

HETEROCYCLES, Vol. 81, No. 6, 2010, pp. 1419 - 1426. © The Japan Institute of Heterocyclic Chemistry
Received, 8th April, 2010, Accepted, 23rd April, 2010, Published online, 26th April, 2010
DOI: 10.3987/COM-10-11961

SYNYHESIS AND ANTI-HEPATITIS C VIRUS ACTIVITY OF MORPHOLINO TRIAZINE DERIVATIVES

Takashi Misawa,^a Mohammed T. A. Salim,^b Mika Okamoto,^b Masanori Baba,^{*b} Hiroshi Aoyama,^a Yuichi Hashimoto,^a and Kazuyuki Sugita^{*a}

^aInstitute of Molecular & Cellular Biosciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan. ^bDivision of Antiviral Chemotherapy, Center for Chronic Viral Diseases, Graduate School of Medical and Dental Sciences, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima 890-8544, Japan. (*Corresponding authors: K. Sugita for chemical part and M. Baba for biological part)

E-mail : sugitakazu@iam.u-tokyo.ac.jp; E-mail : m-baba@vanilla.ocn.ne.jp

Abstract – A series of morpholino triazines was synthesized and evaluated for anti-hepatitis C virus (HCV) activity. Incorporation of OMe, CN and F into the phenyl moiety afforded analogues with moderate potency and good selectivity, as assessed with the subgenomic HCV RNA replicon assay.

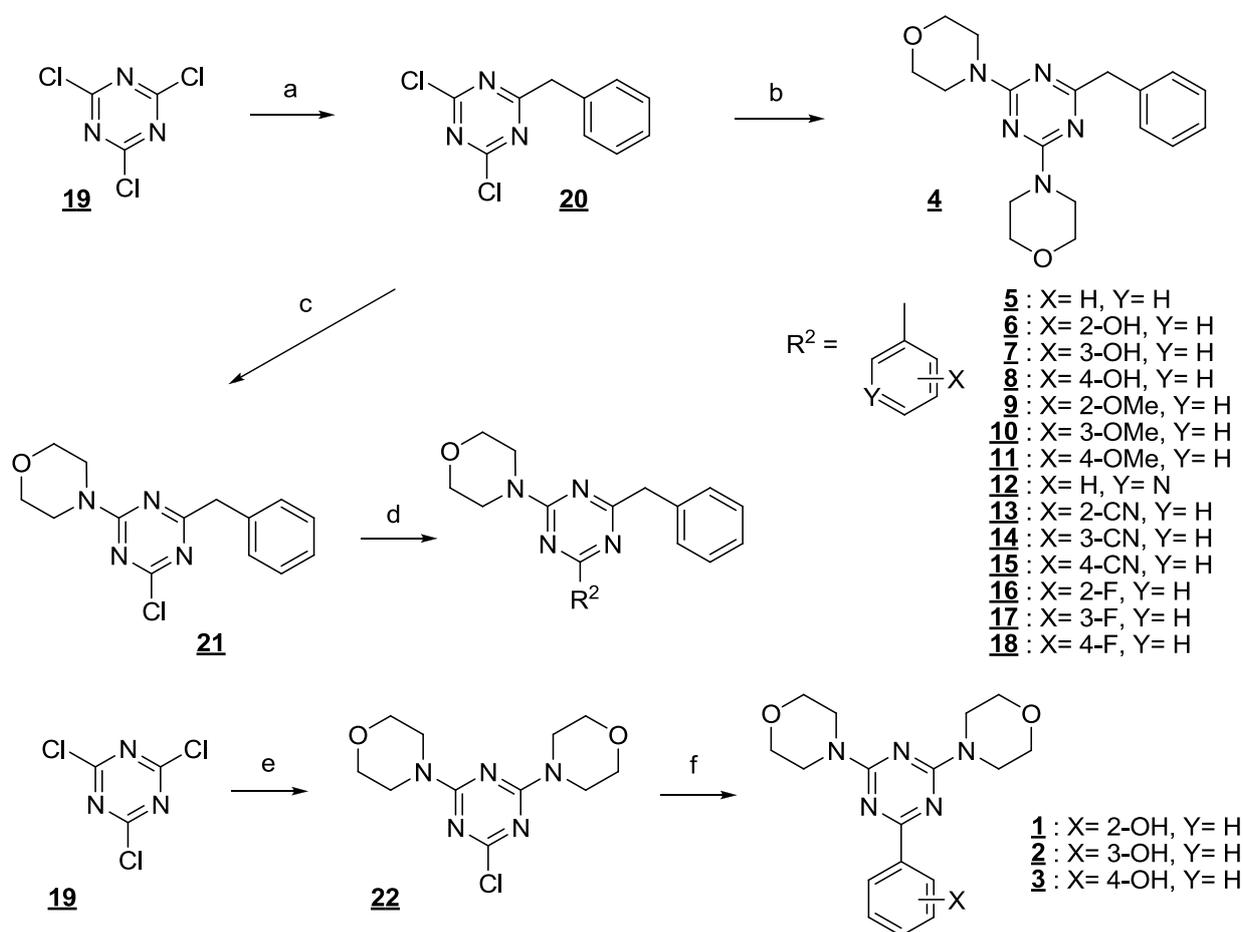
Hepatitis C virus (HCV) infection is a principle cause of chronic liver disease^{1,2} leading to cirrhosis, hepatocellular carcinoma or liver failure in humans.^{3,4} HCV is estimated to infect over 170 million people worldwide.⁵ The best current treatment option is a pegylated interferon / ribavirin combination, but this has only limited efficacy against the most prominent HCV genotype (1a/1b), and has significant side effects.⁶ Chronic HCV infection has been associated with liver fibrosis, liver cirrhosis, hepatocellular carcinoma, and other forms of liver dysfunction. In industrialized nations, HCV infection has become a major reason for orthotopic liver transplantation. Given the widespread impact of this disease, there is a substantial medical need for new anti-HCV agents to complement current therapies.

