Synthesis and Antiviral Activities of Some 2,4,6-Trisubstituted 1,3,5-Triazines

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We describe the synthesis and results of biological evaluation of newly designed 2,4,6-trisubstituted symmetrical 1,3,5-triazine (TAZ) derivatives. Among the tested trisubstituted TAZ derivatives, some C₃-symmetrical alkoxy-amino-substituted TAZ derivatives, including 7gpp and 6dpp, showed significant antiviral activity against herpes simplex virus type 1 (HSV-1). The compound with the highest level of antiviral activity was C₃-symmetrical trialkoxy-TAZ derivative 4bbb, which showed a considerably high selectivity index (IC₅₀/EC₅₀=256.6). The structure–activity relationships for anti-HSV-1 activity of the tested 2,4,6-trisubstituted TAZ derivatives are also described.

Key words 1,3,5-triazine; anti-herpes simplex virus type 1; cytotoxic activity; C₃ symmetry; C₃ symmetry; plaque reduction assay

Supramolecular interaction of two-fold (C₂) or three-fold (C₃) symmetrical geometry macromolecules with many biologically active compounds is one of the common features of many important biological processes and small molecules having C₂, C₃, or C₅-symmetrical geometry often appear in various biologically active compounds contrasted on a symmetrical template. We have therefore expected that such small symmetrical molecules would be promising new candidates or leads in the search for biologically active compounds that interfere with the sugar recognition process in a controlled biological response. From this aspect of molecular symmetry, we have already reported a few examples of such types of new symmetrical molecules for the purpose of finding new biologically active compounds.

We have recently reported some molecular modifications of 2,4,6-trichloro-1,3,5-triazine (TCTAZ) to C₃-, C₅-, or C₇-symmetrical geometry with trisubstituted TAZ molecules and the results of biological evaluation of synthesized symmetrical 2,4,6-trisubstituted TAZ derivatives. Among previously targeted TAZ derivatives, some alkoxy-amino-substituted derivatives showed significant anti-herpes simplex virus type 1 (HSV-1) activities. The previous analysis of anti-HSV-1 active molecular features indicated that a C₅-symmetrical TAZ derivative with two alkoxy groups and one amine moiety seemed to be a required structure for preferred anti-HSV-1 activity with a good selectivity index.

For an extension of our study, we examined further modifications of this symmetrical class of compounds in order to investigate the structure–activity relationship (SAR) of alkoxy-amino-substituted TAZ molecules as well as their biological evaluation. In this paper, we report the results of preparation of newly targeted C₃-symmetrical TAZ derivatives together with the results of biological evaluation of obtained symmetrical 2,4,6-trisubstituted TAZ derivatives.

Chemistry In our previous article, we reported that synthesis of target alkoxy-amino-trisubstituted TAZ derivatives is easily achieved by a procedure via alkoxy-substituted chloro-TAZ intermediates starting from TCTAZ (1). This procedure consists of two-stage nucleophilic substitutions of compound 1 with alcohols (Step 1) and then amines (Step 2) in one pot. The predominant formation of a monoalkoxy-diamino-TAZ derivative (6) or dialkoxy-monoamino-TAZ derivative (7) in an employed reaction depended on the stoichiometry of TCTAZ and alcohol in the first reaction stage (Step 1). As an amine nucleophile for introduction on a TAZ template in this study, we employed only 4-piperidinemethanol (pH) because many molecules having this amine substituent designed previously showed considerable antiviral activities.

The overall reaction stage for the preparation of target molecules (6 and 7) is shown in Chart 1 together with obtained by-products. The results of the reactions of TCTAZ (1) with various alcohols (ROH = a–gH) and 4-piperidinemethanol (pH = XH) are summarized in Table 1.

Most of the reactions were performed first by our reported procedure (Method A), in which we used collidine and DIPEA as bases to trap HCl generated in both reaction stages (Steps 1 and 2). As shown in Table 1, target monoalkoxy-diamino-TAZ derivatives (6app–fpp) were obtained in good to excellent yields from the various reactions under conditions using Method A (Entries 1, 2, 6, 11, 13, 14, 16, and 18) with an excess amount of alcohols ROH (a–fH).

Among the compounds isolated from reactions of applied entries (Entries 1 and 2), a few products from the reactions of TCTAZ and water were isolated (see compounds 6wp and 7wpap). When the reactions were conducted in dry tetrahydrofuran (THF) or dry acetone in both Steps 1 and 2 under a N₂ atmosphere (Entries 3 and 4) using Method A, there was a tendency for decrease in yields of the target compounds (6app and 7app).

