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ANTIVIRAL ACTIVITIES OF SOME NEW 2,4,6-TRISUBSTITUTED 1,3,5-TRIAZINES HAVING ALKOXY AND/OR ALKYLAMINO GROUPS

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Abstract – We report the preparation of C_3- and C_S-symmetrical 2,4,6-trisubstituted 1,3,5-triazine derivatives having alkoxy and/or alkylamino groups and results of biological evaluation of their anti-herpes simplex virus type 1 (anti-HSV-1) activity and cytotoxic activity against Vero cells. New targeted symmetrical molecules were obtained by using a method starting with 2,4,6-trichloro-1,3,5-triazine (**1**). Among the synthesized compounds, C_S-symmetrical tri-aliphatic alkylamino-substituted compound **6s** showed high anti-HSV-1 activity (EC_{50} = 5.4 μM) and low cytotoxicity (CC_{50} > 200 μM). The results of an SAR study suggested that the presence of two hydrogen bond donor protons of *sec*-amine functionality in the molecule is an important structural factor for expression of potential anti-HSV-1 activities.

INTRODUCTION

Specific interactions between carbohydrate-containing glycoproteins, proteoglycans and glicolipids on the cell surface and various types of lectins (protein receptors) are important biological processes for various cell-to-cell communications, including the processes of bacterial or viral infection and tumor metastasis.[1-3] Molecular recognition of two-fold (C_2) or three-fold (C_3) symmetrical geometry macromolecules is one of the common features in many important biological responses. From the viewpoint of molecular symmetry, many host receptors that consist of homo-oligometric units (homo-multiligands) often form symmetric macromolecule architectures such as C_2- or C_3-symmetrical

geometry receptor systems.[4] These phenomena of bio-macromolecules have encouraged us to develop new multivalent symmetrical synthetic molecules to find new bioactive compounds or leads. Regarding such geometrical molecules, we have already designed and synthesized a few new symmetrical molecules and evaluated their bioactivities in order to find new types of bioactive compounds.[5-10]

In connection with the above projects, we have recently reported some symmetrical 2,4,6-trisubstituted 1,3,5-triazine (TAZ) derivatives and the results of biological evaluation of the synthesized symmetrical TAZ derivatives.[11] Among previously targeted tri-substituted TAZ derivatives, we found that a C_3-symmetrical TAZ derivative with three isopropoxy groups on a TAZ template (compound **4b**) showed a high level of anti-HSV-1 activity and a low level of cytotoxicity. This compound is considered to be a potential lead in the search for preferred anti-HSV-1 activity with a good selectivity index.[5]

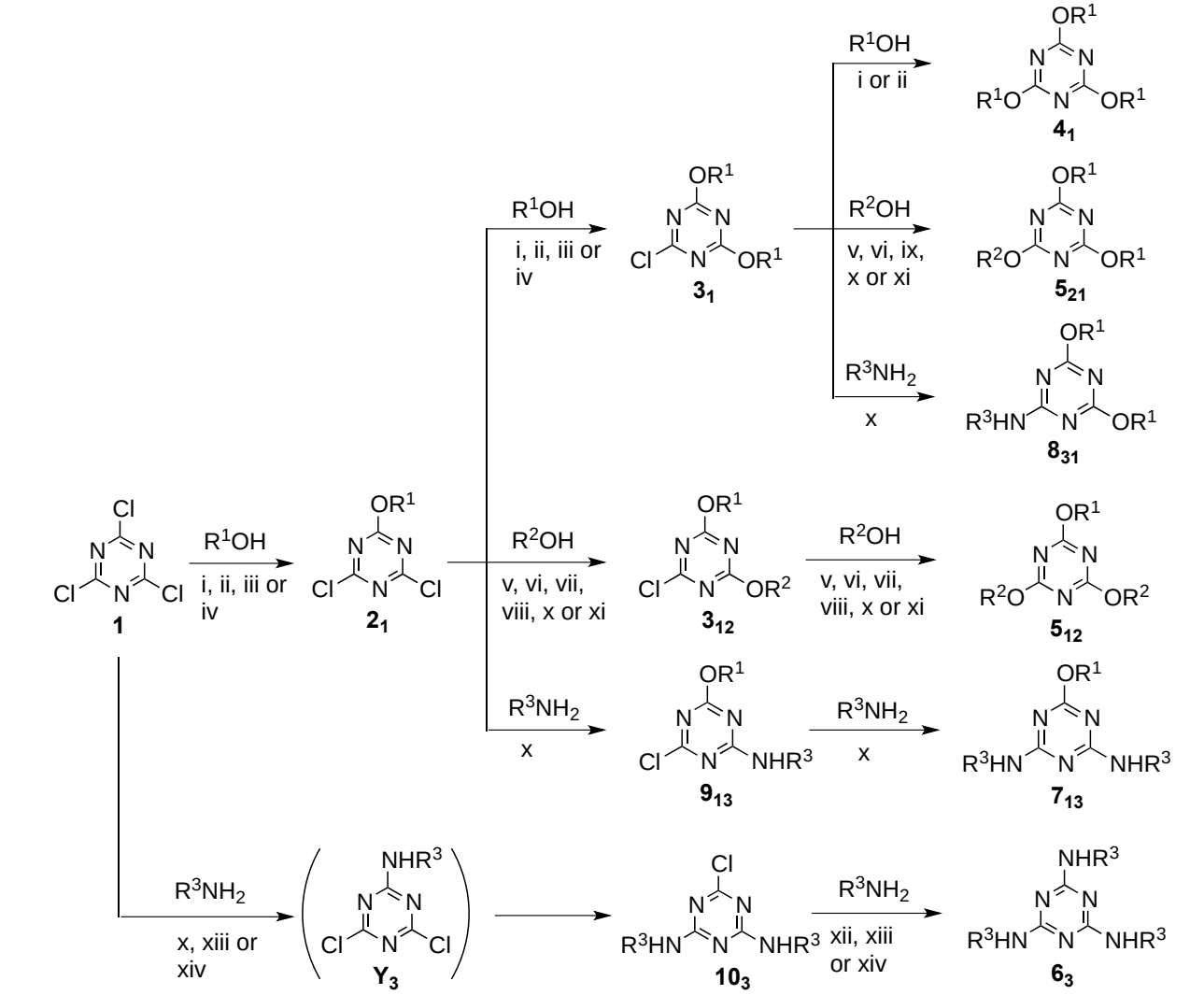
The results of a few trials for molecular modifications of symmetrical 2,4,6-trialkoxy-TAZ derivatives[12-15] in order to find new bioactive molecules have recently been reported. Our previous works revealed the importance of three isopropoxy groups including the C_3-type TAZ molecule **4b** for expression of anti-HSV-1 activity with a high selectivity index and also the contribution of these isopropoxy groups to potential diastereoselective sugar-recognition in some monosaccharides probably in a manner through hydrophobic interaction. It is also thought that the ability to form multiple hydrogen bonds plays an important role in guest molecule recognition of many artificial receptor-type symmetrical molecules.[7,11]

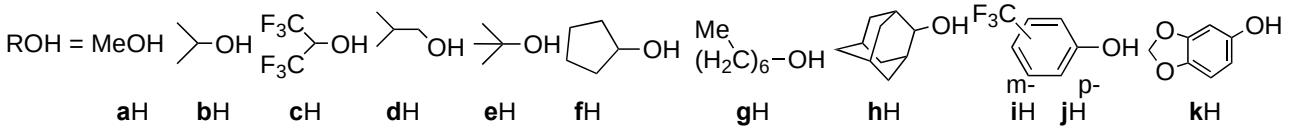
In this paper, we report the results of further preparation of newly targeted 2,4,6-trisubstituted TAZ derivatives (**4**-**8**) together with the results of evaluation of the antiviral activities of synthesized TAZ derivatives in order to reveal the noncovalent reversible bonds such as hydrogen bonds. We describe the structure-activity relationships (SARs) of these tri-substituted TAZ derivatives that have branched C3~C4 alkoxy and/or amino groups in the TAZ template.

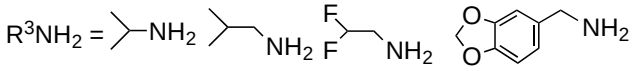
SYNTHESIS OF NEW TARGETED 2,4,6-TRISUBSTITUTED 1,3,5-TRIAZINES

Target 2,4,6-trisubstituted TAZ derivatives (**4**-**8**) were synthesized from 2,4,6-trichloro-1,3,5-triazine (TCTAZ, **1**) as a starting material using stepwise nucleophilic substitution of three active chlorine atoms of TCTAZ by various alcohols (ROH) and/or alkylamines (RNH_2) (as nucleophiles). The overall process for the preparation of these target molecules is shown in Scheme 1.

Preparation of C_3-symmetrical alkoxy- or alkylamino-trisubstituted TAZ derivatives (**4** or **6**) was conducted by nucleophilic substitution of TCTAZ (**1**) in one pot with alcohols (**c**-**e**, **h**H) or alkylamines (**p**-**t**H). As we mentioned previously,[6,11] it is well known as Moffatt's rule[16,17] that decreased reactivity of the final chlorine atom in the TAZ template to nucleophiles requires drastic reaction conditions with strong bases (such as NaH, *t*-BuOK) or under microwave irradiation (MW). As can be seen in Tables S1







i: R^1OH, NaH, rt to D; then **1**, rt to D, THF (for **4c**, **4d**, **4h**) ii: *t*-BuOK, 0 °C to rt, THF (for **4e**)
iii: collidine, rt, acetone (for **2b**, **2d**, **2f**, **2g**, **2j**, **3j**) or THF (for **2h**)
iv: R^1OH, NaH, 0 °C; then **1**, -78 °C to rt, THF (for **3b**, **3f**) or R^1OH, NaH, D; then **1**, D, benzene (for **3d**)
v: R^2OH, NaH, rt to D or rt; then $\mathbf{2}_1$, rt to D or D,THF (for **5ab**, **5bh**, **5hb**, **5jg**)
vi: Et_3N, rt, THF (for **5ka**, **5kb**) or D, acetone (for **5gj**)
vii: collidine, rt and/or D, acetone (for **5bi**, **5bk**, **3bk**, **5fi**, **5fj**·(**3fj**)$_2$, **5fk**, **5gi**, **3jg**), acetone-THF (for **5ak**, **3ak**)
viii: collidine, MW, dioxane (for **5bj**, **3bj**) ix: collidine, rt to D, acetone; then MW, dioxane (for **5jb**)
x: MW, dioxane (for **7dp**, **7dq**, **8pb**, **8qd**) xi: DIPEA, D, THF (for **7bp**, **7bq**, **9bq**, **7fq**, **9fq**, **8qb**, **8pd**)
xii: MW, dioxane (for **6p**, **10p**) xiii: 0 °C to rt; then MW, dioxane (**6q**, **6r**, **6s**)
xiv: DIPA, D, THF (for **6q**, **10q**, **10r**) or DIPA, MW, dioxane (for **6q**,**10q**)
DIPEA = diisopropylethylamine, DIPA = diisopropylamine

Scheme 1. Synthesis of compounds **4**-**8**

and S2, overall yields in the preparation of target C_3-symmetrical TAZ derivatives (**4**, **6**) were moderate, but the reproducibility of the method was variable (see Tables S1 and S2 for Supplementary Materials of the online version for details).

Preparation of C_S-symmetrical alkoxy- and/or alkylamino-trisubstituted TAZ derivatives (**5**, **7** or **8**) was also achieved from stepwise substitution reactions of TCTAZ (**1**) by various alcohols (ROH) and alkylamines (RNH_2). Thus, reactions with different ratios of two reagents (**1** : ROH = 1 : 1 and **1** : ROH = 1 : 2) afforded intermediate monoalkoxy- or dialkoxy-substituted TAZ derivatives mainly (**2** and **3**, respectively), and the intermediate TAZ derivatives **2** and **3** obtained were further used for subsequent substitution reactions of chlorine atoms on the TAZ template with other needed nucleophiles (ROH or RNH_2) giving target C_S-symmetrical trialkoxy-TAZ derivatives (**5**) or alkoxy-alkylamino-trisubstituted TAZ derivatives (**7**, **8**). All of the intermediate mono- or dichloro-substituted TAZ derivatives (**2**, **3**) and target C_S-symmetrical tri-substituted TAZ derivatives (**5**, **7**, **8**) were obtained in moderate to good yields (see Tables S3-S5 for Supplementary Materials of the online version for details).