We have previously found extremely versatile mother nuclei⁷⁻¹¹ so-called multi-templates¹²⁻¹⁶ that act as highly efficient scaffolds for the creation of biologically active compounds. This time, we focused on a diphenylmethane template, which has already yielded several potent compounds.^{8,9,11} Along this line, we

have already reported some anti-HCV compounds with good activity.¹⁷ The benzyl triazine unit was chosen as an extension of the diphenylmethane template. A series of 2-benzyl-4-(morpholin-4-yl)-1,3,5-triazine derivatives was synthesized, together with bismorpholino-1,3,5-triazine derivatives, and their anti-HCV activity was examined.

The compounds described in this paper were prepared according to usual organic synthetic methods.¹⁸ The general synthesis of morpholino triazine compounds (**1**) – (**18**) is outlined in Chart 1. Starting from cyanuric trichloride, the benzyl unit, morpholine ring and phenyl substituent were introduced.

Chart 1. Synthesis of morpholino triazine compounds

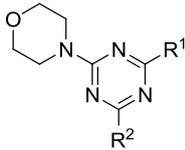
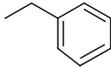
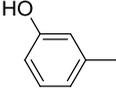
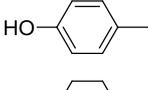
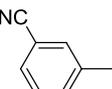
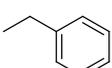
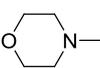
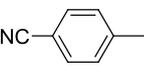
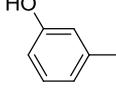
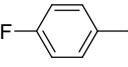
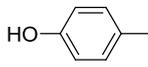
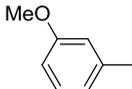
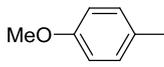


Reagents and conditions : (a) BnMgCl, THF, -78°C, 1hr, 82%; (b) morpholine, (*i*-Pr)₂NEt, dioxane, rt, 1h, 89%; (c) morpholine, (*i*-Pr)₂NEt, THF, 0°C, 0.5h, 61%; (d) arylboronic acid, Pd(PPh₃)₄, Na₂CO₃, dioxane-H₂O=2:1, 90°C, 2h, 17-98%; (e) morpholine, NaHCO₃, DCM, 0-40°C, 3h, quant.; (f) arylboronic acid, Pd(PPh₃)₄, Na₂CO₃, dioxane-H₂O=2:1, 90°C, 3-5h, 98%-quant.