To improve the yield of target dialkoxy-monoamino-TAZ derivatives (7), we tried the procedure of Method A with various conditions. In the reactions with a primary alcohol aH, improvement in the yield of product 7app was achieved by the reaction using a large amount of alcohol and a base as an ad-
Table 1. Synthesis of Alkoxo-amino-TAZ Derivatives (6 and 7) from Reactions of TCTAZ (1) with Various Alcohols (ROH) and 4-Piperidinemethanol (pH)

| Entry | ROH | Method | Ratio of 1:ROH: (Additive 1):pH: (Additive 2) | Conditions in Step 1 | Conditions in Step 2 | Products (yield %) |
|-------|-----|--------|---------------------------------------------|----------------------|----------------------|-------------------|
| 1     | a   | A      | 1:1.2:(1.2):4:(4)                            | 0°C 1 h              | rt 14 h              | 6app (61), 7app (trace) |
| 2     | a   | A      | 1:2.4:(2.4):2:(2)                            | 0°C 1 h              | rt 14 h              | 6app (79), 7app (3), 8app (8) |
| 3     | a   | A      | 1:2:(8):2                                  | 0°C 15 min to reflux 16 h, N2, THF | rt 19 h, reflux 49 h, N2, THF | 6app (13), 5pp (1), 8app (62) |
| 4     | a   | A      | 1:25.5:(3):2:(2)                            | rt 1 h, N2           | rt 1.5 h to reflux 39 h, N2, acetone | 6app (21), 8app (8) |
| 5     | a   | A      | 1:10:(5):2:(2)                              | rt 0.5 h to 60°C 2.5 h, N2 | rt 18 h, N2         | 6app (8), 7app (60) |
| 6     | b   | A      | 1:10:(2):2:(2)                              | rt 0.5 h to reflux 4 h, N2 | rt 21 h             | 6bpp (84) |
| 7     | b   | A      | 1:10:(2):2:(2)                              | rt 1 h to reflux 19 h, N2 | rt 21 h             | 6bpp (73), 7bfp (26) |
| 8     | b   | B      | 1:4.8:(3)                                  | rt 1 h to reflux 17 h, CHCl3 | —                   | 2b (28) |
| 9     | b   | B      | 1:6:(3)                                    | rt 7d, N2, THF | —                   | 3bb (2), 4bb (9) |
| 10    | e   | A      | 1:10:(5):2:(2)                              | rt 30 min, N2         | rt 23 h, N2         | 6cpp (72) |
| 11    | e   | A      | 1:10:(2.5):2:(2)                           | rt 1 h to reflux 22 h, N2 | rt 38 h             | 6cpp (12), 7cpp (10) |
| 12    | e   | C      | 1:2:(2):1.6                                | rt 30 min to reflux 2.5 h, N2 | rt 30 min          | 7cpp (73) |
| 13    | d   | A      | 1:2.2:(2.2):2:(2)                          | rt 1 h to reflux 16 h, N2 | rt 24 h             | 6dpp (62), 7dpp (6) |
| 14    | d   | A      | 1:10:(2):2:(2)                             | rt 2.5 h to reflux 17 h, N2 | rt 21 h             | 6dpp (67), 7dpp (25) |
| 15    | d   | C      | 1:2:(2):1.6                                | rt 30 min to reflux 2 h, N2 | rt 30 min          | 7dpp (67), 7pp (detected) |
| 16    | e   | A      | 1:10:(5):2:(2)                              | rt 1 h to reflux 3 h, N2 | rt 19 h             | 6ep (80) |
| 17    | e   | A      | 1:10:(2):2:(2)                             | rt 1 h to reflux 1 d, N2 | rt 20 h             | 6ep (22), 7ep (54) |
| 18    | f   | A      | 1:2.2:(2.2):2:(2)                          | rt 1 h to reflux 19 h, N2 | rt 23 h             | 6fp (54), 7fp (38) |
| 19    | f   | A      | 1:10:(2):2:(2)                             | rt 1 h to reflux 20 h, N2 | rt 4h               | 6fp (31), 7fp (52) |
| 20    | g   | A      | 1:2:(2):2:(2)                              | rt 5.5 h             | rt 2h               | 6gpp (4), 7gpp (47) |
| 21    | g   | A      | 1:2.6:(2):2:(2)                            | rt 4 d, acetone | —                   | 6gpp (16), 7gpp (52) |
|       |     |        |                                             |                      |                      |                   |

a) DIPEA stands for N,N-diisopropylethylamine. Dry solvents were used in all reactions except for CHCl3 in the reaction of Entry 8. b) The additives and solvents used are as follows: Method A (Additive 1 = collidine, Solvent 1 = acetone, Additive 2 = DIPEA, Solvent 2 = CH3CN), Method B (Additive 1 = NaHCO3, Solvent 1 = CH3CN), and Method C (Additive 1 = n-BuLi, Solvent 1 = THF, no Additive 2, Solvent 2 = CH3CN). c) Yield obtained from TCTAZ (1). d) The by-products 6pp (16%) and 7wap (12%) (Entry 1), 6wp (14%) (Entry 2), 6pp (25%) (Entry 5), 7wp (5%) (Entry 6), 7wp (2%) (Entry 7), and 7wp (5%) (Entry 18) were also isolated. These compounds apparently suffer from hydrolysis of intermediates by moisture in the commercial alcohols used in each entry. In Entry 3, the by-product 5pp (structure shown below) derived from the reaction with DIPEA was further applied to the reported procedure using NaHCO3 (Method B) to obtain an intermediate 3bb; however, a few of our trials were unsuccessful and resulted in the isolation of monoalkoxy-dichloro-TAZ intermediate 2h (22) (Entry 8) or trialkoxy TAZ (4bhb) (Entry 9) as a main product in low yields.