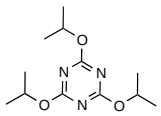
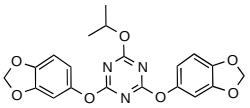
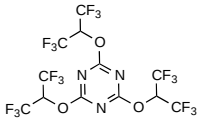
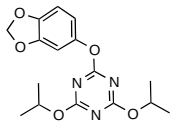
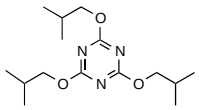
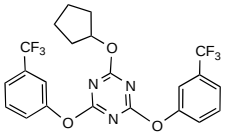
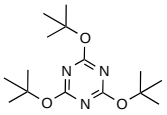
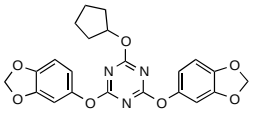
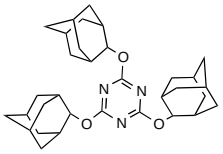
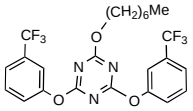
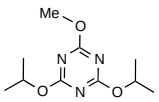
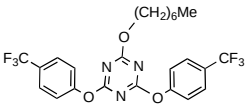
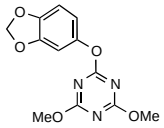
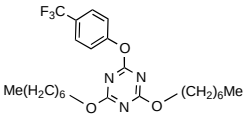
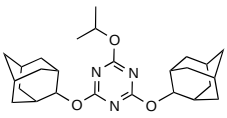
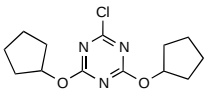
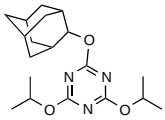
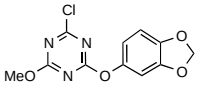
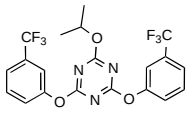
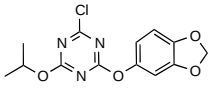
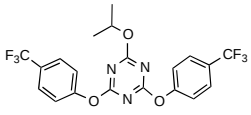
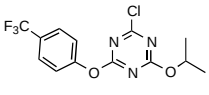
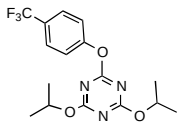
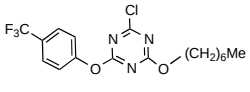
BIOLOGICAL ACTIVITY AND DISCUSSION

It is thought that the ability to form multiple hydrogen bonds plays an important role in guest molecule recognition of many artificial receptor-type molecules. Title tripodal receptor-type C_3- or C_S-geometrical molecules that have donors or acceptors for hydrogen bonds on a symmetrical TAZ template are thought to offer new biologically active interesting molecules.

EC_{50} values of the anti-HSV-1 activities of synthesized TAZ derivatives were obtained by plaque reduction assays,[18] and cytotoxicities (CC_{50}) against Vero cells were determined (Tables 1 and 2). Among the new C_3- and C_S-symmetrical tri-substituted TAZ derivatives, most of the C_3- and C_S-symmetrical compounds (**4**, **5**) that have three alkoxy groups showed no significant anti-HSV-1 (EC_{50} > 100 μM) activity or cytotoxic activity (CC_{50} > 200 μM) as was previously reported for tri-alkoxy substituted TAZ derivatives.[11] Only a few compounds showed anti-HSV-1 activity and moderate cytotoxic activity. Three C_S-symmetrical compounds, **5ab**, **5bk** and **5kb**, showed anti-HSV-1 activity (EC_{50} = 26.1, 21.8 and 34.3 μM, respectively) and three C_S-symmetrical compounds, **5hb**, **5bk** and **5kb**, showed moderate cytotoxic activity (CC_{50} = 85.9, 26.4 and 138.0 μM, respectively). Compounds **5hb**, **5jb** and **5kb** have two isopropoxy groups on the TAZ template, and neither of the prepared TAZ derivatives **5** showed significantly higher anti-HSV-1 activity than that of the C_3-symmetrical prototype **4b**. From these modifications, we reconfirmed the importance of the presence of three isopropoxy groups on the (C_3-symmetrical) TAZ template (**4b**) for showing high anti-HSV-1 activity (EC_{50} = 1.87 μM) and low cytotoxic activity (CC_{50} = 479.8 μM) (see Table 1).[5,11] Calculated log *P* values for the compounds are also shown in Table 1. There was no distinct correlation between log *P* values and EC_{50} values or

between log *P* values and CC_{50} values among the compounds listed in Table 1.

Table 1. Anti-HSV-1 Activity (EC_{50}) and Cytotoxicity (CC_{50}) against Vero Cells of Target TAZ Derivatives (**4**, **5**) and Byproducts (**3**)

Compound		EC_{50} (μM)	CC_{50} (μM)	Log $P^{a)}$	Compound		EC_{50} (μM)	CC_{50} (μM)	Log $P^{a)}$
	**4b**$^{b)}$	1.87	479.8	3.36		**5bk**	21.8	26.4	4.94
	**4c**	>100	>200	7.21		**5kb**	34.3	133.0	4.15
	**4d**	>100	>200	5.06		**5fi**	>100	>200	7.69
	**4e**	>100	>200	4.02		**5fk**	>100	>200	5.41
	**4h**	>100	>200	7.42		**5gi**	>100	>200	9.06
	**5ab**	26.1	>200	2.71		**5gj**	>100	>200	9.06
	**5ka**	>100	>200	2.84		**5jg**	>100	>200	8.97
	**5bh**	>100	>200	6.07		**3f**	>100	>200	3.97
	**5hb**	>100	85.9	4.72		**3ak**	>100	>200	3.15
	**5bi**	>100	>200	7.22		**3bk**	>100	>200	3.8
	**5bj**	>100	>200	7.22		**3bj**	>100	>200	4.95
	**5jb**	>100	>200	5.29		**3jg**	>100	132	6.78

a) All log *P* values were calculated by using ChemDrawUltra 15.1. *b*) Data were taken from referene 5.

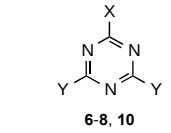
Regarding *Cs*-symmetrical molecules as shown in Table 2, many alkylamino- and alkyloxy-substituted TAZ derivatives (**7** and **8**) that have branched C3~C5 alkoxy (**b**, **d**, **f**H) or alkylamino (**p-r**H) functionalities on the TAZ template showed high levels of anti-HSV-1 activity (EC_{50} = 18.5~47.7 μM) and relatively high levels of cytotoxic activity (CC_{50} = 13.8~139.2 μM). Three *Cs*-symmetrical TAZ derivatives (**8pb**, **8qb** and **8qd**) that have the same two alkoxy and alkylamino functionalities as those of **7bp**, **7bq** and **7dq**, respectively, showed no anti-HSV-1 or cytotoxic activity (EC_{50} > 100 μM and CC_{50} > 200 μM, respectively). Compounds **7bp** and **7dq** showed no anti-HSV-1 activity (EC_{50} >100 μM) but showed a low or moderate level of cytotoxic activity (CC_{50} = 139.2 and 28.3 μM, respectively). All of these molecules (**7** and **8**) have calculated log *P* values below 5.0 (see Table 2). We consider that two *sec*-alkylamino groups as donors for hydrogen bonds on a symmetrical TAZ template contribute to the biological activity. In fact, most of the C_3-and C_S-symmetrical tri-aliphatic alkylamino-substituted TAZ derivatives (**6p**, **6q**, **6r**, **6s**, **7bq** and **7dp**), except for two compounds (**7bp** and **7dq**) that have the same alkyl moiety in alkoxy and alkylamino substituents, showed considerably high levels of anti-HSV-1 activity (EC_{50} = 5.4~45.0 μM). Among these compounds, compound **6s** showed decreased levels of cytotoxic activity (CC_{50} > 200 μM). In this series, the overall results strongly suggested that at least the presence of two hydrogen bond donor protons of *sec*-alkylamine functionality at the 2, 4 and 6 positions of the TAZ template is an important factor for expression of anti-HSV-1 activity. This consideration is supported by previous observations that most of the C_3-symmetrical TAZ derivatives that have a tri-aromatic amine and/or *tert*-amine-substituted TAZ template were almost inactive (both EC_{50} and CC_{50} values being over 100 μM).[6]

Compared with trialkoxy-substituted TAZ series such as prototype **4b**, we consider that the above-described results may indicate a different mode of antiviral action of these new tri-substituted TAZ series (such as **6**, **7** and **8**) from that of trialkoxy-substituted TAZ series.

Regarding the isolated intermediates including a chloro-substituent in the TAZ template (**3**, **9** and **10**) that are listed in Tables 1 and 2, none of these compounds showed anti-HSV-1 activity (EC_{50} > 100 μM) and only a few compounds showed a low level of cytotoxic activity (CC_{50} = 132~249 μM).

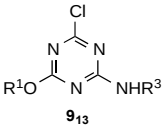
On the basis of the information obtained by the above-described structural modifications for biological activities in these tri-substituted TAZ series together with recent information on the tris(2-aminoethyl)amine (TAEA) series,[8] further molecular modifications of the highest antiviral active compound **6s** and new hybrid TAZ-TAEA-type molecules are now under investigation in order to find new promising bioactive compounds.

Table 2. Anti-HSV-1 Activity (EC_{50}), Cytotoxicity (CC_{50}) against Vero Cells, and Calculated Log *P* of Target TAZ Derivatives (**6**-**8**) and Byproducts (**9**, **10**)



6-**8**, **10**

	6_3	7_{13}	8_{31}	10_3
X	R^3NH	R^1O	R^3NH	Cl
Y	R^3NH	R^3NH	R^1O	R^3NH

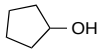


9_{13}

R^1OH
R^2OH =

bH

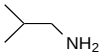
dH



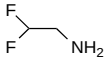
fH

R^3NH_2 =

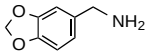
pH



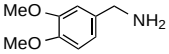
qH



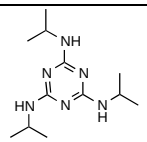
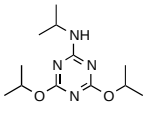
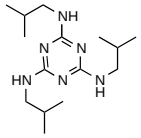
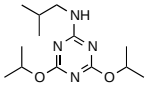
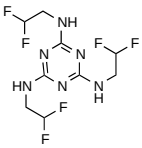
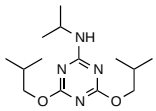
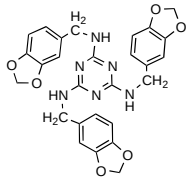
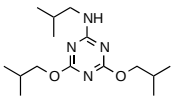
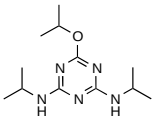
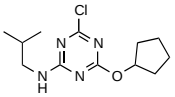
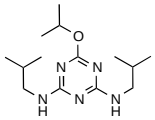
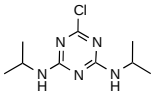
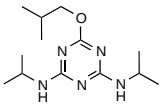
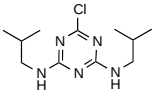
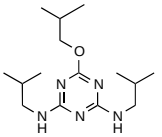
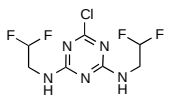
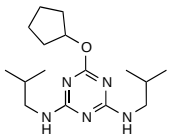
rH



sH



tH

Compound		EC_{50} (μM)	CC_{50} (μM)	Log *P*[a]	Compound		EC_{50} (μM)	CC_{50} (μM)	Log *P*[a]
	**6p**	27.3	80.4	2.23		**8pb**	>100	>200	2.99
	**6q**	29.8	10.9	3.93		**8qb**	>100	>200	3.55
	**6r**	24.4	>200	1.23		**8pd**	47.7	57.2	4.12
	**6s**	5.4	>200	4.8		**8qd**	>100	>200	4.69
	**7bp**	>100	139.2	2.61		**9fq**	>100	249	3.68
	**7bq**	46.3	78.3	3.74		**10p**	>100	>200	2.26
	**7dp**	45.0	22.2	3.18		**10q**	>100	>200	3.4
	**7dq**	>100	28.3	4.31		**10r**	>100	142.4	1.6
	**7fq**	18.5	13.8	4.22	Aciclovir[b]		1.1	>444	-0.76

a) All log *P* values were calculated by using ChemDrawUltra 15.1. *b*) Data were taken from reference 19.

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. MS/MS analysis of compound **4c** was conducted with an API4000 Qtrap tandem mass spectrometer (AB Sciex, Concord, Ontario, Canada) with an ESI interface. ^{1}H- and ^{13}C-NMR spectra were obtained by JEOL JNM A-500 (**2b**, **2h**, **2j**, **3f**, **3j**, **3ak**, **3bj**, **3bk**, **3jg**, **4d**, **4e**, **4h**, and **5** except for **5hb**) and ECG600R (**2d**, **2f**, **3b**, **3d**, **4c**, **5hb**, **6-10**). 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 abbreviations qu=quintet, dd=double doublets, dt=double triplets, and dm=double multiplets are used for the multiplicity of ^{1}H-NMR data. The signal assignments were confirmed by two-dimensional (2D)-NMR analyses: ^{1}H-^{1}H 2D correlation spectroscopy (COSY), ^{1}H-^{13}C heteronuclear multiple-quantum coherence (HMQC), and ^{1}H-^{13}C heteronuclear multiple-bond connectivity (HMBC). Microanalyses were performed with a Yanaco MT-6 CHN corder. Routine monitoring of reactions was carried out using precoated Kieselgel 60F_{254} plates (E. Merck). Microwave irradiation experiments were carried out in a CEM Discover Focused Microwave System. Visualization was accomplished with UV light, iodine, ninhydrin, or phosphomolybdic acid. 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 and/or RI detector. Commercially available starting materials were used without further purification, and dry solvents were used in all reactions.

General Procedure for *C*$_3$-Symmetrical Trialkoxy-substituted TAZ derivatives (4) (Table S1): Example: Synthesis of 2,4,6-Tris[(1,1,1,3,3,3-hexafluoropropan-2-yl)oxy]-1,3,5-triazine (4c):

(Step 1): To a solution of hexafluoroisopropyl alcohol (**c**H, 2.69 g, 1.60 mmol) in THF (10 mL) was added NaH (55% in mineral oil, 384 mg, 16.0 mmol) at room temperature under a N_2 atmosphere. A suspension of sodium *n*-heptyloxide was prepared by stirring at room temperature for 15 min and then refluxing for 1 h.