The anti-HCV activity of morpholino triazine compounds was determined in the established HCV RNA replicon cells.¹⁹ Briefly, #50-1 cells carrying sub-genomic HCV RNA replicons were cultured in the presence of various concentrations of the test compounds for 3 days. The intracellular HCV RNA and

glyceraldehyde-3-phosphate dehydrogenase (GAPDH) RNA levels were determined by real-time reverse transcription (RT)-PCR. The anti-HCV activity and cytotoxicity of test compounds were expressed as 50% effective concentration (EC₅₀) and 50% cytotoxic concentration (CC₅₀), defined in terms of decrease of HCV RNA and GAPDH RNA levels to 50% of the respective control levels. The results are shown in Figure 1 and Figure 2.

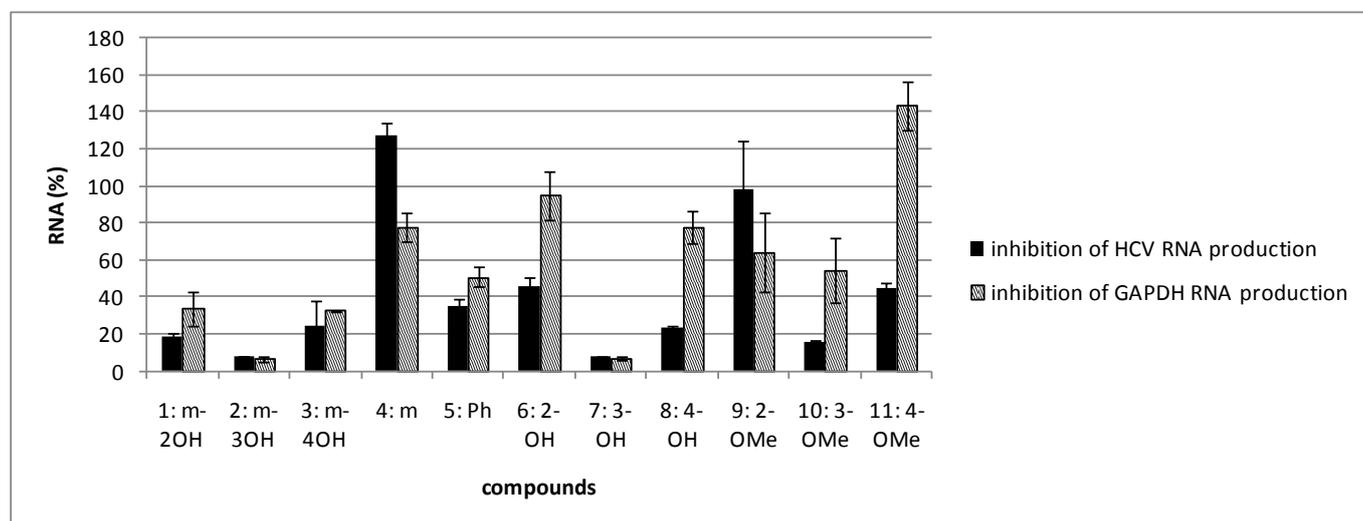
Table 1. Structures of synthesized morpholino triazine compounds

					
R ¹ =	R ² =	compound	R ¹ =	R ² =	compound
		1			12
		2			13
		3			14
		4			15
		5			16
		6			17
		7			18
		8			
		9			
		10			
		11			

As shown in Figure 1, dimorpholino-hydroxyphenyl triazine derivatives (**1**~**3**) showed relatively strong cytotoxicity. Among these compounds, the 3-hydroxyl analog (**2**) was the most cytotoxic. Substitution of

the hydroxyphenyl group with a benzyl group, i.e., compound (**4**), resulted in decreased cytotoxicity, though (**4**) was completely inactive toward HCV RNA transcription. Then, we replaced one morpholino group with a phenyl group to obtain (**5**), which showed moderate anti-HCV activity (approximately 60% inhibition) with moderate cytotoxicity (approximately 55% inhibition). This led us to choose a 2-benzyl-4-morpholino-6-phenyl-1,3,5-triazine skeleton as a lead scaffold, and the effects of a substituent introduced into the phenyl moiety were examined. Introduction of a hydroxyl group into position 2 (*ortho*) or 4 (*para*) (**6** and **8**, respectively) resulted in the appearance of selective anti-HCV activity (Figure 1). In contrast, the 3-hydroxy analog (**7**) showed strong cytotoxicity. As was the case in the dimorpholino-hydroxyphenyl triazine derivatives (**1**~**3**), a *meta*-hydroxyl group seems to induced potent cytotoxicity. In the case of methoxybenzyl derivatives (**9**~**11**), the 2-methoxy analog (**9**) was inactive, and the 3- and 4-methoxy derivatives (**10** and **11**, respectively) showed selective anti-HCV activity. It is noteworthy that compound (**11**) showed approximately 60% inhibition of HCV RNA transcription at 10 μ M, with almost no cytotoxicity.