With the aim of improvement of the yield of the target dialkoxy TAZ derivatives (7), we also attempted reactions with secondary alcohols (eH and dH) (Entries 12 and 15) and found that the use of n-BuLi (Method C) is effective for the formation of the desired dialkoxy-TAZ derivatives (7cpp and 7cpp). The generated alkoxide anion (RO-) probably works as a better nucleophile to give the target TAZ derivatives (7) in high yields. For the preparation of dialkoxy-monoamino-TAZ derivatives (7), this method has a considerable advantage over the others (Methods A and B) in terms of reaction yield.5)

In the case of a phenolic alcohol (sesamol: gH), the target derivative (7gpp) was smoothly obtained by reactions of TCTAZ (1) with gH (Entries 20 and 21) using Method A, to-
From these reactions of TCTAZ with various alcohols (a–gH) and an amine (pH) described above, we could achieve conventional preparation for targeted symmetrical TAZ derivatives (6 and 7). In some runs, we also isolated other trisubstituted TAZ derivatives including 4bbb, 6wpp, 7wap, 7wbp, 7wep, 7wfp, and 8ap formed as by-products (see Table 1).

All structures of the synthesized compounds were easily confirmed by spectroscopic and analytical data. The geometries of C₃-symmetrical structures of target TAZ derivatives described in this article were also confirmed by ¹³C-NMR spectroscopic data.

### Results and Discussion

With respect to a three-dimensional interaction of a bioactive molecule for its binding site, it is expected that van der Waals interactions or formation of hydrogen bonds between substituents in the bioactive molecule and a host macromolecule play an important role for biological activity. The results obtained in our previous experiments ⁷ seemed to indicate that a C₃-symmetrical TAZ structure with an amine and/or two alkoxy groups on a TAZ template is required for anti-HSV-1 active interaction.

The structures of targeted C₃-symmetrical 2,4,6-trisubstituted TAZ derivatives in this study obtained from TCTAZ and results of biological evaluations [anti-HSV-1 activities (EC₅₀) by plaque reduction assays ⁶ and their cytotoxicities against Vero cells (IC₅₀)] are summarized in Table 2 together with the data of aciclovir. Calculated log P values ⁸ for the compounds are also shown in Table 2. There were few distinct correlations between log P values and EC₅₀ values or between log P values and IC₅₀ values among the compounds listed in Table 2.

C₃-symmetrical derivatives (6app and 6bpp) having a relatively small aliphatic alkoxy group showed no significant anti-HSV-1 activity (EC₅₀ = >100µM) or cytotoxic activity (IC₅₀ = >200µM). Introduction of two same alkoxy groups in the above TAZ template (7aap and 7bbp) also resulted in no significant biological activities, indicating no enhancement effect of this modification. However, modifications of TAZ derivatives having a more bulky alkoxy group than the isopropoxy group in the TAZ template (such as 6dpp, 6epp, and 6fpp) to TAZ derivatives having two bulky alkoxy groups in the template (such as 7ddp, 7eep and 7ffp) resulted in C₃-symmetrical compounds with greater cytotoxicity as shown in Table 2. In contrast, a similar modification of compound 6gpp by introduction of an aryloxy group resulted in reverse cytotoxic activity affording compound 7ggp with lower cytotoxicity.

Anti-HSV-1 activities of some other 2,4,6-trisubstituted TAZ derivatives (4bbb, 6wpp, 7wap, 7wfp, and 8ap) obtained through our synthetic trials were also evaluated and the results are shown in Table 2. It is noteworthy that the C₃-symmetrical TAZ derivative 4bbb showed surprisingly high anti-HSV activity (EC₅₀ = 1.87µM) and low cytotoxic activity (IC₅₀ = 479.8µM), thus resulting in a better selectivity index (IC₅₀/EC₅₀ = 256.6). This unexpected result provides useful information for modification of this symmetrical class of compounds.

Triamino-substituted C₃-type derivatives reported in our previous paper ⁷ showed no anti-HSV activity at a concent-
lation less than 100 μM. On the basis of previous data, we considered the dialkoxo-amino-substituted TAZ structure to be a probable core structural feature for an anti-HSV-1 active molecule for this series. In terms of high anti-HSV-1 activity with a good selectivity index, new trialkoxy-substituted TAZ derivatives such as 4bbb appear to have a great potential as leads in the search for antiviral compounds. In order to verify this potential information, we have already begun to perform further various structural modifications of compound 4bbb and biological evaluation of the TAZ derivatives obtained as a new project. We are also investing the sugar recognition properties of highly antiviral active tri-substituted TAZ derivatives by using isothermal titration calorimetry. The results of modification and SAR studies of the trialkoxy-substituted TAZ derivatives will be described in the following paper.