(Step 2): After cooling to room temperature, compound **1** (922 mg, 5.00 mmol) was added and stirred for 15 min at room temperature under a N_2 atmosphere. Then the reaction mixture was refluxed for 1 h. After cooling to room temperature, saturated aq. ammonium chloride (10 mL) was added to the resulting mixture, and the mixture was extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was washed with brine (10 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residue was recrystallized

by *n*-hexane to give **4c** (2.11 g, 3.65 mmol, 73%) as colorless needles. Mp 87-89 ºC (from *n*-hexane). IR (KBr) cm^{-1}: 1586 (C=N), 1388 (C-F), 1195, 1141, 1107 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 6.25 (3H, heptet, *J* = 9.2 Hz, H1'). ^{13}C-NMR ($CDCl_3$) δ: 70.69 (qu, *J* = 35.4 Hz, C1'), 119.99 (q, *J* = 282.7 Hz, C2', 3'), 172.23 (C2, 4, 6). Negative-ion EPI-MS *m/z*: 578.2. Anal. Calcd for $C_{12}H_3F_{18}N_3O_3$•$0.7H_2O$: C, 24.36; H, 0.75; N, 7.10. Found: C, 24.28; H, 0.66; N, 7.27. [299929-60-5]

2,4,6-Tris(2-methylpropoxy)-1,3,5-triazine (4d): Colorless crystals. Mp 34-38 ºC (from *i*-PrOH). IR (KBr) cm^{-1}: 1559 (C=N), 1147, 1119 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.01 (18H, d, *J* = 6.7 Hz, H1', 4'), 2.11 (3H, qu, *J* = 6.7 Hz, H2'), 4.16 (6H, d, *J* = 6.7 Hz, H3'). ^{13}C-NMR ($CDCl_3$) δ: 19.10 (C3', 4'), 27.77 (C2'), 74.40 (C1'), 173.25 (C2, 4, 6). Positive-ion FAB-MS *m/z*: 298 $(M+H)^+$. HR-FAB-MS *m/z*: 298.2121 (Calcd for $C_{15}H_{28}N_3O_3$: 298.2131). Anal. Calcd for $C_{15}H_{27}N_3O_3$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.53; H, 9.35; N, 13.96. [30895-05-7]

2,4,6-Tris(tricyclo[3.3.1.13,7]dec-2-yloxy)-1,3,5-triazine (4h): A white powder. Mp > 300 ºC (from CH_2Cl_2). IR (KBr) cm^{-1}: 1567, 1548 (C=N), 1140 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.56 (6H, d, *J* = 12.8 Hz, H4', 9'), 1.76 (6H, br s, H6'), 1.80 (6H, d, *J* = 12.5 Hz, H8', 10'), 1.84-1.93 (12H, m, H5', 7', 8', 10'), 2.19 (6H, br s, H1', 3'), 2.20 (6H, d, *J* = 12.8 Hz, H4', 9'), 5.16 (3H, br s, H2'). ^{13}C-NMR ($CDCl_3$) δ: 27.15 (C5' or 7'), 27.24 (C7' or 5'), 31.58 (C1', 3' or 4', 9'), 31.79 (C4', 9' or 1', 3'), 36.46 (C8', 10'), 37.48 (C6'), 80.50 (C2'), 172.80 (C2, 4, 6). Positive-ion FAB-MS *m/z*: 532 $(M+H)^+$. HR-FAB-MS *m/z*: 532.3531 (Calcd for $C_{33}H_{46}N_3O_3$: 532.3539). Anal. Calcd for $C_{33}H_{45}N_3O_3$•$1.5H_2O$: C, 70.94; H, 8.66; N, 7.52. Found: C, 70.91; H, 8.42; N, 7.44.

Synthesis of 2,4,6-Tris(1,1-dimethylethoxy)-1,3,5-triazine (4e): To a solution of TCTAZ (**1**, 922 mg, 5.0 mmol) in THF (30 mL), potassium *t*-butoxide (1 M THF solution, 15 mL, 15.0 mmol) was added at 0 ºC under a N_2 atmosphere and the reaction mixture was continuously stirred for 10 min at 0 ºC and then for another 1 h at room temperature. After addition of brine (70 mL), the mixture was extracted with $CHCl_3$ (3×70 mL) and dried over $MgSO_4$. After evaporation of the solvent, the obtained crude product **4e** (1.08 g, 3.6 mmol, 72%) was recrystallized from EtOH to give colorless crystals. Mp 130-135 ºC (from EtOH). IR (KBr) cm^{-1}: 1562 (C=N), 1164, 1130 (C-O of ether). ^{1}H-NMR ($CDCl_3$) δ: 1.60 (27H, s, H1', 3', 4'). ^{13}C-NMR ($CDCl_3$) δ: 28.38 (C1', 3', 4'), 81.84 (C2'), 171.87 (C2, 4, 6). Positive-ion FAB-MS *m/z*: 298 $(M+H)^+$. HR-FAB-MS *m/z*: 298.2130 (Calcd for $C_{15}H_{28}N_3O_3$: 298.2131). Anal. Calcd for $C_{15}H_{27}N_3O_3$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.50; H, 9.28; N, 14.09. [500334-23-6]

General Procedure for *C*$_3$-Symmetrical Trialkyamino-substituted TAZ derivatives (6) (Table S2): Example: Synthesis of *N*^{2},*N*^{4},*N*^{6}-Triisobutyl-1,3,5-triazine-2,4,6-triamine (6q):

(MW Method): To a solution of TCTAZ (**1**, 277 mg, 1.50 mmol) in dioxane (2 mL), a solution of isobutylamine **q**H (1.10 g, 15.0 mmol) in dioxane (1 mL) was added dropwise at 0 ºC, and then the mixture was continuously stirred for 25 min at room temperature and then for another 1 h at room

temperature. Then the mixture was subjected to microwave irradiation (MW) at 100 ºC (100 W) for 25 min with stirring. After addition of water (30 mL), the mixture was extracted with EtOAc (2×25 mL). The combined organic layer was dried over $MgSO_4$. After evaporation of the solvent, the crude compound **6q** (405 mg, 1.50 mmol, 92%) was obtained as a white solid. An analytically pure sample was obtained as colorless crystals after recrystallization from EtOH.

(Reflux Method): To a solution of **1** (371 mg, 2.00 mmol) in THF (20 mL) was added a mixture of **q**H (483 mg, 6.60 mmol) and diisopropylamine (DIPA) to give a white suspension. After reflux for 22 h, water (25 mL) and EtOAc (40 mL) were added to the mixture. The organic layer was separated 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 compounds **10q** (65.3 mg, 0.253 mmol, 13%) and **6q** (263 mg, 0.891 mmol, 45%), both as a white solid. An analytically pure sample of **10q** was obtained as colorless crystals after recrystallization from *i*-PrOH.

6q: Mp 59-62 ºC (from EtOH). IR (KBr) cm^{-1}: 3309 (NH), 1559, 1532, 1508 (C=N), 1351 (C-N). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (18H, d, *J* = 6.9 Hz, H3', 4'), 1.82 (3H, br s, H2'), 2.13 (1.5H, br s NH), 3.18 (6H, br s, H1'), 4.92 (1.5H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 20.21 (C3', 4'), 28.63 (C2'), 48.19 (C1'), 166.33 (C2, 4, 6). Positive-ion FAB-MS *m/z*: 295 $(M+H)^+$. HR-FAB-MS *m/z*: 295.2610 (Calcd for $C_{15}H_{31}N_6$: 295.2618). Anal. Calcd for $C_{15}H_{30}N_6$•0.15H_2O: C, 60.63; H, 10.28; N, 28.28. Found: C, 60.58; H, 10.42; N, 28.19. [656822-23-0]

6-Chloro-*N*^{2},*N*^{4}-diisobutyl-1,3,5-triazine-2,4-diamine (10q): Mp 208-210 ºC (from *i*-PrOH). IR (KBr) cm^{-1}: 3448 (NH), 1635, 1560 (C=N), 1101 (C-N), 800 (C-Cl). ^{1}H-NMR (DMSO-d_6) δ: 0.85 (*ca*. 4H, d, *J* = 6.2 Hz, H3', 4'), 0.86* (*ca*. 8H, d, *J* = 6.2 Hz, H3', 4'), 1.75-1.85 (2H, m, H2'), 2.99-3.07 (4H, m, H1'), 7.52 (0.2H, t, *J* = 5.5 Hz, NH), 7.71-7.76 (0.8H, m, NH), 7.88* (1H, t, *J* = 5.5 Hz, NH). ^{13}C-NMR (DMSO-d_6) δ: 20.04, 20.09* (C3', 4'), 27.46, 27.75, 27.83* (C2'), 47.69, 47.75* (C1'), 165.17, 165.46*, 165.74 (C2, 4), 167.52*, 168.03 (C6). (The observed signals of the predominant tautomer are asterisked.) Positive-ion FAB-MS *m/z*: 258 $(M+H)^+$. HR-FAB-MS *m/z*: 258.1474 (Calcd for $C_{11}H_{21}ClN_5$: 258.1485). Anal. Calcd for $C_{11}H_{20}ClN_5$: C, 51.26; H, 7.82; N, 27.17. Found: C, 51.32; H, 8.08; N, 27.19.

***N*^{2},*N*^{4},*N*^{6}-Triisopropyl-1,3,5-triazine-2,4,6-triamine (6p):** Colorless crystals. Mp 129-130 ºC (from EtCN). IR (KBr) cm^{-1}: 3445 (NH), 1584, 1506 (C=N), 1192 (C-N). ^{1}H-NMR ($CDCl_3$) δ: 1.17 (18H, d, *J* = 6.2 Hz, H2', 3'), 2.23 (1.5H, br s, NH), 4.11 (3H, br s, H1'), 4.67 (1.5H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 23.05 (C2', 3'), 42.02 (C1'), 165.43 (C2, 4, 6). Positive-ion FAB-MS *m/z*: 253 $(M+H)^+$. HR-FAB-MS *m/z*: 253.2139 (Calcd for $C_{12}H_{25}N_6$: 253.2141). Anal. Calcd for $C_{12}H_{24}N_6$: C, 57.11; H, 9.59; N, 33.30. Found: C, 56.86, H, 9.58; N, 33.14. [5465-03-2]

6-Chloro-*N*^{2},*N*^{4}-diisopropyl-1,3,5-triazine-2,4-diamine (10p): Colorless solid. Mp 179-184 ºC. IR (KBr) cm^{-1}: 1620, 1579, 1550 (C=N), 1169, 1130 (C-N), 805 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ: 1.09 (*ca.* 5.3H,

d, *J* = 6.2 Hz, H2', H3'), 1.12* (*ca.* 6.7H, d, *J* = 6.9 Hz, H2', 3'), 3.95-4.04* (2H, br s, H2'), 7.53 (*ca.* 0.9H, d, *J* = 8.2 Hz, NH), 7.65* (*ca.* 0.56H, d, *J* = 7.5 Hz, NH). ^{13}C-NMR ($CDCl_3$) δ: 21.89* (C2', 3'), 22.11 (C2'&3' or C2"&3"), 22.24 (C2"&3" or C2'&3'), 41.51 (C1' or C1"), 41.73 (C1" or C1'), 41.94* (C1'), 164.06 (C2), 164.42* (C2, 4), 164.67 (C4), 167.48* (C6), 168.07 (C6). (In the ^{13}C-NMR spectrum of compound **10p**, signals that appeared are fully consistent with the tautomeric mixture of two isomers shown below (**T₁** and **T₂**). The signals assignable to the predominant tautomer **T₁** are asterisked.)[20] Positive-ion FAB-MS *m/z*: 230 $(M+H)^+$. HR-FAB-MS *m/z*: 230.1167 (Calcd for $C_9H_{17}ClN_5$: 230.1172). Anal. Calcd for $C_9H_{16}ClN_5$: C, 47.06; H, 7.02; N, 30.49. Found: C, 47.15; H, 6.97; N, 30.22. [139-40-2]

***N*²,*N*⁴,*N*⁶-Tris(2,2-difluoroethyl)-1,3,5-triazine-2,4,6-triamine (6r):** Pale yellow solid. Mp 73 °C. IR (KBr) cm^{-1}: 3463 (NH), 1619, 1582, 1542, 1513 (C=N), 1117, 1046 (C-N), 810 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ: 3.74 (6H, br s, H1'), [5.24 (1H), 5.62 (2H)] (br s, NH), 5.89 (3H, tt, *J* = 56.5, 4.1 Hz, H2'). ^{13}C-NMR ($CDCl_3$) δ: 43.06 (t, *J* = 26.8 Hz, C1'), 114.00 (t, *J* = 241.3 Hz, C2'), 166.19 (C2, 4, 6). Positive-ion FAB-MS *m/z*: 319 $(M+H)^+$. HR-FAB-MS *m/z*: 319.1104 (Calcd for $C_9H_{13}F_6N_6$: 319.1106). Anal. Calcd for $C_9H_{12}F_6N_6$: C, 33.97; H, 3.80; N, 26.41. Found: C, 33.93; H, 3.70; N, 26.27.

