture was extracted with CH₂Cl₂ (30 mL×3). The combined organic layer was washed with brine (10 mL) and dried over MgSO₄. After evaporation of the solvent, the obtained oil was purified by centrifugal chromatography (CH₂Cl₂ : EtOH = 98 : 2) to give compound **3b-2** (309 mg, 0.643 mmol, 43%) as a colorless solid. Mp 100-103 °C. IR cm⁻¹: 3410, 3249 (NH), 1561, 1530 (C=N), 1153 (C-N). ¹H-NMR (CDCl₃) δ: 2.32 (9H, s, CH₃), *ca.* 2.34* (2H, br s, NH), 2.82 (6H, br s, Hb), 3.60 (6H, br s, Ha), 4.93 (0.3H, br s, NH), 5.10 (0.6H, br s, NH), 5.52 (0.1H, br s, NH), 7.09 (12H, br s, ArH). (The observed ¹³C-signals assignable to the predominant tautomer are asterisked.) ¹³C-NMR (CDCl₃) δ: 20.99 (CH₃), 35.56 (Cβ), 42.17 (Cα), 128.65 (C2', 6'), 129.19 (C3', 5'), 135.76 (C4'), 136.12 (C1'), 165.65 (br s, C2, 4, 6). Positive-ion FAB-MS *m/z*: 481 (M+H)⁺. HR-FAB-MS *m/z*: 481.3074 (Calcd for C₃₀H₃₇N₆: 481.3080). *Anal.* Calcd for C₃₀H₃₆N₆·1/3EtOH: C, 74.26; H, 7.72; N, 16.94. Found: C, 74.16; H, 7.68; N, 16.69.

***N*²,*N*⁴,*N*⁶-Tris[2-(benzo[*d*][1,3]dioxol-5-yl)ethyl]-1,3,5-triazine-2,4,6-triamine (3c-2)**

To a solution of TCTAZ (**1**, 277 mg, 1.50 mmol) in dioxane (2.5 mL) was added homopiperonylamine (2.48 g, 15.0 mmol) in dioxane (1.5 mL) at room temperature with stirring, and the reaction mixture was stirred for another 10 min at room temperature. Then the mixture was subjected to MW (120 W) at 120 °C for 30 min with stirring. After addition of water (20 mL), the mixture was extracted with CH₂Cl₂ (30 mL×3). The combined organic layer was washed with water (10 mL) and dried over MgSO₄. After evaporation of the solvent, the residual oil was purified by centrifugal chromatography (CH₂Cl₂ : EtOH =

98 : 2) to give compound **3c-2** (406 mg, 0.711 mmol, 47%) as a white solid. Mp 73-76 °C. IR cm^{-1} : 3418, 3263 (NH), 1560, 1502 (C=N), 1246, 1038 (C-N or C-O). $^1\text{H-NMR}$ (CDCl_3) δ : 2.77 (6H, br s, $\text{H}\beta$), 3.57 (6H, br s, $\text{H}\alpha$), 4.89 (0.4H, br s, NH), 5.09* (2.6H, br s, NH), 5.90 (6H, br s, $\text{H}2'$), 6.6-6.75 (9H, m, ArH). (The observed ^{13}C -signals assignable to the predominant tautomer are asterisked.) $^{13}\text{C-NMR}$ (CDCl_3) δ : 35.72 ($\text{C}\beta$), 42.18 ($\text{C}\alpha$), 100.77 ($\text{C}2'$), 108.22 ($\text{C}7'$), 109.10 ($\text{C}4'$), 121.58 ($\text{C}6'$), 133.03 ($\text{C}5'$), 145.96 ($\text{C}7\text{a}'$), 147.63 ($\text{C}3\text{a}'$), 166.01 (br s, C2, 4, 6). Positive-ion FAB-MS m/z : 571 ($\text{M}+\text{H}$) $^+$. HR-FAB-MS m/z : 571.2331 (Calcd for $\text{C}_{30}\text{H}_{31}\text{N}_6\text{O}_6$: 571.2305). *Anal.* Calcd for $\text{C}_{30}\text{H}_{30}\text{N}_6\text{O}_6 \cdot 0.3\text{H}_2\text{O}$: C, 62.56; H, 5.35; N, 14.59. Found: C, 62.57; H, 5.33; N, 14.53.

***N*²-[2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl]-*N*⁴,*N*⁶-bis(benzo[*d*][1,3]dioxol-5-ylmethyl)-1,3,5-triazine-2,4,6-triamine (3d)**