**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 spectropho-

| Compound | EC₅₀ (μM) | IC₅₀ (μM) | Log P<sup>a</sup> |
|----------|-----------|-----------|------------------|
| 6app     | >100      | >200      | 1.93             |
| 7aap     | >100      | >200      | 1.43             |
| 6bpp     | >100      | >200      | 2.74             |
| 7bbp     | >100      | >200      | 3.05             |
| 6cpp     | >100      | 116.8     | 3.71             |
| 6dpb     | 67.2      | 295.4     | 3.21             |
| 7dpb     | >100      | 28        | 4.00             |
| 6epp     | 124.3     | 224.9     | 3.63             |
| 7eep     | >100      | 85.1      | 4.83             |

| Compound | EC₅₀ (μM) | IC₅₀ (μM) | Log P<sup>a</sup> |
|----------|-----------|-----------|------------------|
| 6fpp     | >25       | 81.2      | 4.05             |
| 7ffp     | >12.5     | 27        | 5.67             |
| 6gpp<sup>b)</sup> | >6.3 | 42.2 | 3.52 |
| 7ggp     | 32.2      | 303.6     | 4.62             |
| 4bbb     | 1.87      | 479.8     | 3.36             |
| 6wpp     | >100      | >200      | 1.82             |
| 7wbp     | >100      | >200      | 1.32             |
| 7wfp     | >100      | >200      | 3.44             |
| 8ap      | >100      | >200      | 1.89             |

<sup>a</sup> Log P was calculated by using ChemBioDraw 13.0.2.3021. <sup>b</sup> Data were taken from ref. 7. <sup>c</sup> Data were taken from ref. 17.
tometer. Low- and high-resolution mass spectra (LR-MS and HR-MS) were obtained by a JEOL JMS SX-110 double-focusing model equipped with an FAB ion source interfaced with a JEOL JMAS-DX 7000 data system. 1H- and 13C-NMR spectra were obtained by JEOL JNM A-500. Chemical shifts were expressed in δ ppm downfield from an internal TMS signal for 1H-NMR and the carbon signal of the corresponding solvent [CDCl3 (77.00 ppm), DMSO-d6 (39.50 ppm), and THF-d8 (68.60 ppm)] for 13C-NMR. The abbreviations qu=quintet, dm=double multiplets and tm=triplet multiplets are used for the multiplicity of 1H-NMR data, respectively. The signal assignments were confirmed by two-dimensional (2D) NMR analyses; 1H–1H 2D correlation spectroscopy (COSY); 1H–13C heteronuclear multiple-quantum coherence (HMQC), 1H–13C heteronuclear multiple-bond connectivity (HMBC). Microanalyses were performed with a Yanaco MT-6 CHN chorder. Routine monitoring of reactions was carried out using precoated Kieselgel 60F254 plates (E. Merck). Centrifugal or flash column chromatography was performed on silica gel (Able-Biott or Kanto 60N) with a UV detector. Commercially available starting materials were used without further purification, and dry solvents were used in all reactions except for Entry 8.

**General Procedure for the Preparation of Alkoxo-amino-1,3,5-triazine Derivatives (Method A): Example: Preparation of 1,1′-[6-(2-Methoxyethoxy)-1,3,5-triazin-2,4-diyl]-bis(4-piperidinemethanol) (6app) (Entry 1): (Step 1)** To a solution of 2,4,6-trichlorotriazine (TAZ: cyanuric chloride) (1, 922 mg, 5.0 mmol) and collidine (727 mg, 6.0 mmol) in dry acetone (10 mL) was added 2-methoxyethanol (aill, 457 mg, 6.0 mmol) at 0°C. After stirring for 1 h at 0°C, the resulting colorless precipitated collidine HCI was removed by filtration, and then the solvent was evaporated to afford a yellow oily residue. (Step 2) This material was dissolved in dry CH2CN (15 mL), and 4-piperidinemethanol (dill, 2.3 g, 20.0 mmol) and N,N-diisopropylethylamine (DIPA, 2.58 g, 20.0 mmol) were added, and the resulting mixture was stirred for 14 h at room temperature. After evaporation of the solvent, the residue was separated by flash chromatography (CH2Cl2:95% EtOH:28% NH4OH:3:6.5:0.5 to 85:14.5:0.5) to give 6app (1.17 g, 61% yield) as a yellow solid. Compounds 6wpp [4,6-bis[4-((hydroxymethyl)piperidin-1-yl)-1,3,5-triazin-2(1H)-one] (253 mg, 16% yield) as a pale yellow solid and 7wapp 4-[(4-(hydroxymethyl)piperidin-1-yl)-6-(2-methoxyethoxy)-1,3,5-triazin-2(1H)-one] (173 mg, 12% yield) as a colorless opaque solid were also isolated in reaction products. Compound 7wapp was also detected by TLC. Recrystallization from Et2O or EtOH gave an analytically pure product 6app or 6wpp.