6-Chloro-*N*²-(2,2-difluoroethyl)-*N*⁴-(difluoromethyl)-1,3,5-triazine-2,4-diamine (10r): Colorless needles. Mp 189-190 °C (from EtCN). IR (KBr) cm^{-1}: 3253, 3115 (NH), 1636, 1557 (C=N), 1111, 1182, 1064 (C-N), 801 (C-Cl). ^{1}H-NMR (DMSO-d_6) δ: 3.59-3.71 (4H, m, H1'), [6.86 (tm, *J* = 56.1 Hz), 6.12 (tm, *J* = 56.1 Hz), 6.13* (tt, *J* = 56.1, 4.2 Hz)] (2H, H2'), [8.07 (0.15H, t, *J* = 6.2 Hz), 8.24* (0.85H, q, *J* = 6.2 Hz), 8.34 (1H, t, *J* = 6.2 Hz)] (NH). (The observed ^{1}H-signals assignable to the predominant tautomer are asterisked.) ^{13}C-NMR (DMSO-d_6) δ: 42.65 (t, *J* = 27.4 Hz, C1'), 114.33 (t, *J* = 239.9 Hz, C2'), 165.79 (C2, 4), 168.20 (C6). (Signals for only the predominant tautomer are shown.) Positive-ion FAB-MS *m/z*: 274 $(M+H)^+$. HR-FAB-MS *m/z*: 274.0487 (Calcd for $C_7H_9ClF_4N_5$: 274.0483). Anal. Calcd for $C_7H_8ClF_4N_5$: C, 30.73; H, 2.95; N, 25.60. Found: C, 30.86; H, 3.23; N, 25.52.

***N*²,*N*⁴,*N*⁶-Tris(benzo[*d*][1,3]dioxol-5-ylmethyl)-1,3,5-triazine-2,4,6-triamine (6s):** Colorless crystals. Mp 128 °C (from MeCN). IR (ATR) cm^{-1}: 3451, 3355, 3277 (NH), 1522, 1487, 1471 (C=N), 1245, 1215, 1036 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.76 (3H, br s, NH), 4.45 (6H, br s, $ArCH_2$), 5.91 (6H, s, H2), 6.69-6.74 (6H, m, H6, 7), 6.78 (3H, br s, H4). ^{13}C-NMR ($CDCl_3$) δ: 44.43 ($ArCH_2$), 100.92 (C2'), 108.12 (C7'), 108.20 (C4'), 120.63 (C6'), 133.39 (C5'), 146.64 (C3a'), 147.74 (C7a'), 166.14 (C2, 4, 6). Positive-ion FAB-MS *m/z*: 529 $(M+H)^+$. HR-FAB-MS *m/z*: 529.1843 (Calcd for $C_{27}H_{25}N_6O_6$: 529.1836). Anal. Calcd for $C_{27}H_{24}N_6O_6$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.36; H, 4.61; N, 15.94.

General Procedure for Intermediate Monoalkoxy-dichloro-TAZ derivatives (2) (Table S3): Example: Synthesis of 2,4-Dichloro-6-(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)-1,3,5-triazine (2h): To a solution of **1** (1.84 g, 10.0 mmol) in THF (25 mL), 2-adamantanol **h**H (1.83 g, 12.0 mmol) and collidine (1.45 g, 12.0 mmol) were added at room temperature under an Ar atmosphere. The mixture was stirring

for 2.5 h to give an orange suspension. After filtration of white solids (collidine•HCl salt) and evaporation of the solvent, the residue was purified by flash chromatography (CH_2Cl_2 : *n*-hexane = 30 : 70 → 40 : 60) to give compound **2h** (1.88 g, 6.26 mmol, 63%) as a white solid. Mp *ca.* 280 °C (decomp). IR (KBr) cm^{-1}: 1556, 1497 (C=N), 1249, 1046 (C-O), 849, 803 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ: 1.62 (2H, dm, *J* = 12.8 Hz, H4', 9'), 1.78 (2H, br s, H6'), 1.84 (2H, dm, *J* = 12.5 Hz, H8', 10'), 1.88-1.96 (4H, m, H5', 7', 8',10'), 2.15 (2H, dm, *J* = 12.8 Hz, H4', 9') 2.20 (2H, br s, H1', 3'), 5.30 (1H, br t, *J* = 3.4 Hz, H2'). ^{13}C-NMR ($CDCl_3$) δ: 26.86 (C5' or 7'), 27.03 (C7' or 5'), 31.45 (C1', 3'), 31.55 (C4', 9'), 36.23 (C8', 10'), 37.21 (C6'), 83.95 (C2'), 170.57 (C6), 172.50 (C2, 4). Positive-ion FAB-MS *m/z*: 300 $(M+H)^+$. HR-FAB-MS *m/z*: 300.0697 (Calcd for $C_{13}H_{16}Cl_2N_3O$: 300.0670).

2,4-Dichloro-6-(1-methylethoxy)-1,3,5-triazine (2b):[5,11] IR (NaCl) cm^{-1}: 2987 (CH), 1542, 1500 (C=N), 1100, 1036 (C-O), 861, 807 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ: 1.44 (6H, d, *J* = 6.1 Hz, C1', 3'), 5.41 (1H, qu, *J* = 6.1 Hz, C2'). ^{13}C-NMR ($CDCl_3$) δ: 21.42 (C1', 3'), 74.90 (C2'), 170.51 (C6), 172.47 (C2, 4). The positive FAB mass spectra of this compound showed no significant molecular ion for the determination of its chemical formula, indicating instability of the corresponding molecular ion in the mass range as well as that of compound **2d**. [6684-27-1]

2,4-Dichloro-6-isobutoxy-1,3,5-triazine (2d): Pale yellow oil. IR (NaCl) cm^{-1}: 1542, 1509 (C=N), 1047 (C-O), 849 (C-Cl).^{1}H-NMR ($CDCl_3$) δ: 1.05 (6H, d, *J* = 6.9 Hz, H3', 4'), 2.16 (1H, qu, *J* = 6.9 Hz, H2'), 4.28 (2H, d, *J* = 6.2 Hz, H1').^{13}C-NMR($CDCl_3$) δ: 18.71 (C3', 4'), 27.53 (C2'), 76.29 (C1'), 171.02 (C6), 172.32 (C2, 4). The positive FAB mass spectra of this compound showed no significant molecular ion for the determination of its chemical formula, indicating instability of the corresponding molecular ion in the mass range as well as that of compound **2b**. [30886-23-8]

2,4-Dichloro-6-(cyclopentyloxy)-1,3,5-triazine (2f): Pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.63-1.74 (2H, m, H3', 4'), 1.80-1.95 (4H, m, H3', 4', 2', 5'), 1.97-2.05 (2H, m, H2', 5'), 5.56 (1H, heptet, *J* = 3.1 Hz, H1').^{13}C-NMR($CDCl_3$) δ: 23.57 (C3', 4'), 32.56 (C2', 5'), 84.01 (C1'), 170.65 (C6), 172.34 (C2, 4). Positive-ion FAB-MS *m/z*: 234 $(M+H)^+$. HR-FAB-MS *m/z*: 234.0208 (Calcd for $C_8H_{10}Cl_2N_3O$: 234.0201). [107392-86-9]

2,4-Dichloro-6-(heptyloxy)-1,3,5-triazine (2g): See reference 6. [107392-85-8]

4,6-Dichloro-2-[4-(trifluoromethyl)phenoxy]-1,3,5-triazine (2j): White solid. IR (KBr) cm^{-1}: 1542, 1508 (C=N), 1325 (CF_3), 1204, 1174 (C-O), 800 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ: 7.32 (2H, d, *J* = 8.4 Hz, H2', 6'), 7.75 (2H, d, *J* = 8.4 Hz, H3', 5'). ^{13}C-NMR ($CDCl_3$) δ: 121.71 (C2', 6'), 123.62 (q, *J* = 272.1 Hz, CF_3), 127.39 (q, *J* = 4.1 Hz, C3', 5'), 129.42 (q, *J* = 33.1 Hz, C4'), 153.30 (C1'), 170.71 (C2), 173.35 (C4, 6). Positive-ion FAB-MS *m/z*: 310 $(M+H)^+$. HR-FAB-MS *m/z*: 309.9762 (Calcd for $C_{10}H_5Cl_2F_3N_3O$: 309.9770).

6-Chloro-2,4-bis[4-(trifluoromethyl)phenoxy]-1,3,5-triazine (3j): Colorless needles. IR (KBr) cm^{-1}:

1552 (C=N), 1320 (CF_3), 1122, 1109 (C-O), 836, 812 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ: 7.27 (4H, d, *J* = 8.4 Hz, H2', 6'), 7.68 (4H, d, *J* = 8.4 Hz, H3', 5'). ^{13}C-NMR ($CDCl_3$) δ: 121.83 (C2', 6'), 123.63 (q, *J* = 272.1 Hz, CF_3), 127.13 (q, *J* = 4.1 Hz, C3', 5'), 129.12 (q, *J* = 33.1 Hz, C4'), 153.51 (C1'), 172.04 (C2, 4), 174.20 (C6). Positive-ion FAB-MS *m/z*: 436 $(M+H)^+$. HR-FAB-MS *m/z*: 436.0285 (Calcd for $C_{17}H_9ClF_6N_3O_2$: 436.0287). [112748-53-5]

General Procedure for Intermediate Dialkoxy-monochloro-TAZ derivatives (3) (Table S3): Example: Synthesis of 2-Chloro-4,6-bis(1-methylethoxy)-1,3,5-triazine (3b):[5]

(Step 1): To a solution of 2-propanol (**b**H, 1.80 g, 30.0 mmol) in dry THF (30 mL) was added NaH (55% in mineral oil, 1.96 g, 45.0 mmol) at 0 ºC under an Ar atmosphere. A suspension of sodium *i*-propyloxide was prepared by stirring at 0 ºC for 1.5 h.

(Step 2): After cooling to -77 ºC, compound **1** (2.77 g, 15.0 mmol) was added and stirred for 10 min at -77 ºC under an Ar atmosphere. Then the reaction mixture was allowed to stand at room temperature. Saturated aq. ammonium chloride (30 mL) was added to the resulting mixture, and the mixture was extracted with EtOAc (3×50 mL). The combined organic layer was washed with brine (30 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash chromatography (*n*-hexane : EtOAc = 95 : 5) to give compound **3b** (2.15 g, 9.28 mmol, 62%) as a colorless oil. IR (NaCl neat) cm^{-1}: 1558 (C=N), 1096 (C-O), 814 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ: 1.40 (12H, d, *J* = 6.1 Hz, H1', 3'), 5.35 (2H, qu, *J* = 6.1 Hz, H 2'). ^{13}C-NMR ($CDCl_3$) δ: 21.59 (C1', 3'), 71.94 (C2'), 171.60 (C4, 6), 172.58 (C2). Positive ion FAB-MS *m/z*: 232 $(M+H)^+$. HR-FAB-MS *m/z*: 232.0856 (Calcd for $C_9H_{15}ClN_3O_2$: 232.0853). [30894-76-9]

2-Chloro-4,6-diisobutoxy-1,3,5-triazine (3d): Pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (12H, d, *J* = 6.9 Hz, C3', 4'), 2.12 (2H, qu, *J* = 6.9 Hz, C2'), 4.16 (4H, d, *J* = 6.9 Hz, C1'). ^{13}C-NMR ($CDCl_3$) δ: 19.12 (C3', 4'), 27.73 (C2'), 74.42 (C1'), 172.48 (C2), 173.17 (C4, 6). Positive-ion FAB-MS *m/z*: 260 $(M+H)^+$. HR-FAB-MS *m/z*: 260.1159 (Calcd for $C_{11}H_{19}ClN_3O_2$: 260.1166).

2-Chloro-4,6-bis(cyclopentyloxy)-1,3,5-triazine (3f): Pale yellow transparent needles. Mp 46-49 ºC. IR (KBr) cm^{-1}: 1550 (C=N), 1296, 1110 (C-O), 807 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ: 1.60-1.69 (4H, m, H3', 4'), 1.78-1.92 (8H, m, H2', 3', 4', 5'), 1.93-2.02 (4H, m, H2', 5'), 5.49 (2H, heptet, *J* = 3.1 Hz, H1'). ^{13}C-NMR ($CDCl_3$) δ: 23.68 (C3', 4'), 32.64 (C2', 5'), 82.17 (C1'), 171.67 (C4, 6), 172.39 (C2). Positive-ion FAB-MS *m/z*: 284 $(M+H)^+$. HR-FAB-MS *m/z*: 284.1147 (Calcd for $C_{13}H_{19}ClN_3O_2$: 284.1166). Anal. Calcd for $C_{13}H_{18}ClN_3O_2$: C, 55.03; H, 6.39; N, 14.81. Found: C, 55.04; H, 6.42; N, 14.89. [852671-76-2]

General Procedure for *Cs*-Symmetrical Trialkoxy-substituted TAZ derivatives (5) (Table S4): Example 1 (using NaH): Synthesis of 2,4-Bis(1-methylethoxy)-6-(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)-1,3,5-triazine (5hb):

(Step 1): To a solution of 2-propanol (**b**H, 451 mg, 7.50 mmol) in THF (10 mL) was added NaH (55% in mineral oil, 275 mg, 6.30 mmol) at room temperature under an Ar atmosphere. A suspension of sodium 2-propyloxide was prepared by stirring at room temperature for 10 min and then refluxing for 30 min.
(Step 2): After cooling to room temperature, a solution of compound **2h** (901 mg, 3.00 mmol) in THF (10 mL) was added and stirred for 15 min at room temperature under a N_2 atmosphere. Then the reaction mixture was refluxed for 2 h. After cooling to room temperature, saturated aq. ammonium chloride (10 mL) was added to the resulting mixture, and the mixture was extracted with EtOAc (3×20 mL). The combined organic layer was washed with brine (10 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash chromatography (CH_2Cl_2 : *n*-hexane = 20 : 80 → 30 : 70) to give **5hb** (589 mg, 1.70 mmol, 57%) as a colorless solid. Mp 119-121 ºC. IR (KBr) cm^{-1}: 1570 (C=N), 1141, 1096 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.38 (12H, d, *J* = 6.2 Hz, H1'', 3''), 1.56 (2H, d, *J* = 13.1 Hz, H4', 9'), 1.75 (2H, br s, H6'), 1.82 (2H, br d, *J* = 12.4 Hz, H8', 10), 1.87 (2H, br s, H5', 7'), 1.88 (2H, br d, *J* = 12.4 Hz, H8', 10'), 2.18 (2H, br s, H1', 3'), 2.19 (2H, br d, *J* = 13.1 Hz, H4', 9'), 5.21 (1H, br s, H2'), 5.33 (2H, qu, *J* = 6.2 Hz, H2"). ^{13}C-NMR ($CDCl_3$) δ: 21.78 (C1'', 3''), 27.02 (C5' or 7'), 27.17 (C7' or 5'), 31.56 (C4', 9'), 31.68 (C1', 3'), 36.28 (C8', 10'), 37.40 (C6'), 71.24 (C2''), 80.25 (C2'), 172.61 (C4, 6), 172.67 (C2). Positive-ion FAB-MS *m/z*: 348 $(M+H)^+$. HR-FAB-MS *m/z*: 348.2291 (Calcd for $C_{19}H_{30}N_3O_3$: 348.2287). Anal. Calcd for $C_{19}H_{29}N_3O_3$: C, 65.68; H, 8.41; N, 12.09. Found: C, 65.13; H, 8.58; N, 12.28.