Figure 1. Anti-HCV activity of morpholino triazine compounds at 10 μ M
(Percent inhibition of HCV gene and host cell gene (GAPDH) expression at 10 μ M)

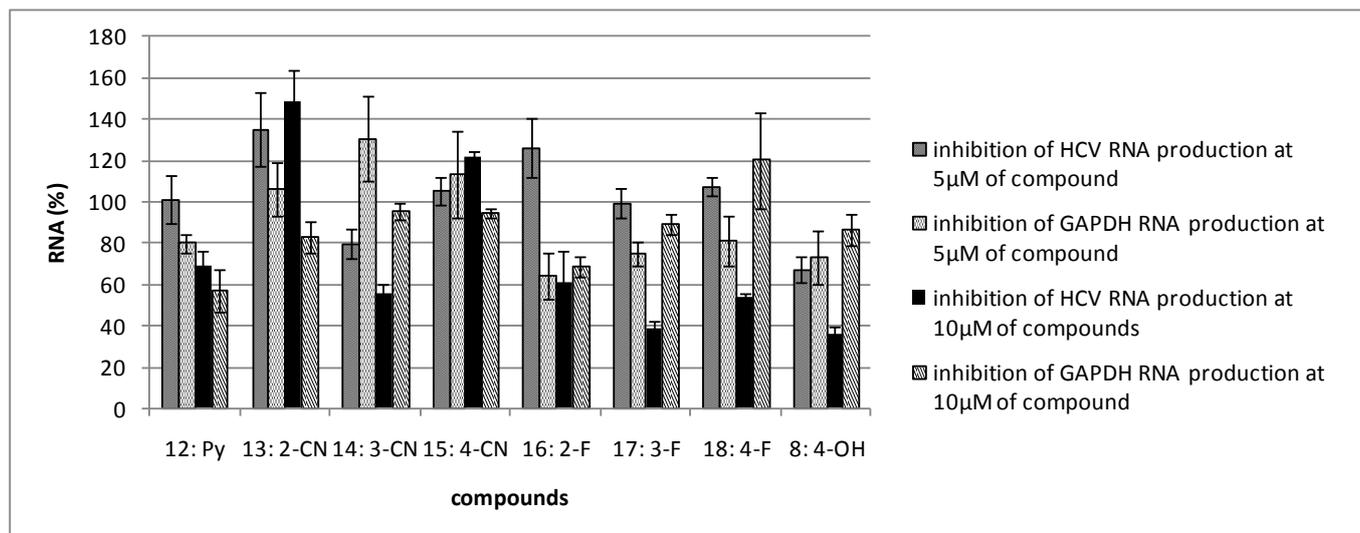


Based on the results shown in Figure 1, replacement of the phenyl group with a pyridyl group, and introduction of an electron-withdrawing group into the phenyl group were carried out for further structural development (Figure 2). Replacement of the phenyl ring with a 3-pyridine (**12**; Py) did not improve the anti-HCV activity or selectivity. Among the cyanophenyl derivatives (**13**~**15**), only the 3-cyano analog (**14**) showed selective anti-HCV activity (Figure 2). In the case of fluorophenyl

derivatives, the 3-fluoro and 4-fluoro analogs (**17** and **18**, respectively) showed selective anti-HCV activity at 10 μ M.

Figure 2. Anti-HCV activity of morpholino triazine compounds at 5 and 10 μ M

(Percent inhibition of HCV gene and host cell gene (GAPDH) expression at 5 and 10 μ M)



In summary, compounds which bear a hydroxyl group (**8**; 4-OH), a cyano moiety (**14**; 3-CN) or a fluorine atom (**17**; 3-F), (**18**; 4-F) on the phenyl ring showed moderate anti-HCV activity (approximately 45-65% inhibition of HCV RNA transcription at 10 μ M) and good selectivity (almost no cytotoxicity or less than 15% inhibition of GAPDH RNA transcription) in subgenomic HCV RNA replicon assay. Although the values for biological data vary from experiment to experiment, they are intrinsically reproducible. At this stage, we cannot fully characterize the structure-activity relationship. Even though, our substituted triazine derivatives appear to have potential for the development of anti-HCV agents, and further extensive investigation of compounds based on the benzyl triazine nucleus is expected to provide promising drug candidates.