**Preparation of [1-[4-Chloro-6-(2-methoxyethoxy)-1,3,5-triazin-2-yl]piperidin-4-yl)methanol (8ap) and [1-[4-Chloro-6-[Ethyl(isopropyl)amino]-1,3,5-triazin-2-yl]piperidin-4-yl)methanol (5rp) (Entry 3): (Step 1)** To a solution of 1 (922 mg, 5.0 mmol) and DIPA (2.58 g, 20.0 mmol) in dry THF (125 mL) was added aill (380 mg, 5.0 mmol) at 0°C under an N2 atmosphere with stirring. After stirring for 15 min at 0°C and for 10 min at room temperature, additional DIPA (2.58 g, 20.0 mmol) and aill (380 mg, 5.0 mmol) were added, and then the reaction mixture was stirred for 16 h at room temperature. (Step 2) To this yellow reaction mixture was added pH (1.15 g 10.0 mmol), and the resulting mixture was stirred at 70°C for 1 h under an N2 atmosphere. After filtration of the separated amine hydrochloride (pH-HCl), the filtrate was evaporated and the residue was separated by flash chromatography (CH2Cl2:95% EtOH:28% NH4OH:3:6.5:0.5 to 93:6.6:0.4) to give 5rp (221 mg, 14%), 8ap (941 mg, 62%), 6app (253 mg, 13%), and 5pp (22 mg, 1%). An analytical sample of 8ap was obtained by recrystallization from EtOH–H2O.

**8ap:** Colorless crystals, mp 86–87°C (EtOH–H2O). IR (KBr) cm⁻¹: 3416 (OH of alcohol), 1573, 1503 (C=O), 1099 (C–N), 1253, 1099, 1032 (C–O of alcohol and ether). 1H-NMR (CDCl3) δ: 1.17 (4H, m, H3β’, 5’β’), 1.77 (6H, dm, J=12.8Hz, H3α’, 5α’, 4α’), 1.82 (2H, brs, OH), 2.80 (4H, tm, J=13.1Hz, H2β’, 6’β’), 3.40 (3H, s, OCH3), 3.49 (4H, d, J=6.1Hz, H1), 3.71 (2H, t, J=5.2Hz, H2’), 4.42 (2H, t, J=5.2Hz, H2’), 4.76 (4H, br d, J=13.1Hz, H2α’, 6α’). 13C-NMR (CDCl3) δ: 28.55 (C3’, 5’), 39.08 (C4’), 43.27 (C2’, 6’), 58.89 (OCH3), 65.05 (C1’), 67.54 (C1), 70.60 (C2’), 165.80 (C2’, 4’), 170.73 (C6’).

Positive-ion FAB-MS m/z: 382 (M+H⁺). HR-FAB-MS m/z: 382.2454 (C31H31N5O4); 382.2454. Anal. Caled for C31H31N5O4: C, 56.67; H, 8.19; N, 18.36. Found: C, 56.60; H, 8.17; N, 18.40.
18.40. Found: C, 47.23; H, 6.22; N, 18.39.

7bbp: mp 95–96°C (from methyclyclohexane). IR (KBr) cm\(^{-1}\): 3398 (OH of alcohol), 1580, 1540 (C=O). 1H-NMR (CDCl\(_3\)): \(\delta\) 1.20 (2H, m, H3β/5′β), 1.36 (12H, d, J=6.4 Hz, CH2), 1.79 (4H, m, H3α, 5′a, 4′α, OH), 2.85 (2H, dt, J=12.8, 2.4 Hz, H2β, 6′β), 3.52 (2H, d, J=6.1 Hz, H1), 4.40 (4H, t, J=4.9 Hz, H2′), 4.47 (4H, t, J=4.9 Hz, H1′), 4.79 (2H, dm, J=13.1 Hz, H2′α, 6′a). 13C-NMR (CDCl\(_3\)) \(\delta\): 28.85 (C3′, 5′), 39.00 (C4′), 43.54 (C2′, 6′), 58.78 (OCH3), 66.05 (C1′), 67.19 (C1), 70.30 (C26), 166.26 (C27), 171.2 (C6′). Positive-ion FAB-MS m/z: 343 (M+H\(^+\)). HR-FAB-MS m/z: 269.1614 (Calcd for C\(_{12}\)H\(_{21}\)N\(_4\)O\(_3\): 269.1608).

1-[4-(6-Diisopropoxy-1,3,5-triazin-2-yl)piperidin-4-yl]methanol (7bbp) (Entry 7) This compound was prepared from 4bH by method A under the conditions shown in Table 1. Separation of the products by flash chromatography (CH\(_2\)Cl\(_2\): 95% EtOH:28% NH\(_4\)OH:95:4.7:0.3→93:6.6:0.4) gave 7bbp (26%) and 6bwp (73%) as a pale yellow oil and pale yellow solid, respectively. An analytical sample of 7bbp was obtained by recrystallization from methyclyclohexane as pale yellow crystals.