2,4-Di(1-methylethoxy)-6-methoxy-1,3,5-triazine (5ab): Colorless solid. Mp 70-71 ºC. IR (KBr) cm^{-1}: 1568 (C=N), 1148, 1096 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.39 (12H, d, *J* = 6.1 Hz, H1', 3'), 4.00 (3H, s, OCH_3), 5.36 (2H, qu, *J* = 6.1 Hz, H2'). ^{13}C-NMR ($CDCl_3$) δ: 21.81 (C1', 3'), 55.16 (OCH_3"), 71.65 (C2'), 172.71 (C2, 4), 173.64 (C6). Positive-ion FAB-MS *m/z*: 228 $(M+H)^+$. HR-FAB-MS *m/z*: 228.1346 (Calcd for $C_{10}H_{18}N_3O_3$: 228.1348). Anal. Calcd for $C_{10}H_{17}N_3O_3$: C, 52.85; H, 7.54; N, 18.49. Found: C, 52.85; H, 7.67; N, 18.31.

2-(1-Methylethoxy)-4,6-bis(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)-1,3,5-triazine (5bh): Colorless crystals. Mp 233-238 ºC (from *i*-Pr_2O-$CHCl_3$). IR (KBr) cm^{-1}: 1568 (C=N), 1139 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.37 (6H, d, *J* = 6.4 Hz, H1", 3"), 1.56 (4H, d m, *J* = 12.5 Hz, H4', 9'), 1.76 (4H, br s, H6'), 1.81 (4H, br d, *J* = 12.2 Hz, H8', 10'), 1.85-1.93 (12H, m, H5', 7', 8', 10'), 2.18 (4H, br s, H1', 3'), 2.20 (4H, br d, *J* = 12.5 Hz, H4', 9'), 5.18 (2H, br s, H2'), 5.30 (1H, qu, *J* = 6.4 Hz, H2"). ^{13}C-NMR ($CDCl_3$) δ: 21.80 (C1", 3"), 27.14 (C5'or 7'), 27.25 (C7'or 5'), 31.60 (C4', 9'), 31.79 (C1', 3'), 36.42 (C8', 10'), 37.48 (C6'), 71.23 (C2"), 80.41 (C2'), 172.75 (C2), 172.77 (C4, 6). Positive-ion FAB-MS *m/z*: 440 $(M+H)^+$. HR-FAB-MS *m/z*: 440.2902 (Calcd for $C_{26}H_{38}N_3O_3$: 440.2913). Anal. Calcd for $C_{26}H_{37}N_3O_3$•0.3H_2O: C, 70.18; H, 8.52; N, 9.44. Found: C, 70.21; H, 8.58; N, 9.20.

4,6-Bis(1-heptyloxy)-2-[4-(trifluoromethyl)phenoxy]-1,3,5-triazine (5jg): Colorless oil. IR (KBr) cm^{-1}:

1578 (C=N), 1324 (C-F), 1129, 1065 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (6H, t, *J* = 7.0 Hz, H7''), 1.24-1.35 (12H, m, H4'', 5'', 6''), 1.35-1.44 (4H, m, H3''), 1.76 (4H, q, *J* = 7.1 Hz, H2''), 4.35 (4H, t, *J* = 6.7 Hz, H1''), 7.31 (2H, d, *J* = 8.4 Hz, H2', 6'), 7.67 (2H, d, *J* = 8.4 Hz, H3', 5'). ^{13}C-NMR ($CDCl_3$) δ: 13.98 (C7''), 22.52 (C6''), 25.69 (C3''), 28.54 (C2"), 28.87 (C4''), 31.67 (C5''), 68.96 (C1''), 122.13 (C2', 6'), 123.88 (q, *J* = 272.1 Hz, CF_3), 126.85 (q, *J* = 4.1 Hz, C3', 5'), 128.16 (q, *J* = 32.8 Hz, C4'), 154.30 (C1'), 172.70 (C2), 173.49 (C4, 6). Positive-ion FAB-MS *m/z*: 470 $(M+H)^+$. HR-FAB-MS *m/z*: 470.2632 (Calcd for $C_{24}H_{35}F_3N_3O_3$: 470.2631). Anal. Calcd for $C_{24}H_{34}F_3N_3O_3$: C, 61.39; H, 7.30; N, 8.95. Found: C, 61.17; H, 7.45; N, 8.84.

General Procedure for *Cs*-Symmetrical Trialkoxy-substituted TAZ derivatives (5) (Table S4): Example 2 (using collidine by MW): Synthesis of 2-Isopropoxy-4,6-bis[4-(trifluoromethyl)-phenoxy]-1,3,5-triazine (5bj): To a solution of compound **2b** (624 mg, 2.00 mmol) in dioxane (5 mL), 4-(trifuluoromethyl)phenol (**j**H, 972 mg, 6.00 mmol) and collidine (727 mg, 6.00 mmol) were added at room temperature. Then the mixture was subjected to MW at 160 ºC (300 W) for 40 min with stirring. After removal of white solids (collidine•HCl salt) by filtration, the solvent was evaporated. The residue was purified by flash chromatography (*n*-hexane : EtOAc = 95 : 5 → 90 : 10) to obtain compound **5bj** (461 mg, 1.00 mmol, 50%) and **3bj** (140 mg, 0.420 mmol, 21%), both as colorless solids. Mp 125-126 ºC. IR (KBr) cm^{-1}: 1577 (C=N of either), 1324 (CF_3), 1126, 1065 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.33 (6H, d, *J* = 6.1 Hz, H1', 3'), 5.19 (1H, qu, *J* = 6.1 Hz, H2'), 7.28 (4H, d, *J* = 8.4 Hz, H2'', 6''), 7.65 (4H, d, *J* = 8.4 Hz, H3'', 5''). ^{13}C-NMR ($CDCl_3$) δ: 21.45 (C1', 3'), 73.26 (C2'), 122.04 (C2'', 6''), 123.75 (q, *J* = 272.1 Hz, CF_3), 126.48 (q, *J* = 4.1 Hz, C3'', 5''), 128.41 (q, *J* = 33.1 Hz, C4''), 158.01 (C1''), 173.03 (C4, 6), 173.17 (C2). Positive-ion FAB-MS *m/z*: 460 $(M+H)^+$. HR-FAB-MS *m/z*: 460.1115 (Calcd for $C_{20}H_{16}F_6N_3O_3$: 460.1096). Anal. Calcd for $C_{20}H_{15}F_6N_3O_3$: C, 52.30; H, 3.29; N, 9.15. Found: C, 52.30; H, 3.26; N, 9.18.

2-Chloro-4-isopropoxy-6-[4-(trifluoromethyl)phenoxy]-1,3,5-triazine (3bj): Mp 109-110 ºC. IR (KBr) cm^{-1}: 1565 (C=N), 1324 (CF_3), 1117, 1065 (C-O), 807 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ: 1.37 (6H, d, *J* = 6.4 Hz, H1', 3'), 5.27 (1H, qu, *J* = 6.4 Hz, H2'), 7.31 (2H, d, *J* = 8.2 Hz, H2'', 6''), 7.71 (2H, d, *J* = 8.2 Hz, H3'', 5''). ^{13}C-NMR ($CDCl_3$) δ: 21.47 (C1', 3'), 74.06 (C2'), 121.95 (C2'', 6''), 123.77 (q, *J* = 272.1 Hz, CF_3), 127.10 (q, *J* = 4.1 Hz, C3'', 5''), 128.75 (q, *J* = 33.1 Hz, C4"), 153.81 (C1''), 171.77 (C4 or C6), 171.87 (C6 or C4), 173.37 (C2). Positive-ion FAB-MS *m/z*: 334 ($M+H^+$). HR-FAB-MS *m/z*: 334.0572 (Calcd for $C_{13}H_{12}ClF_3N_3O_2$: 334.0570). Anal. Calcd for $C_{13}H_{11}ClF_3N_3O_2$: C, 46.79; H, 3.32; N, 12.59. Found: C, 46.79; H, 3.34; N, 12.59.

2,4-Diisopropoxy-6-[4-(trifluoromethyl)phenoxy]-1,3,5-triazine (5jb): White solid. Mp 98-99 ºC (from *i*-PrOH). IR (KBr) cm^{-1}: 1589 (C=N), 1325 (CF_3), 1222, 1134, 1065 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.36 (12H, d, *J* = 6.1 Hz, H1', 3'), 5.28 (2H, qu, *J* = 6.1 Hz, H2'), 7.30 (2H, d, *J* = 8.4 Hz, H2'', 6''), 7.67

(2H, d, *J* = 8.4 Hz, H3', 5'). ^{13}C-NMR ($CDCl_3$) δ: 21.67 (C1', 3'), 72.28 (C2'), 122.14 (C2'', 6''), 123.90 (q, *J* = 272.1 Hz, CF_3), 126.85 (q, *J* = 4.1 Hz, C3'', 5''), 128.08 (q, *J* = 33.1 Hz, C4''), 154.34 (C1''), 172.78 (C6), 172.94 (C2, 4). Positive-ion FAB-MS *m/z*: 358 $(M+H)^+$. HR-FAB-MS *m/z*: 358.1372 (Calcd for $C_{16}H_{19}F_3N_3O_3$: 358.1379). Anal. Calcd for $C_{16}H_{18}F_3N_3O_3$: C, 53.78; H, 5.08; N, 11.76. Found: C, 53.78; H, 5.11; N, 11.48.

General Procedure for *Cs*-Symmetrical Trialkoxy-substituted TAZ derivatives (5) (Table S4): Example 3 (using collidine or Et$_3$N by reflux): Synthesis of 6-(1-Heptyloxy)-2,4-bis[3-(trifluoromethyl)phenoxy]-1,3,5-triazine (5gi): To a solution of compound **2g** (646 mg, 2.45 mmol) in acetone (10 mL), 3-(trifuluoromethyl)phenol (**i**H, 851 mg, 5.25 mmol) and collidine (636 mg, 5.25 mmol) were added at room temperature, and the reaction mixture was stirred for 30 min at room temperature and then refluxed for 1 h. After removal of white solids (collidine•HCl salt) by filtration, the solvent was evaporated. The residue was purified by centrifugal chromatography (CH_2Cl_2 : *n*-hexane = 30 : 70) to obtain compound **5gi** (1.17 g, 2.27 mmol, 93%) as a sticky solid. Mp 45-48 °C. IR (KBr) cm^{-1}: 1578 (C=N), 1322 (C-F), 1127, 1092 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J* = 7.0 Hz, H7''), 1.20-1.33 (6H, m, H4'', 5'', 6''), 1.33-1.40 (2H, m, H3''), 1.72 (2H, qu, *J* = 7.0 Hz, H2''), 4.32 (2H, t, *J* = 6.7 Hz, H1''), 7.32-7.35 (2H, m, H6'), 7.42 (2H, br s, H2'), 7.47-7.52 (4H, m, H4',5'). ^{13}C-NMR ($CDCl_3$) δ: 13.98 (C7''), 22.51 (C6''), 25.61 (C3''), 28.42 (C2''), 28.81 (C4''), 31.65 (C5''), 69.47 (C1''), 118.92 (q, *J* = 4.1 Hz, C2'), 122.91 (q, *J* = 4.1 Hz, C4'), 123.43 (q, *J* = 272.1 Hz, CF_3), 132.07 (q, *J* = 33.1 Hz, C3'), 151.66 (C1'), 173.12 (C2, 4), 173.84 (C6). Positive-ion FAB-MS *m/z*: 516 $(M+H)^+$. HR-FAB-MS *m/z*: 516.1729 (Calcd for $C_{24}H_{24}F_6N_3O_3$: 516.1722). Anal. Calcd for $C_{24}H_{23}F_6N_3O_3$: C, 55.92; H, 4.50; N, 8.15. Found: C, 56.15; H, 4.72; N, 8.30.