To a solution of intermediate **2c-1**⁷ (414 mg, 1.00 mmol) in dioxane (3.5 mL) was added homopiperonylamine (413 mg, 2.50 mmol) in dioxane (1.5 mL) at room temperature with stirring. Then the mixture was subjected to MW (120 W) at 120 °C for 50 min with stirring. After addition of water (20 mL), the mixture was extracted with CH_2Cl_2 (30 mL \times 3). The combined organic layer was washed with brine (10 mL) and dried over MgSO_4 . After evaporation of the solvent, the residual oil was purified by centrifugal chromatography (CH_2Cl_2 : EtOH = 98 : 2) to give compound **3d** (429 mg, 0.791 mmol, 79%) as a colorless solid. Mp 43-47 °C. IR cm^{-1} : 3412, 3261 (NH), 1567, 1501 (C=N), 1248 (C-N or C-O), 1038 (C-N or C-O). $^1\text{H-NMR}$ (CDCl_3) δ : 2.11 (0.3H, br s, NH), 2.72 (2H, br s, $\text{H}\beta'$), 3.4-3.6 (2H, m, $\text{H}\alpha'$), *ca.* 4.4, 4.45 (4H, br s, $\text{H}\alpha$), 4.88 (0.1H, br s, NH), 5.05 (0.7H, br s, NH), 5.35 (0.8H, br s, NH), 5.43 (0.8H, br s, NH), 5.90 (2H, s, $\text{H}2''$), 5.91 (4H, s, $\text{H}2'$), 6.60 (1H, br d, J = 6.9 Hz, $\text{H}6''$), 6.65 (1H, br s, $\text{H}4''$), 6.68-6.75 (5H, m, $\text{H}6'$, $7'$, $7''$), 6.75-6.85 (2H, m, $\text{H}4'$). $^{13}\text{C-NMR}$ (CDCl_3) δ : 35.71 ($\text{C}\beta'$), 42.21 ($\text{C}\alpha'$), 44.34 ($\text{C}\alpha$), 100.77 ($\text{C}2''$), 100.89 ($\text{C}2'$), 108.08 ($\text{C}7'$), 108.14 ($\text{C}4'$), 108.23 ($\text{C}7''$), 109.10 ($\text{C}4''$), 120.55 ($\text{C}6'$), 121.60 ($\text{C}6''$), 133.04 ($\text{C}5''$), 133.47 ($\text{C}5'$), 145.96 ($\text{C}7\text{a}''$), 146.57 ($\text{C}3\text{a}'$), 147.63 ($\text{C}3\text{a}''$), 147.69 ($\text{C}7\text{a}'$), 166.09 (C2, 4, 6). Positive-ion FAB-MS m/z : 543 ($\text{M}+\text{H}$) $^+$. HR-FAB-MS m/z : 543.2016 (Calcd for $\text{C}_{28}\text{H}_{27}\text{N}_6\text{O}_6$: 543.1992). *Anal.* Calcd for $\text{C}_{28}\text{H}_{26}\text{N}_6\text{O}_6$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.97; H, 4.95; N, 15.28.

***N*²,*N*⁴,*N*⁶-Tris[2-(1*H*-indol-3-yl)ethyl]-1,3,5-triazine-2,4,6-triamine (3e)**

To a solution of TCTAZ (**1**, 277 mg, 1.50 mmol) in dioxane (2.0 mL) was added tryptamine (1.68 g, 10.5 mmol) in dioxane (2.0 mL) at room temperature with stirring, and the reaction mixture was stirred for another 10 min at room temperature. Then the mixture was subjected to MW (120 W) at 120 °C for 20 min with stirring. After addition of water (20 mL), the mixture was extracted with CH_2Cl_2 (30 mL \times 3). The combined organic layer was washed with brine (10 mL) and dried over MgSO_4 . After evaporation of

the solvent, the residual yellow oil was purified by centrifugal chromatography (CH₂Cl₂ : EtOH = 95 : 5) to give compound **3e** (480 mg, 0.863 mmol, 58%) as a colorless solid. Mp 79-84 °C. IR cm⁻¹: 3411, 3266 (NH), 1561, 1518 (C=N), 1227, 1092 (C-N). ¹H-NMR (CDCl₃) δ: *ca.* 2.85, 2.94* (6H, br s, H_β), 3.45-3.75 (6H, m, H_α), 4.89 (1H, br s, NH), 5.06 (2H, br s, NH), *ca.* 6.62, 6.69* (3H, br s, H_{2'}), 7.04*, 7.06 (3H, br s, H_{5'}), 7.12 (3H, br s, H_{6'}), 7.22 (3H, br s, H_{7'}), 7.57 (3H, br s, H_{4'}), 8.32* (2H, br s, NH of indole), 8.44 (1H, br s, NH of indole). ¹³C-NMR (CDCl₃) δ: 25.43 (br s, C_β), 40.78 (br s, C_α), 111.22 (C_{7'}), 112.87 (br s, C_{3'}), 118.68 (C_{4'}), 119.16 (C_{5'}), 121.88 (C_{6'}), 122.16 (C_{2'}), 127.30 (C_{3a'}), 136.35 (C_{7a'}), 165.52, 165.92* (br s, C₂, 4, 6). (The observed ¹³C-signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS *m/z*: 556 (M+H)⁺. HR-FAB-MS *m/z*: 556.2931 (Calcd for C₃₃H₃₄N₉: 556.2937). *Anal.* Calcd for C₃₃H₃₃N₉·2/3EtOH·1/3H₂O: C, 69.61; H, 6.41; N, 21.28. Found: C, 69.69; H, 6.36; N, 21.01.

Antiviral Activity Assay and Cytotoxicity

The anti-HSV-1 activities (EC₅₀) of the synthesized TAZ derivatives (**3a-g**) were measured by using a plaque reduction assay,¹⁵ and their cytotoxicity against Vero cells (CC₅₀) was also evaluated as we described previously. The results are summarized in Table 1 together with data for aciclovir.¹⁴

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