7bbp: mp 95–96°C (from methyclyclohexane). IR (KBr) cm\(^{-1}\): 3398 (OH of alcohol), 1580, 1540 (C=O). 1H-NMR (CDCl\(_3\)): \(\delta\) 1.20 (2H, m, H3β/5′β), 1.36 (12H, d, J=6.4 Hz, CH2), 1.79 (4H, m, H3α, 5′a, 4′α, OH), 2.85 (2H, dt, J=12.8, 2.4 Hz, H2β, 6′β), 3.52 (2H, d, J=6.1 Hz, H1), 4.40 (2H, dm, J=13.4 Hz, H2′α, 6′a), 5.29 (1H, qu, J=6.4 Hz, OCH3). 13C-NMR (CDCl\(_3\)) \(\delta\): 21.90 (CH3), 28.85 (C3′, 5′), 39.00 (C4′), 43.54 (C2′, 6′), 67.41 (C1), 70.08 (OCH3), 166.63 (C27), 171.46 (C4′, 6′). Positive-ion FAB-MS m/z: 311 (M+H\(^+\)). HR-FAB-MS m/z: 311.2080 (Calcd for C\(_{12}\)H\(_{21}\)N\(_4\)O\(_3\): 311.2083). Anal. Caled for C\(_{12}\)H\(_{21}\)N\(_4\)O\(_3\): 0.25H\(_2\)O: C, 58.04; H, 8.44; N, 18.60. Found: C, 57.84; H, 8.56; N, 18.02.

4.6-Dichloro-2-isopropoxo-1,3,5-triazine (2b) (Entry 8): (Step 1) To a mixture of NaHCO\(_3\) (2.52 g, 30 mmol) and dry 4bH (2.88 g, 48 mmol) in dry CHCl\(_3\) (4 mL) was added compound 1 (1.84 g, 10 mmol) at room temperature with stirring. After stirring for 1 h at room temperature, the reaction mixture was refluxed for 17 h. After addition of CHCl\(_3\) (10 mL), the resulting mixture was washed with 1% aqueous NaHCO\(_3\) solution (10 mL×3) and the organic layer was dried with MgSO\(_4\). After evaporation of the solvent, the residue was separated by centrifugal chromatography (n-hexane:EtOAc=95:5) to give 2b (583 mg, 28% yield) as a colorless oil.

2b: IR (NaCl) cm\(^{-1}\): 2987 (CH), 1542, 1500 (C=N), 1100, 1036 (C=O of ether), 861, 807 (C=Cl). 1H-NMR (CDCl\(_3\)) \(\delta\): 1.44 (6H, d, J=6.1 Hz, CH3), 5.41 (1H, qu, J=6.1 Hz, O–CH<). 13C-NMR (CDCl\(_3\)) \(\delta\): 21.42 (CH3), 74.90 (O–CH<), 170.51 (C2), 172.47 (C4, 6). The positive FAB mass spectra of this compound showed no significant molecular ion to determine its chemical formula, indicating the instability of the corresponding molecular ion in the mass range.

Procedure for the Synthesis of 2,4,6-Trisopropoxy-1,3,5-triazine (4bhp) and 2-Chloro-4,6-diisopropoxy-1,3,5-triazine (3bb) (Method B) (Entry 9): (Step 1) To a mixture of NaHCO\(_3\) (0.54 g, 60 mmol) and dry 4bH (7.20 g, 120 mmol) in dry THF (40 mL) was added compound 1 (3.69 g, 20 mmol) at room temperature under an N\(_2\) atmosphere with stirring. After stirring for 7 d at room temperature, the reaction mixture was filtered over celite and the filtrate was evaporated. To the residual oil was added CH\(_2\)Cl\(_2\) (50 mL) and the separated insoluble material was removed by filtration. The solvent was evaporated and the residual oil was separated by centrifugal chromatography (n-hexane:EtOAc=98:2→90:10) to give 3bb (79 mg, 2%), 4bhp (442 mg, 9%).

4bhp: Colorless crystals, mp 92–94°C. IR (KBr) cm\(^{-1}\): 3433 (OH of H\(_2\)O), 1563 (C=O), 1148, 1095 (C=O of ether). 1H-NMR (CDCl\(_3\)) \(\delta\): 1.38 (18H, d, J=6.4 Hz, CH3), 5.35 (3H, qu, J=6.4 Hz, O–CH<). 13C-NMR (CDCl\(_3\)) \(\delta\): 21.81 (CH3), 71.32 (O–CH<), 172.67 (C=N). Positive-ion FAB-MS m/z: 256...
the conditions shown in Table 1. Purification of the product by flash chromatography (CHCl₃: EtOH: 28% NH₃ = 2:7.2:0.3 → 9.5:0.5) gave 7ddp (25%) and 6ddp (67%) as a pale yellow oil and pale yellow solid, respectively. An analytical sample of 6ddp was obtained by recrystallisation from CH₂CN as pale yellow crystals.