2-(1,3-Benzodioxol-5-yloxy)-4-chloro-6-methoxy-1,3,5-triazine (3ak): White solid. Mp 140-141 °C. IR (KBr) cm^{-1}: 1577 (C=N), 1292, 1177, 1011 (C-O), 812 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ: 4.03 (3H, s, OCH_3), 6.01 (2H, s, H2'), 6.62 (1H, dd, *J* = 8.2, 2.4 Hz, H6'), 6.67 (1H, d, *J* = 2.4 Hz, H4'), 6.80 (1H, d, *J* = 8.2 Hz, H7'). ^{13}C-NMR ($CDCl_3$) δ: 56.17 (OCH_3), 101.91 (C2'), 103.40 (C6'), 108.09 (C7'), 113.72 (C4'), 145.73 (C5' or 7a'), 145.87 (C7a' or 5'), 148.23 (C3a'), 172.52, 172.81, 173.28 (C2, 4, 6). Positive-ion FAB-MS *m/z*: 282 $(M+H)^+$. HR-FAB-MS *m/z*: 282.0280 (Calcd for $C_{11}H_9ClN_3O_4$: 282.0282). Anal. Calcd for $C_{11}H_8ClN_3O_4$•0.1H_2O: C, 46.61; H, 2.92; N, 14.82. Found: C, 46.76; H, 2.98; N, 14.55. [1485339-02-3]

6-(2-Propoxy)-2,4-bis[3-(trifluoromethyl)phenoxy]-1,3,5-triazine (5bi): White powder. Mp 132-134 °C (from EtOH). IR (KBr) cm^{-1}: 1577 (C=N), 1211, 1174, 1132 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.33 (6H, d, *J* = 6.1 Hz, H1", 3"), 5.16 (1H, qu, *J* = 6.1 Hz, H2''), 7.32-7.36 (2H, m, H6'), 7.42 (2H, br s, H2'), 7.48-7.51 (4H, m, H4', 5'). ^{13}C-NMR ($CDCl_3$) δ: 21.49 (C1", 3"), 73.25 (C2"), 118.96 (q, *J* = 4.1 Hz, C2'), 122.88 (q, *J* = 4.1 Hz, C4'), 123.45 (q, *J* = 272.1 Hz, CF_3), 124.53 (C6'), 130.09 (C5'), 132.05 (q, *J*

= 33.1 Hz, C3'), 151.71 (C1'), 173.17 (C2, 4), 173.22 (C6). Positive-ion FAB-MS *m/z*: 460 $(M+H)^+$. HR-FAB-MS *m/z*: 460.1098 (Calcd for $C_{20}H_{16}F_6N_3O_3$: 460.1096). Anal. Calcd for $C_{20}H_{15}F_6N_3O_3$: C, 52.30; H, 3.29; N, 9.15. Found: C, 52.13; H, 3.35; N, 9.16.

2,4-Bis(1,3-benzodioxol-5-yloxy)-6-(1-methylethoxy)-1,3,5-triazine (5bk): White solid. Mp 167-170 °C (from $CHCl_3$). IR (KBr) cm^{-1}: 1570 (C=N), 1174, 1137, 1041 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.33 (6H, d, *J* = 6.1 Hz, H1", 3"), 5.20 (1H, qu, *J* = 6.1 Hz, H2"), 5.98 (4H, s, H2'), 6.60 (2H, dd, *J* = 8.2, 2.1 Hz, H6'), 6.66 (2H, d, *J* = 2.1 Hz, H4'), 6.76 (2H, d, *J* = 8.2 Hz, H7'). ^{13}C-NMR ($CDCl_3$) δ: 21.59 (C1", 3"), 72.71 (C2"), 101.75 (C2'), 103.77 (C4'), 107.94 (C7'), 113.93 (C6'), 145.50 (C7a'), 146.15 (C5'), 148.03 (C3a'), 173.16 (C6), 173.79 (C2, 4). Positive-ion FAB-MS *m/z*: 412 $(M+H)^+$. HR-FAB-MS *m/z*: 412.1162 (Calcd for $C_{20}H_{18}N_3O_7$: 412.1145). Anal. Calcd for $C_{20}H_{17}N_3O_7$•$0.2H_2O$: C, 57.89; H, 4.23; N, 10.13. Found: C, 57.81; H, 4.03; N, 10.12.

2-(1,3-Benzodioxol-5-yloxy)-4-chloro-6-(1-methylethoxy)-1,3,5-triazine (3bk): White solid. Mp 104-106 °C. IR (KBr) cm^{-1}: 1561 (C=N), 1177, 1093 (C-O of ether), 809 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ: 1.37 (6H, d, *J* = 6.1 Hz, H1", 3"), 5.27 (1H, qu, *J* = 6.1 Hz, H2"), 6.01 (2H, s, H2'), 6.61 (1H, dd, *J* = 8.5, 2.4 Hz, H6'), 6.67 (1H, d, *J* = 2.4 Hz, H4'), 6.79 (1H, d, *J* = 8.5, H7'). ^{13}C-NMR ($CDCl_3$) δ: 21.49 (C1", 3"), 73.71 (C2"), 101.88 (C2'), 103.46 (C4'), 108.07 (C7'), 113.77 (C6'), 145.80 (C5' or C7a'), 145.82 (C7a' or C5'), 148.21 (C3a'), 171.84 (C6), 172.51 (C2), 173.17 (C4). Positive-ion FAB-MS *m/z*: 309 $(M)^+$. HR-FAB-MS *m/z*: 309.0498 (Calcd for $C_{13}H_{12}ClN_3O_4$: 309.0516). Anal. Calcd for $C_{13}H_{12}ClN_3O_4$: C, 50.42; H, 3.91; N, 13.57. Found: C, 50.18; H, 3.87; N, 13.60. [1478568-21-6]

6-(Cyclopentyloxy)-2,4-bis[3-(trifluoromethyl)phenoxy]-1,3,5-triazine (5fi): Pale yellow solid. Mp 65-70 °C. IR (KBr) cm^{-1}: 1577, 1557 (C=N), 1169, 1122 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.55-1.67 (2H, m, H3", 4"), 1.74-1.83 (6H, m, H3", 4", 2", 5"), 5.26-5.35 (1H, m, H1"), 7.30-7.36 (2H, m, H6'), 7.42 (2H, br s, H2'), 7.46-7.53 (4H, m, H4', 5'). ^{13}C-NMR ($CDCl_3$) δ: 23.62 (C3'', 4"), 32.48 (C2'', 5"), 82.39 (C1''), 118.93 (q, *J* = 4.1 Hz, C2'), 122.80 (q, *J* = 4.1 Hz, C4'), 123.42 (q, *J* = 272.1 Hz, CF_3), 125.05 (C6'), 130.03 (C5'), 131.96 (q, *J* = 33.1 Hz, C3'), 151.68 (C1'), 173.02 (C2, 4), 173.39 (C6). Positive-ion FAB-MS *m/z*: 486 $(M+H^+)$. HR-FAB-MS *m/z*: 486.1250 (Calcd for $C_{22}H_{18}F_6N_3O_3$: 486.1252). Anal. Calcd for $C_{22}H_{17}F_6N_3O_3$: C, 54.44; H, 3.53; N, 8.66. Found: C, 53.49; H, 3.64; N, 9.36.

6-(Cyclopentyloxy)-2,4-bis[4-(trifluoromethyl)phenoxy]-1,3,5-triazine (5fj) and 6-Chloro-4-(cyclopentyloxy)-2-[4-(trifluoromethyl)phenoxy]-1,3,5-triazine (3fj) (1 : 2) complex: This complex consisting of two triazine derivatives, **5fj•(3fj)$_2$**, was isolated as a colorless solid. Mp 98-101 °C. Anal. Calcd for $C_{52}H_{43}Cl_2F_{12}N_9O_7$: C, 51.84; H, 3.60; N, 10.46. Found: C, 51.99; H, 3.58; N, 10.36. This complex showed no anti-HSV-1 or cytotoxic activity (EC_{50} > 100 μM and CC_{50} > 200 μM, respectively). The obtained spectroscopic data of this complex are shown below.

5fj: ^{1}H-NMR ($CDCl_3$) δ: 1.54-1.67 (2H, m, H3", 4"), 1.73-1.95 (6H, m, H3", 4", 2", 5"), 5.27-5.32 (1H,

m, H1''), 7.26 (4H, d, *J* = 8.5 Hz, H2', 6'), 7.65 (4H, d, *J* = 8.5 Hz, H3', 5'). ^{13}C-NMR ($CDCl_3$) δ: 23.70 (C3'', 4''), 32.56 (C2'', 5''), 82.48 (C1''), 122.08 (C2', 6'), 123.77 (q, *J* = 272.1 Hz, CF_3), 126.86 (q, *J* = 4.1 Hz, C3', 5'), 128.45 (q, *J* = 33.1 Hz, C4'), 154.05 (C1'), 172.94 (C2, 4), 173.41 (C6). Positive-ion FAB-MS *m/z*: 486 $(M+H)^+$. HR-FAB-MS *m/z*: 486.1245 (Calcd for $C_{22}H_{18}F_6N_3O_3$: 486.1252).

3fj: ^{1}H-NMR ($CDCl_3$) δ: 1.54-1.67 (2H, m, H3'', 4''), 1.73-1.95 (6H, m, H3'', 4'', 2'', 5''), 5.37-5.42 (1H, m, H1''), 7.31 (2H, d, *J* = 8.5 Hz, H2', 6'), 7.71 (2H, d, *J* = 8.5 Hz, H3', 5'). ^{13}C-NMR ($CDCl_3$) δ: 23.64 (C3'', 4''), 32.56 (C2'', 5''), 83.19 (C1''), 121.96 (C2', 6'), 123.77 (q, *J* = 272.1 Hz, CF_3), 127.06 (q, *J* = 4.1 Hz, C3', 5'), 128.71 (q, *J* = 33.1 Hz, C4'), 153.84 (C1'), 171.63 (C2 or C6), 172.03 (C4), 173.25 (C6 or C2). Positive-ion FAB-MS *m/z*: 360 $(M+H)^+$. HR-FAB-MS *m/z*: 360.0721 (Calcd for $C_{15}H_{14}ClF_3N_3O_2$: 360.0727).

2,4-Bis(1,3-benzodioxol-5-yloxy)-6-cyclopentyloxy-1,3,5-triazine (5fk): White solid. Mp 194-195 °C (from CH_2Cl_2). IR (KBr) cm^{-1}: 1568 (C=N), 1174, 1135 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.54-1.62 (2H, m, H3'', 4''), 1.73-1.85 (4H, m, H2'', 3'', 4'', 5''), 1.85-1.92 (2H, m, H2'', H5''), 5.31 (1H, qu, *J* = 3.1 Hz, H1''), 5.98 (4H, s, H2'), 6.60 (2H, dd, *J* = 8.5, 2.4 Hz, H6'), 6.66 (2H, d, *J* = 2.4 Hz, H4'), 6.76 (2H, d, *J* = 8.5 Hz, H7'). ^{13}C-NMR ($CDCl_3$) δ: 23.77 (C3'', 4''), 32.57 (C2'', 5''), 81.92 (C1''), 101.73 (C2'), 103.77 (C4'), 107.90 (C7'), 113.93 (C6'), 145.45 (C5' or C7a'), 146.15 (C7a' or C5'), 147.99 (C3a'), 173.36 (C6), 173.64 (C2, 4). Positive-ion FAB-MS *m/z*: 438 $(M+H)^+$. HR-FAB-MS *m/z*: 438.1299 (Calcd for $C_{22}H_{20}N_3O_7$: 438.1301). Anal. Calcd for $C_{22}H_{19}N_3O_7$: C, 60.41; H, 4.38; N, 9.61. Found: C, 60.20; H, 4.36; N, 9.72.

6-(1-Heptyloxy)-2,4-bis[4-(trifluoromethyl)phenoxy]-1,3,5-triazine (5gj): White solid. Mp 66-67 °C (from EtOH). IR (KBr) cm^{-1}: 1579 (C=N), 1330 (C-F), 1224, 1123, 1066 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J* = 7.0 Hz, H7''), 1.24-1.32 (6H, m, H4'', 5'', 6''), 1.32-1.37 (2H, m, H3''), 1.69-1.75 (2H, m, H2''), 4.32 (2H, t, *J* = 6.7 Hz, H1''), 7.27 (4H, d, *J* = 8.4 Hz, H2', 6'), 7.65 (4H, d, *J* = 8.4 Hz, H3', 5'). ^{13}C-NMR ($CDCl_3$) δ: 13.98 (C7''), 22.51 (C6''), 25.62 (C3''), 28.42 (C2''), 28.83 (C4''), 31.64 (C5''), 69.53 (C1''), 122.07 (C2', 6'), 123.77 (q, *J* = 272.1 Hz, CF_3), 126.90 (q, *J* = 4.1 Hz, C3', 5'), 128.53 (q, *J* = 33.1 Hz, C4'), 154.02 (C1'), 173.04 (C2, 4), 173.82 (C6). Positive-ion FAB-MS *m/z*: 516 $(M+H)^+$. HR-FAB-MS *m/z*: 516.1721 (Calcd for $C_{24}H_{24}F_6N_3O_3$: 516.1722). Anal. Calcd for $C_{24}H_{23}F_6N_3O_3$: C, 55.92; H, 4.50; N, 8.15. Found: C, 55.78; H, 4.57; N, 8.21.