ACKNOWLEDGEMENTS

The work described in this paper was partially supported by Grants-in-Aid for Scientific Research from the Science and Technology Incubation Program in Advanced Regions, Japan Science and Technology Agency (JST), and The Ministry of Education, Culture, Sports, Science and Technology, Japan, and a grant from the Japan Society for the Promotion of Science.

REFERENCES AND NOTES

1. T. J. Liang, B. Rehermann, L. B. Seeff, and J. H. Hoofnagle, *Ann. Intern. Med.*, 2000, **132**, 296.
2. P. H. Hayashi and A. M. Di Bisceglie, *Med. Clin. North Am.*, 2005, **89**, 371.
3. J. M. Echevarria-Mayo, *Enferm. Infecc. Microbiol. Clin.*, 2006, **24**, 45.
4. F. X. Bosch, J. Ribes, R. Cleries, and M. Diaz, *Clin. Liver Dis.*, 2005, **9**, 191.
5. M. I. Memon and M. A. Memon, *J. Viral Hepat.*, 2002, **9**, 84.
6. J. G. McHutchison, S. C. Gordon, E. R. Schiff, M. L. Shiffman, W. M. Lee, V. K. Rustgi, Z. D. Goodman, M. H. Ling, S. Cort, and J. K. Albrecht, *N. Engl. J. Med.*, 1998, **339**, 1485.
7. Y. Hashimoto, *Arch. Pharm. Life Sci.*, 2008, **341**, 536.
8. S. Hosoda, D. Matsuda, H. Tomoda, and Y. Hashimoto, *Mini-Rev. Med. Chem.*, 2009, **9**, 572.
9. S. Hosoda, H. Aoyama, Y. Goto, M. T. A. Salim, M. Okamoto, M. Hashimoto, M. Baba, and Y. Hashimoto, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 3157.
10. M. Nakamura, T. Hamasaki, M. Tokitou, M. Baba, Y. Hashimoto, and H. Aoyama, *Bioorg. Med. Chem.*, 2009, **17**, 4740.
11. S. Hosoda, D. Matsuda, H. Tomoda, M. Hashimoto, H. Aoyama, and Y. Hashimoto, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 4228.
12. Y. Hashimoto, *Curr. Med. Chem.*, 1998, **5**, 163.
13. Y. Hashimoto, *Bioorg. Med. Chem.*, 2002, **10**, 461.
14. Y. Hashimoto, *Mini-Rev. Med. Chem.*, 2002, **2**, 543.
15. Y. Hashimoto, A. Tanatani, K. Nagasawa, and H. Miyachi, *Drugs. Future*, 2004, **29**, 383.
16. Y. Hashimoto, *Cell Biol. Rev.*, 1991, **25**, 209.
17. M. Nakamura, A. Aoyama, M. T. A. Salim, M. Okamoto, M. Baba, H. Miyachi, and Y. Hashimoto, *Bioorg. Med. Chem.*, 2010, doi: 10.1016/j.bmc.2010.02.057.
18. Data for the compounds:
2-(2-Hydroxyphenyl)-4,6-bis(morpholin-4-yl)-1,3,5-triazine (1): $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 3.75–3.80 (8H, m), 3.80–3.88 (8H, m), 6.87–6.92 (1H, m), 6.92–6.96 (1H, m), 7.35–7.41 (1H, m), 8.31–8.34 (1H, m), 13.6 (1H, s). HR-FAB-MS m/z : 343.1611 (Calcd for $\text{C}_{17}\text{H}_{21}\text{N}_5\text{O}_3$: (M) $^+$, 343.1644).
2-(3-Hydroxyphenyl)-4,6-bis(morpholin-4-yl)-1,3,5-triazine (2): $^1\text{H-NMR}$ 500MHz, CDCl_3) δ : 3.73–3.80 (8H, m), 3.80–4.10 (8H, m), 6.95–6.98 (1H, m), 7.26–7.29 (1H, m), 7.82–7.84 (1H, m), 7.87–7.91 (1H, m). Anal. Calcd for $\text{C}_{17}\text{H}_{21}\text{N}_5\text{O}_3 \cdot 0.5\text{H}_2\text{O}$: C, 57.94; H, 6.29; N, 19.87. Found: C, 57.53; H, 5.89; N, 19.73.
2-(4-Hydroxyphenyl)-4,6-bis(morpholin-4-yl)-1,3,5-triazine (3): $^1\text{H-NMR}$ (500MHz, CDCl_3) δ : 3.72–3.79 (8H, m), 3.79–4.02 (8H, m), 5.13 (1H, s), 6.86 (2H, d, $J=18.3$ Hz), 8.30 (2H, d, $J=18.3$ Hz). HR-FAB-MS m/z : 343.1692 (Calcd for $\text{C}_{17}\text{H}_{21}\text{N}_5\text{O}_3$: (M) $^+$, 343.1644).
2-Benzyl-4,6-dimorpholino-1,3,5-triazine (4): $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 3.68–3.78 (16H, m), 3.80 (2H, s), 7.21 (1H, t, $J=7.3$ Hz), 7.28 (2H, t, $J=7.3$ Hz), 7.36 (2H, d, $J=7.3$ Hz). MS (FAB) m/z 342 (M+H) $^+$.