6ddp: mp 178–179°C (from CH₂CN). IR (KBr) cm⁻¹: 3427 (OH of alcohol), 1568, 1519 (C=O), 1253, 1105, 1039 (C–O). ¹H-NMR (CDCl₃) δ: 1.18 (4H, m, H₃β, 5β), 1.56 (2H, m, H₃", 4"), 1.59 (2H, br, OH), 1.71–1.87 (10H, m, H4α, 3", 4", 3'α, 5α, 2", 5"), 1.94 (2H, m, H2", 5"), 2.79 (4H, dt, J = 12.8, 12.1 Hz, H2'/β, 6'/β), 3.50 (4H, d, J = 5.88 Hz, H1), 4.78 (4H, br d, J = 12.8 Hz, H2'/α, 6'/α), 5.33 (1H, m, H"α), ¹³C-NMR (CDCl₃) δ: 24.04 (C3", 4"), 28.58 (C3', 5'), 32.77 (C2", 5"), 39.14 (C4'), 43.26 (C2', 6'), 67.65 (C1), 78.65 (C1"), 165.90 (C2', 4"), 170.71 (C6'). Positive-ion FAB-MS m/z: 392 (M⁺+H'). HR-FAB-MS m/z: 392.2662 (Calcd for C₂₃H₂₈N₅O₃: 392.2662). Anal. Calcd for C₂₃H₂₈N₅O₃: C, 61.36; H, 8.50; N, 17.89. Found: C, 61.34; H, 8.70; N, 17.89.

[1-i,4,6-Bis(cyclopentenyl)-1,3,5-triazin-2-yl]pyridin-4-yl)methanol (7dpd) (Entry 15) This compound was prepared from d11 by method C under the conditions shown in Table 1. Purification of the product by flash chromatography (n-hexane:i-PrOH:Et₂NH=120:30:0.1) gave 7dpd (67%) as a colorless oil. An analytical sample of 7dpd was obtained by recrystallisation from methylcyclohexane as colorless crystals. Formation of compound 5pp was also detected by TLC.

7dpd: mp 62–66°C (from methylcyclohexane). IR (KBr) cm⁻¹: 3333 (OH of alcohol), 1584, 1544 (C=O), 1273, 1130, 1108, 1046 (C–O). ¹H-NMR (CDCl₃) δ: 1.21 (2H, m, H₃β, 5β), 1.58 (5H, m, OH, H₃", 4"), 1.79 (11H, m, H4α, 3", 4", 3'α, 5α, 2", 5"), 1.95 (4H, m, H2", 5"), 2.85 (4H, dt, J = 13.2, 2.71 Hz, H2'/β, 6'/β), 3.51 (2H, d, J = 6.11 Hz, H1), 4.80 (2H, d, J = 15.66 Hz, H2'/α, 6'/α), 5.40 (2H, m, H"α). ¹³C-NMR (CDCl₃) δ: 23.98 (C3", 4"), 28.56 (C3', 5'), 32.75 (C2", 5"), 39.00 (C4'), 43.55 (C2', 6'), 67.49 (C1), 79.56 (C1"), 166.52 (C2'), 171.64 (C6'). Positive-ion FAB-MS m/z: 363 (M⁺+H'). HR-FAB-MS m/z: 363.2397 (Calcd for C₁₃H₁₈N₅O₃: 363.2396). Anal. Calcd for C₁₃H₁₈N₅O₃: 0.44-H₂O: C, 65.17; H, 8.93; N, 13.95. Found: C, 65.07; H, 9.10; N, 13.68.

1,1’-(6-Cyclohexylenoxyl)-1,3,5-triazin-2-4-diybispiperidin-4-yl)methanol (6epp) (Entry 16) This compound was prepared from cyclohexanol (e1l) by method A under the conditions shown in Table 1. Purification of the product by flash chromatography (CH₂Cl₂: EtOH: 28% NH₃ = 930:66:4) gave 6epp (80%) as a yellow solid. Recrystallisation from CH₂CN gave an analytically pure product 6epp.

6epp: mp 172–173°C (from CH₂CN). IR (KBr) cm⁻¹: 3466, 3275 (OH of alcohol) 1252, 1038 (C–O of ether). ¹H-NMR (CDCl₃) δ: 1.18 (4H, m, H₃β, 5β), 1.25 (1H, m, H₄"), 1.35 (2H, m, H₃", 5"), 1.51 (2H, m, H₂", 6"), 1.58 (1H, m, H₄"), 1.7–1.9 (10H, m, H4', 3'α, 5'α, 2', 5'), 5.03 (4H, d, J = 5.88 Hz, H1), 4.76 (4H, d, J = 13.46 Hz, H2'/α, 6'/α), 4.91 (1H, m, H"α). ¹³C-NMR (CDCl₃) δ: 24.28 (C3", 5"), 25.56 (C4"), 28.58 (C3', 5'), 31.87 (C2", 6"), 39.11 (C4'), 43.24 (C2', 6'), 67.60 (C1), 74.54 (C1"), 165.95 (C2', 4"), 170.38 (C6'). Positive-ion FAB-MS m/z: 406 (M⁺+H'). HR-FAB-MS m/z: 406.2820 (Calcd for C₂₃H₂₈N₅O₃: 406.2818). Anal. Calcd for C₂₃H₂₈N₅O₃: C, 62.20; H, 8.70; N, 17.27. Found: C, 62.04; H,
1H-NMR (CDCl₃): δ: 1.23 (2H, m, 3β, 5β), 1.45 (2H, m, H3β, 6β), 1.57 (4H, m, H4α, 5α), 1.71 (2H, m, H3α, 6α), 1.7–1.9 (6H, m, OH, H2β, 7α, 7β, 3α, 5α), 2.01 (2H, m, H2β, 7β), 2.89 (2H, m, H2/6β), 3.52 (2H, m, H1), 4.72 and 4.92 (2H, brs, H2α, 6a), 5.18 (1H, m, H1α). 13C-NMR (CDCl₃): δ: 22.86 (C3), 28.30 (C4), 28.44 (C5), 33.46 (C2, 7α), 38.81 (C4), 43.17 (C2, 6α), 67.29 (C1), 79.83 (C1', 159.62 (C2), 161.30 (C4 or C6), 164.43 (C6 or C4). Positive-ion FAB-MS m/z: 323 (M+H⁺). HR-FAB-MS m/z: 323.2087 (Calcd for C₂₂H₂₅N₃O₃: 323.2083). Anal. Calcd for C₂₂H₂₅N₃O₃: C, 59.61; H, 8.13; N, 17.38. Found: C, 59.44; H, 8.25; N, 17.47.