2-Chloro-4-heptyloxy-6-[4-(trifluoromethyl)phenoxy]-1,3,5-triazine (3jg): Colorless crystals. Mp 63-66 °C (from *n*-hexane). IR (KBr) cm^{-1}: 1585, 1527 (C=N), 1337 (C-F), 1129, 1067 (C-O), 808 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J* = 7.0 Hz, H7''), 1.25-1.35 (6H, m, H4'', 5'', 6''), 1.35-1.45 (2H, m, H3''), 1.76 (2H, q, *J* = 7.0 Hz, H2''), 4.38 (2H, t, *J* = 6.7 Hz, H1''), 7.31 (2H, d, *J* = 8.9 Hz, H2', 6'), 7.71 (2H, d, *J* = 8.9 Hz, H3', 5'). ^{13}C-NMR ($CDCl_3$) δ: 13.98 (C7''), 22.51 (C6''), 25.60 (C3''), 28.36 (C2''), 28.81 (C4''), 31.63 (C5''), 70.05 (C1''), 121.94 (C2', 6'), 123.74 (q, *J* = 273.1 Hz, CF_3), 127.10 (q,

J = 4.1 Hz, C3', 5'), 128.78 (q, *J* = 33.1 Hz, C4'), 153.80 (C1'), 171.73 (C2 or C6), 172.47 (C4), 173.37 (C6 or C2). Positive-ion FAB-MS *m/z*: 390 $(M+H)^+$. HR-FAB-MS *m/z*: 390.1194 (Calcd for $C_{17}H_{20}ClF_3N_3O_2$: 390.1196). Anal. Calcd for $C_{17}H_{19}ClF_3N_3O_2$: C, 52.38; H, 4.91; N, 10.78. Found: C, 52.35; H, 4.82; N, 10.80.

2-(1,3-Benzodioxol-5-yloxy)-4,6-diisopropoxy-1,3,5-triazine (5kb): Colorless needles. Mp 128-129 ºC (from EtOH). IR (ATR) cm^{-1}: 1562 (C=N), 1175, 1098 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.36 (12H, d, *J* = 6.2 Hz, H2'', 3''), 5.29 (2H, qu, *J* = 6.2 Hz, H1''), 6.00 (2H, s, H2'), 6.62 (1H, dd, *J* = 8.2, 2.1 Hz, H6'), 6.68 (1H, d, *J* = 2.1 Hz, H4'), 6.78 (1H, d, *J* = 8.2 Hz, H7'). ^{13}C-NMR ($CDCl_3$) δ: 21.69 (C2'', 3''), 71.98 (C1''), 101.68 (C2'), 103.81 (C4'), 107.92 (C7'), 113.97 (C6'), 145.33 (C7a'), 146.18 (C5'), 147.95 (C3a'), 172.83 (C4, 6), 173.45 (C2). Positive-ion FAB-MS *m/z*: 334 $(M+H)^+$. HR-FAB-MS *m/z*: 334.1399 (Calcd for $C_{16}H_{20}N_3O_5$: 334.1403). Anal. Calcd for $C_{16}H_{19}N_3O_5$: C, 57.65; H, 5.75; N, 12.61. Found: C, 57.49; H, 5.75; N, 12.58.

2-(1,3–Benzodioxol-5-yloxy)-4,6-dimethoxy-1,3,5-triazine (5ka):[6] Colorless crystals. Mp 118-119 ºC (from EtOH). IR (KBr) cm^{-1}: 1570 (C=N), 1191, 1170, 1121, 1039 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 4.01 (6H, s, OCH_3), 6.00 (2H, s, H2'), 6.62 (1H, dd, *J* = 8.2, 2.4 Hz, H6'), 6.68 (1H, d, *J* = 2.4 Hz, H4'), 6.79 (1H, d, *J* = 8.2 Hz, H7'). ^{13}C-NMR ($CDCl_3$) δ: 55.47 (OCH_3), 101.75 (C2'), 103.71 (C4'), 107.96 (C7'), 113.91 (C6'), 145.51 (C7a'), 146.05 (C5'), 148.03 (C3a'), 173.55 (C4, 6), 174.00 (C2). Positive-ion FAB-MS *m/z*: 278 $(M+H^+)$. HR-FAB-MS *m/z*: 278.0771 (Calcd for $C_{12}H_{12}N_3O_5$: 278.0777). Anal. Calcd for $C_{12}H_{11}N_3O_5$: C, 51.99; H, 4.00; N, 15.16. Found: C, 51.96; H, 3.98; N, 15.20.

General Procedure for *C*$_S$-Symmetrical Alkoxy-Alkylamino-Trisubstituted TAZ derivatives (7, 8) (Table S5): Example 1 (using DIPEA by reflux): Synthesis of 6-Isopropoxy-*N*^{2},*N*^{4}-diisopropyl-1,3,5-triazine-2,4-diamine (7bp): To a solution of intermediate **2b** (416 mg, 2.00 mmol) in THF (25 mL), 2-propylamine **p**H (473 mg, 8.00 mmol) and diisopropylethylamine (DIPEA, 517 mg, 4.00 mmol) were added at room temperature and the reaction mixture was refluxed for 17 h. After addition of water (20 mL), the mixture was extracted with EtOAc (3×30 mL). The combined organic layer was washed with brine (10 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residue was recrystallized by *n*-hexane to obtain pure compound **7bp** (431 mg, 1.70 mmol, 85%) as colorless crystals. Mp 102.0-102.5 ºC (from *n*-hexane). IR (ATR) cm^{-1}: 3243, 3099 (N-H), 1611, 1578, 1525 (C=N), 1314, 1195, 1099 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.19 (12H, d, *J* = 5.5 Hz, H2', 3'), 1.33 (6H, br s, H2", 3"), 4.17 (2H, br s, H1'), 4.78, 4.87* (2H, br s, NH), 5.23 (1H, br s, H1"). (The observed ^{1}H-signals assignable to the predominant tautomer are asterisked.) ^{13}C-NMR ($CDCl_3$) δ: 21.96 (C2", 3"), 22.98 (C2', 3'), 42.22 (C1'), 69.11 (C1"), 166.73 (C2, 4), 170.26 (C6). (Signals for only the predominant tautomer are shown.) Positive-ion FAB-MS *m/z*: 254 $(M+H)^+$. HR-FAB-MS *m/z*: 254.1973 (Calcd for $C_{13}H_{24}N_5O$: 254.1981). Anal. Calcd for $C_{12}H_{23}N_5O$: C, 56.89; H,

9.15; N, 27.64. Found: C, 56.89; H, 9.33; N, 27.53. [30360-64-6]

***N*²,*N*⁴-Diisobutyl-6-isopropoxy-1,3,5-triazine-2,4-diamine (7bq):** White solid. Mp 131.0-132.5 °C (from *n*-hexane). IR (ATR) cm^{-1}: 3358, 3254, 3111 (NH), 1738, 1618, 1583, 1522 (C=N), 1281, 1178, 1105 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ: 0.94 (12H, d, *J* = 6.9 Hz, H3', 4'), 1.30, 1.33* (6H, br s, H2", 3"), 1.83 (1H, br s, H2'), 3.17, 3.23* (4H, br s, H1'), 5.04*, 5.15 (2H, br s, NH), 5.20 (1H, s, H1"). (The observed ^{1}H-signals assignable to the predominant tautomer are asterisked.) ^{13}C-NMR ($CDCl_3$) δ: 20.12 (C3', 4'), 21.95 (C2", 3"), 28.61 (C2'), 48.20 (C1'), 69.18 (C1"), 167.51 (C2, 4), 170.21 (C6). (Signals for only the predominant tautomer are shown.) Positive-ion FAB-MS *m/z*: 282 $(M+H)^+$. HR-FAB-MS *m/z*: 282.2297 (Calcd for $C_{14}H_{28}N_5O$: 282.2294). Anal. Calcd for $C_{14}H_{27}N_5O$: C, 59.76; H, 9.67; N, 24.89. Found: C, 59.76; H, 9.85; N, 24.85.

4-Chloro-*N*-isobutyl-6-isopropoxy-1,3,5-triazin-2-amine (9bq): White solid. ^{1}H-NMR ($CDCl_3$) δ: 0.956*, 0.963 (6H, d, *J* = 6.9 Hz, H3', 4'), [1.35 (2H), 1.38* (4H)] (d, *J* = 6.2 Hz, H2", 3"), 1.88 (1H, heptet, *J* = 6.9 Hz, H2'), 3.28* (0.67H, dd, *J* = 6.8, 6.2 Hz, H1'), 3.29 (0.33H, dd, *J* = 6.9, 6.2 Hz, H1'), [5.25 (0.33H), 5.30* (0.67H)] (qu, *J* = 6.2 Hz, H1"), [5.55 (0.33H), 5.83* (0.67H)] (br s, NH). (The observed ^{1}H-signals assignable to the predominant tautomer are asterisked.) ^{13}C-NMR ($CDCl_3$) δ: 19.99 (C3', 4'), 21.69 (C2", 3"), 28.31 (C2'), 48.45 (C1'), 71.86 (C1"), 167.22 (C2), 170.34, 173.27 (C4, 6). (Signals for only the predominant tautomer are shown.) Positive-ion FAB-MS *m/z*: 245 $(M+H)^+$. HR-FAB-MS *m/z*: 245.1160 (Calcd for $C_{10}H_{18}N_4O$: 245.1169).

4-Chloro-6-(cyclohexyloxy)-*N*-isobutyl-1,3,5-triazin-2-amine (9fq): Colorless crystals. Mp 101-102 °C (from *i*-Pr_2O). IR (KBr) cm^{-1}: 1638, 1572 (C=N), 1295, 1230 (C-O), 806 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ: 0.96 (6H, d, *J* = 6.7 Hz, H3', 4'), 1.57-1.68 (2H, m, H3'', 4''), 1.77-2.00 (7H, m, H3'', 4'', 2', 2", 5"), 3.26-3.31 (2H, m, H1'), 5.36-5.44 (1H, m, H1"), 5.59 (0.35H, br s, NH), 5.81* (0.65H, br s, NH). (The observed ^{1}H-signals assignable to the predominant tautomer are asterisked.) ^{13}C-NMR ($CDCl_3$) δ: 20.00 (C3'), 23.81 (C3", 4"), 28.35 (C2'), 32.70 (C2", 5"), 48.52 (C1'), 81.18 (C1"), 167.21 (C2), 170.29, 170.57 (C4, 6). (Signals for only the predominant tautomer are shown.) Positive-ion FAB-MS *m/z*: 271 $(M+H)^+$. HR-FAB-MS *m/z*: 271.1329 (Calcd for $C_{12}H_{20}ClN_4O$: 271.1326). Anal. Calcd for $C_{12}H_{19}ClN_4O•0.2H_2O$: C, 52.53; H, 7.13; N, 20.42. Found: C, 52.57; H, 7.08; N, 20.13.

6-(Cyclopentyloxy)-*N*²,*N*⁴-isobutyl-1,3,5-triazine-2,4-diamine (7fq): White solid. Mp 80-81 °C. IR (KBr) cm^{-1}: 3374 (N-H), 1531 (C=N), 1179, 1164, 1122 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (12H, d, *J* = 6.2 Hz, H3', 4'), 1.54-1.62 (2H, m, H3", 4"), 1.76-1.97 (8H, m, H2', 2", 3", 4", 5"), 3.16, 3.23* (4H, br s, H1'), 5.14*, 5.19 (2H, br s, NH), 5.30, 5.35* (1H, br s, H1"). ^{13}C-NMR ($CDCl_3$) δ: 20.11 (C3', 4'), 23.67, 23.88* (C3", 4"), 28.46, 28.58* (C2'), 32.80 (C2", 5"), 48.14, 48.26* (C1'), 78.27*, 78.71 (C1"), 167.03, 167.37*, 167.60 (C2, 4), 169.93, 170.27*, 170.83 (C6). (The observed ^{1}H- and ^{13}C-siganals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS *m/z*: 308 $(M+H)^+$. HR-FAB-MS *m/z*:

308.2452 (Calcd for $C_{16}H_{30}N_5O$: 308.2450). Anal. Calcd for $C_{16}H_{29}N_5O$: C, 62.51; H, 9.51; N, 22.78. Found: C, 62.33; H, 9.73; N, 22.61.

***N*-Isobutyl-4,6-diisopropoxy-1,3,5-triazin-2-amine (8qb):** Colorless needles. Mp 113-114 °C (from *n*-hexane). IR (KBr) cm^{-1}: 3260 (N-H), 1575 (C=N), 1124, 1099 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 0.95 (6H, dd, *J* = 6.9, 2.1 Hz, H3', 4'), 1.34^A, 1.37^B (12H, d, *J* = 4.2 Hz, H2", 3"), 1.81-1.90 (1H, m, H2'), 3.24-3.29 (2H, m, H1'), 5.23-*ca*.5.29^A, *ca*.5.29-5.34^B (2H, m, H1"), 5.49 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 20.05 (C3', 4'), 21.87^{AorB}, 21.93^{BorA} (C2", 3"), 28.47 (C2'), 48.26 (C1'), 70.01^A, 70.41^B (C1"), 168.40 (C2), 171.04^A, 171.64^B (C4, 6). [Signals that appeared in ^{1}H- and ^{13}C-NMR spectra are approximately consistent with the tautomeric mixture of two isomers (**T3** and **T4**)[20] with the ratio of 1 : 1. The signals assignable to each tautomer are marked with a superscript A or B.] Positive-ion FAB-MS *m/z*: 269 $(M+H)^+$. HR-FAB-MS *m/z*: 269.1978 (Calcd for $C_{13}H_{25}N_4O_2$: 269.1978). Anal. Calcd for $C_{13}H_{24}N_4O_2$: C, 58.18; H, 9.01; N, 20.88. Found: C, 58.29; H, 8.95; N, 20.88.