2-Benzyl-4-morpholino-6-phenyl-1,3,5-triazine (5): $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 3.75–3.78 (4H, m), 3.89–4.01 (4H, m), 4.04 (2H, s), 7.23 (1H, t, $J=7.3$ Hz), 7.31 (2H, t, $J=7.3$ Hz), 7.45 (4H, t, $J=7.3$ Hz), 7.51 (1H, t, $J=7.3$ Hz), 8.41 (2H, d, $J=7.3$ Hz). HR-FAB-MS m/z : 332.1620 (Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}$: (M) $^+$, 332.1637).

2-Benzyl-4-(2-hydroxyphenyl)-6-morpholino-1,3,5-triazine (6): $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 3.72–3.76 (4H, m), 3.88–3.91 (4H, m), 6.98 (1H, d, $J=7.3$ Hz), 7.02 (1H, t, $J=7.3$ Hz), 7.21 (1H, t, $J=7.3$ Hz), 7.30 (2H, t, $J=7.3$ Hz), 7.40 (1H, td, $J=7.3, 1.8$ Hz), 7.48 (2H, d, $J=7.3$ Hz), 7.73 (1H, dd, $J=7.3, 1.8$ Hz). MS (FAB) m/z 349 (M+H) $^+$. Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}_2 \cdot 0.2\text{H}_2\text{O}$: C, 68.24; H, 5.84; N, 15.92. Found: C, 68.12; H, 5.97; N, 16.18.

2-Benzyl-4-(3-hydroxyphenyl)-6-morpholino-1,3,5-triazine (7): $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 3.72–3.78 (4H, m), 3.88–3.98 (4H, m), 4.03 (2H, s), 6.99 (1H, d, $J=7.3$ Hz), 7.23 (1H, t, $J=7.3$ Hz), 7.31 (2H, t, $J=7.3$ Hz), 7.32 (1H, t, $J=7.3$ Hz), 7.42 (2H, d, $J=7.3$ Hz), 7.87–7.88 (1H, m), 7.99 (1H, d, $J=7.3$ Hz). MS (FAB) m/z 349 (M+H) $^+$. Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}_2 \cdot 0.1\text{H}_2\text{O}$: C, 68.59; H, 5.81; N, 16.00. Found: C, 68.52; H, 5.80; N, 16.21.

2-Benzyl-4-(4-hydroxyphenyl)-6-morpholino-1,3,5-triazine (8): $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 3.74–3.76 (4H, m), 3.87–3.99 (4H, m), 4.01 (2H, s), 6.87 (2H, dt, $J=7.3, 2.0$ Hz), 7.22 (1H, t, $J=7.3$ Hz), 7.30 (2H, t, $J=7.3$ Hz), 7.42 (2H, d, $J=7.3$ Hz), 8.33 (2H, dt, $J=7.3, 2.0$ Hz). MS (FAB) m/z 349 (M+H) $^+$. Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}_2 \cdot 0.2\text{H}_2\text{O}$: C, 68.24; H, 5.84; N, 15.92. Found: C, 68.08; H, 5.92; N, 15.94.