7fep: mp 127–128°C (from CH₂CN). IR (KBr) cm⁻¹: 3363 (OH of ROH) 1252, 1185, 1123 (C=O of ROH and ether). 1H-NMR (CDCl₃): δ: 1.20 (2H, m, H3β, 5β), 1.46 (4H, m, H3β, 6β), 1.58 (8H, m, H4α, 5α), 1.68–1.84 (12H, m, H3ε, 6ε, 2ε, 7ε, 4ε, 3α, 5α, OH), 2.04 (4H, m, H2β, 7β), 2.84 (2H, dt, J=13.1, 1.8Hz, H2β, 6β), 3.51 (2H, d, J=5.8Hz, H1), 4.79 (2H, dm, J=13.1Hz, H2α, 6α), 5.19 (1H, m, H1α). 13C-NMR (CDCl₃): δ: 23.63 (C3), 25.20 (C4), 28.55 (C5), 31.28 (C2', 6'), 38.72 (C4'), 44.15 (C2', 6'), 67.09 (C1), 75.29 (C1'), 159.98 (C2'), 161.75 (C4' or 6'), 163.90 (C6' or 4'). Positive-ion FAB-MS m/z: 309 (M+H⁺). HR-FAB-MS m/z: 309.292 (Calcd for C₁₂H₂₀N₂O: 309.2927). 1-(6-Cycloheptyloxy-1,3,5-triazin-2-yl)piperidin-4-yl)methanol (7gpp) (Entry 21) This compound was prepared from sesamol (gH) by method A under the conditions shown in Table 1. Purification of the product by flash chromatography (CH₂Cl₂: 95% EtOH: 28% NH₃=950:47.3:930:66:4) gave 7gpp (52%) as a white solid and 6gpp (16%) as a white solid. Recrystallization from EtCN gave an analytically pure product 7gpp as colorless crystals. 7gpp: mp 201–203°C (from EtCN). IR (KBr) cm⁻¹: 3377 (OH of alcohol), 1242, 1177, 1137, 1038 (C=O of alcohol and ether). 1H-NMR (CDCl₃): δ: 1.68 (2H, m, H3β, 5β), 1.34 (1H, brs, OH), 1.75 (3H, m, H4α, 3α, 5α), 2.82 (2H, dt, J=12.8, 2.1Hz, H2β, 6β), 3.51 (2H, d, J=5.8Hz, H1), 4.62 (2H, d, J=13.4Hz, H2α, 6α), 5.97 (4H, s, H2α), 6.59 (2H, dd, J=8.2, 2.1Hz, H6α), 2.66 (2H, d, J=2.1Hz, H4β), 6.74 (2H, d, J=8.2Hz, H7β). 13C-NMR (CDCl₃): δ: 28.45 (C3, 5'), 38.81 (C4'), 43.75 (C2', 6'), 67.35 (C1), 101.58 (C2'), 104.04 (C4'), 107.68 (C7'), 114.11 (C6'), 144.98 (C7a), 146.61 (C5'), 147.73 (C3', 5'). Positive-ion FAB-MS m/z: 476 (M+H⁺). HR-FAB-MS m/z: 476.1572 (Calcd for C₂₂H₂₅N₃O₃: 476.1576). Anal. Calcd for C₂₂H₂₅N₃O₃: C, 59.22; H, 4.75; N, 12.01. Found: C, 59.14; H, 4.82; N, 12.02.

Antiviral Activity Assay and Cytotoxicity of Target Compounds The antiviral activities of synthesized compounds were measured by using a plaque reduction assay(a) as described in our previous paper.(b) Results for antiviral activity (EC₅₀) and cytotoxicity (IC₅₀) with Vero cells are summarized in Table 2.
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11) After chromatography of the reaction products, purification of compound 7ddp by recrystallization was employed, but purification of the product 7cep was very difficult and gave an oily material containing a few contaminants that had similar chemical properties. A small amount of compound Ce or Cd shown below was detected as a contaminant in the obtained product 7cep or 7ddp. We are considering investigation of further improvement in the purification stages of the products. The results of biological evaluations and the calculated log $P$ value for compound 6cpp are shown in Table 2.