4,6-Diisobutoxy-*N*-isopropyl-1,3,5-triazin-2-amine (8pd): Colorless crystals. Mp 63-64 °C. IR (KBr) cm^{-1}: 3444 (N-H), 1598, 1581 (C=N), 1169, 1095 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.00 (12H, t, *J* = 6.2 Hz, H3", 4"), 1.22 (6H, d, *J* = 6.2 Hz, H2', 3'), 2.02-2.16 (1H, m, H2"), 4.05^A (1H, d, *J* = 6.2 Hz, H1"), 4.11^B (1H, d, *J* = 6.9 Hz, H1"), 4.20-4.24 (1H, m, H1'), 5.08, 5.09 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 19.16^A, 19.26^B (C3", 4"), 22.80 (C2', 3'), 27.79 (C2"), 42.67 (C1'), 73.45^A, 73.71^B (C1"), 167.31 (C2), 172.03^A, 172.33^B (C4, 6). [Signals that appeared in ^{1}H- and ^{13}C-NMR spectra are approximately consistent with the tautomeric mixture of two isomers (**T3** and **T4**)[20] with the ratio of 1 : 1. The signals assignable to each tautomer are marked with a superscript A or B.] Positive-ion FAB-MS *m/z*: 283 $(M+H)^+$. HR-FAB-MS *m/z*: 283.2132 (Calcd for $C_{14}H_{27}N_4O_2$: 283.2134). Anal. Calcd for $C_{14}H_{26}N_4O_2$: C, 59.55; H, 9.28; N, 19.84. Found: C, 59.43; H, 9.51; N, 19.63.

General Procedure for *CS*-Symmetrical Alkoxy-Alkylamino-Trisubstituted TAZ derivatives (7, 8) (Table S5): Example 2 (No Base by MW): Synthesis of 4,6-Diisobutoxy-*N*-isobutyl-1,3,5-triazin-2-amine (8qd): To a solution of compound **3d** (327 mg, 1.26 mmol) in dioxane (5 mL) was added a solution of isobutylamine (**q**H, 263 mg, 3.60 mmol) at *ca.* 10 °C. Then the mixture was subjected to MW at 100 °C (100 W) for 30 min with stirring. After addition of water (20 mL), the mixture was extracted with EtOAc (2×25 mL). The combined organic layer was dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by centrifugal chromatography (*n*-hexane : EtOAc = 85 : 15) to obtain compound **8qd** (318 mg, 1.07 mmol, 85%) as a white solid. Mp 93.5-94.0 °C. IR (ATR) cm^{-1}: 3266, 3146 (NH), 1631, 1574, 1550 (C=N), 1351, 1332, 1112 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ: 0.95 (12H, d, *J* = 6.2 Hz, H3', 4'), 0.996^{AorB} (6H, d, *J* = 6.9 Hz, H3", 4"), 1.002^{BorA} (6H, d, *J* = 6.9 Hz, H3", 4"), 1.86 (1H, heptet, *J* = 6.9 Hz, H2'), 2.06^A (1H, heptet, *J* = 6.9 Hz, H2"), 2.11^B (1H, heptet, *J* = 6.9 Hz, H2"), 3.27 (2H, t, *J* = 6.9 Hz, H1'), 4.07^A (2H, d, *J* = 6.9 Hz, H1"),

4.11[B] (2H, d, *J* = 6.9 Hz, H1”), 5.40 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 19.15, 19.24 (C3”, 4”), 20.06 (C3’, 4’), 27.79, 27.81 (C2”), 28.49 (C2’), 48.34 (C1’), 73.47[A], 73.71[B] (C1”), 168.34 (C2), 171.73[A], 172.29[B] (C4, 6). [Signals that appeared in ^{1}H- and ^{13}C-NMR spectra are approximately consistent with the tautomeric mixture of two isomers (**T3** and **T4**)[20] with the ratio of 1 : 1. The signals assignable to each tautomer are marked with a superscript A or B.] Positive-ion FAB-MS *m/z*: 297 $(M+H)^+$. HR-FAB-MS *m/z*: 297.2292 (Calcd for $C_{15}H_{29}N_4O_2$: 297.2291). Anal. Calcd for $C_{15}H_{28}N_4O_2$: C, 60.78; H, 9.52; N, 18.90. Found: C, 60.85; H, 9.48; N, 18.76.

6-Isobutoxy-*N*^{2},*N*^{4}-diisopropyl-1,3,5-triazine-2,4-diamine (7dp): White solid. Mp 85-86 °C. IR (KBr) cm^{-1}: 3250 (N-H), 1532 (C=N), 1193 (C-N), 1100 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 0.98 (6H, d, *J* = 6.9 Hz, H3”, 4”), 1.20 (12H, br d, *J* = 4.8 Hz, H2’, 3’), 2.06 (1H, br s, H2”), 3.97, 4.03* (2H, br s, H1”), 4.17 (2H, br s, H1’), 4.79, 4.89* (2H, br s, NH). (The observed ^{1}H-signals assignable to the predominant tautomer are asterisked.) ^{13}C-NMR ($CDCl_3$) δ: 19.25 (C3”, 4”), 22.92 (C2’, 3’), 27.85 (C2”), 42.28 (br s, C1’), 72.82 (br s, C1”), 166.51 (br s, C2, 4), 170.90 (br s, C6). Positive-ion FAB-MS *m/z*: 268 $(M+H)^+$. HR-FAB-MS *m/z*: 268.2141 (Calcd for $C_{13}H_{26}N_5O$: 268.2137). Anal. Calcd for $C_{13}H_{25}N_5O$: C, 58.16; H, 9.42; N, 26.19. Found: C, 58.27; H, 9.53; N, 26.21.

6-Isobutoxy-*N*^{2},*N*^{4}-diisobutyl-1,3,5-triazine-2,4-diamine (7dq): Pale yellow solid. Mp 40-41 °C. IR (ATR) cm^{-1}: 3264, 3131 (NH), 1575, 1513 (C=N), 1350, 1330, 1168, 1119 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ: 0.94 (12H, d, *J* = 6.9 Hz, H3’, 4’), 0.99 (6H, d, *J* = 6.9 Hz, H3”, 4”), 1.84 (2H, br s, H2’), 2.07 (1H, br s, H2”), 3.17, 3.23* (4H, br s, H1’), 3.97, 4.04* (2H, br s, H1”), 5.00 (0.8H, br s, NH), 5.15* (1.2H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 19.27 (C3”, 4”), 20.14 (C3’, 4’), 27.86 (C2”), 28.61 (C2’), 48.05*, 48.25 (C1’), 72.63*, 72.82 (C1”), 167.46 (C2, 4), 170.49 (C6). (The observed ^{1}H- and ^{13}C-signals assignable to the predominant tautomer are asterisked.) Positive-ion FAB-MS *m/z*: 296 $(M+H)^+$. HR-FAB-MS *m/z*: 296.2457 (Calcd for $C_{15}H_{30}N_5O$: 296.2450). Anal. Calcd for $C_{15}H_{29}N_5O•0.3H_2O$: C, 59.89; H, 9.92; N, 23.28. Found: C, 59.91; H, 10.08; N, 23.10.

4,6-Diisopropoxy-*N*-isopropyl-1,3,5-triazin-2-amine (8pb): White solid. Mp 96-98 °C (from MeOH-H_2O). IR (ATR) cm^{-1}: 3258, 3154 (N-H), 1608, 1573, 1540 (C=N), 1314, 1119, 1092 (C-N and/or C-O). ^{1}H-NMR ($CDCl_3$) δ: 1.21 (6H, d, *J* = 6.9 Hz, H2’, 3’), 1.34[A] (6H, d, *J* = 6.2 Hz, H2’, 3’), 1.37[B] (6H, d, *J* = 6.2 Hz, H2’, 3’), 4.18-4.27 (1H, m, H1’), 5.10, 5.11 (1H, br s, NH), 5.25[A] (1H, qu, *J* = 6.2 Hz, H1”), 5.31[B] (1H, qu, *J* = 6.2 Hz, H1”). ^{13}C-NMR ($CDCl_3$) δ: 21.90 (C2”, 3”), 22.86 (C2’, 3’), 42.57 (C1’), 69.98[A], 70.37[B] (C1”), 167.42 (C2), 171.07[A], 171.69[B] (C4, 6). [Signals that appeared in ^{1}H- and ^{13}C-NMR spectra are approximately consistent with the tautomeric mixture of two isomers (**T3** and **T4**)[20] with the ratio of 1 : 1. The signals assignable to each tautomer are marked with a superscript A or B.] Positive-ion FAB-MS *m/z*: 255 $(M+H)^+$. HR-FAB-MS *m/z*: 255.1820 (Calcd for $C_{12}H_{23}N_4O_2$: 255.1821). Anal. Calcd for $C_{12}H_{22}N_4O_2$: C, 56.67; H, 8.72; N, 22.03. Found: C, 56.76; H, 8.82; N, 21.82.

Antiviral Activity and Cytotoxicity of Synthesized Trisubstituted TAZ derivatives

Antiviral Activity Assay: The antiviral activities of the compounds were measured by the plaque reduction assay.[18] Confluent monolayers of Vero cells (*ca.* 1×10^6 cells/well) in 6-well plastic plates were infected with 100 PFU of HSV-1 (KOS). After a 1-h adsorption period at 37 °C, the cultures were overlaid with 2 mL of Dulbecco's modified Eagle's minimum essential medium (DMEM) containing 2% heat-inactivated fetal calf serum, 2% ɤ-globulin, and various concentrations of the target compounds. The cultures inoculated with HSV-1 were incubated in a CO_2 incubator, fixed with formalin, and stained with crystal violet in methanol at 3 d postinoculation. After washes with water and drying, the plaques were enumerated. Calculated EC_{50} values for the tested compounds are summarized in Tables 1 and 2 together with data for aciclovir.[19]

Cytotoxicity Assay: The antiviral activities of the compounds were examined as described below. Vero cells were seeded in 96-well plastic plates at 1×10^4 cells per well. After 1 day, the cells were re-fed with 100 µL of DMEM containing 5% fetal calf serum and various concentrations of the target compounds. After 69 h incubation, 10 µL of AlamarBlue reagent was added to each culture and then the plates were reincubated for 4 h. The optical density of each culture at 570 nm was determined by a spectrophotometer using a reference wavelength of 630 nm.[18] Calculated cytotoxicity (CC_{50}) values for the tested compounds are also summarized in Tables 1 and 2. Calculated log *P* values for the compounds are also shown in Tables 1 and 2.

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12. Many similar 2,4,6-trisubstituted TAZ derivatives have been prepared and tested herbicidal activity and a few conclusion of structure-activity relation of the 1,3.5-triazine herbicides have been presented. The mode of action of the triazine herbicides has been extensively reviewed. See, 'Bioactive Heterocyclic Compound Classes, Agrochemicals', ed. by C. Lamberth and J. Dinges, WILEY-VCH, 2012, pp. 23-38.
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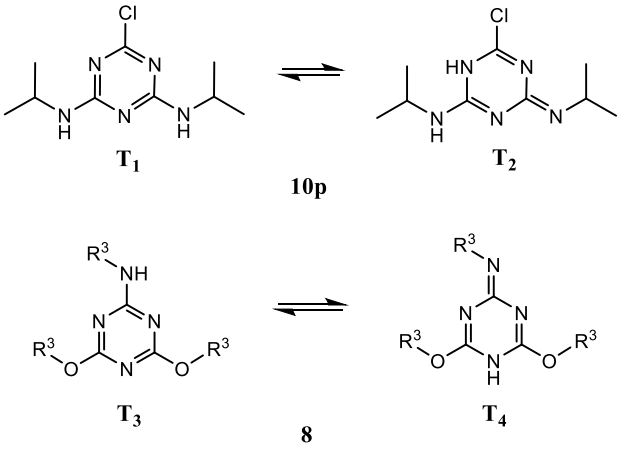
20. Some of the tri-substituted TAZ derivatives described in this paper showed a complicated ^{13}C-NMR signal pattern because of their keto-enol tautomeric isomers in solutions. Compounds (**7bp**, **7bq**, **7dp**, **7dq**, **7fq**, **8pb**, **8pd**, **8qb**, **8qd**, **9bq**, **9fq**, **10p**, **10q**, **10r**) that have *sec*-alkylamino groups on a TAZ template are examples of TAZ derivatives with such a signal pattern. A few compounds showed the presence of two tautomeric isomers in solution. Thus, signals that appeared in the

^{13}C-NMR spectrum of compound **10p** are fully consistent with the tautomeric mixture of two isomers shown below (**T1** and **T2**). Signals that appeared in the ^{13}C-NMR spectra of a few compounds **8** are also consistent with the tautomeric mixture of two isomers shown below (**T3** and **T4**).



Tautomeric Isomerism of TAZ derivatives **10p** and **8**