2-Benzyl-4-(2-methoxyphenyl)-6-morpholino-1,3,5-triazine (9): $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 3.71–3.75 (4H, m), 3.84 (3H, s), 3.83–3.95 (4H, m), 4.04 (2H, s), 7.00 (1H, d, $J=7.3$ Hz), 7.02 (1H, t, $J=7.3$ Hz), 7.23 (1H, t, $J=7.3$ Hz), 7.31 (2H, t, $J=7.3$ Hz), 7.40 (1H, td, $J=7.3, 1.2$ Hz), 7.44 (2H, d, $J=7.3$ Hz), 7.71 (1H, dd, $J=7.3, 1.2$ Hz). MS (FAB) m/z 363 (M+H) $^+$. Anal. Calcd for $\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_2 \cdot 0.4\text{H}_2\text{O}$: C, 68.24; H, 6.22; N, 15.16. Found: C, 68.48; H, 6.11; N, 14.98.

2-Benzyl-4-(3-methoxyphenyl)-6-morpholino-1,3,5-triazine (10): $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : MS (FAB) m/z 363 (M+H) $^+$. Anal. Calcd for $\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_2$: C, 69.59; H, 6.12; N, 15.46. Found: C, 69.31; H, 6.14; N, 15.54.

2-Benzyl-4-(4-methoxyphenyl)-6-morpholino-1,3,5-triazine (11): $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 3.73–3.81 (4H, m), 3.88 (3H, s), 3.91–3.98 (4H, m), 4.04 (2H, s), 7.05 (1H, dd, $J=7.3, 2.0$ Hz), 7.23 (1H, t, $J=7.9$ Hz), 7.31 (2H, t, $J=7.3$ Hz), 7.36 (1H, t, $J=7.9$ Hz), 7.43 (2H, d, $J=7.9$ Hz), 7.96 (1H, d, $J=2.0$ Hz), 8.38 (1H, td, $J=7.9, 2.0$ Hz). MS (FAB) m/z 363 (M+H) $^+$. Anal. Calcd for $\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_2$: C, 69.59; H, 6.12; N, 15.46. Found: C, 69.76; H, 6.09; N, 15.62.

2-Benzyl-4-morpholino-6-(3-pyridinyl)-1,3,5-triazine (12): $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 3.74–3.80 (4H, m), 3.90–4.00 (4H, brs), 4.04 (2H, s), 7.24 (1H, t, $J=7.5$ Hz), 7.31 (2H, t, $J=7.5$ Hz), 7.37 (1H, t, $J=7.5$ Hz), 7.43 (2H, d, $J=7.5$ Hz), 7.64 (1H, dt, $J=7.5, 1.5$ Hz), 7.72 (1H, dd, $J=7.5, 1.5$ Hz), 8.58 (1H, d, $J=1.5$ Hz). HR-FAB-MS m/z : 333.1613 (Calcd for $\text{C}_{19}\text{H}_{19}\text{N}_5\text{O}$: (M) $^+$, 333.1590).

2-Benzyl-4-(2-cyanophenyl)-6-morpholino-1,3,5-triazine (13): $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 3.70–3.76 (4H, m), 3.86–3.94 (4H, m), 4.02 (2H, s), 7.23 (1H, t, $J=8.0$ Hz), 7.31 (2H, t, $J=7.0$ Hz), 7.40 (2H, d, $J=7.0$ Hz), 7.48–7.53 (2H, m), 7.79 (1H, d, $J=7.0$ Hz), 8.09 (1H, t, $J=7.0$ Hz). HR-FAB-MS m/z : 357.1635 (Calcd for $\text{C}_{21}\text{H}_{19}\text{N}_5\text{O}$: (M) $^+$, 357.1590).

2-Benzyl-4-(3-cyanophenyl)-6-morpholino-1,3,5-triazine (14): $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 3.74–3.80 (4H, m), 3.90–4.00 (4H, m), 4.03 (2H, s), 7.24 (1H, t, $J=8.0$ Hz), 7.56 (1H, t, $J=8.0$ Hz), 7.77 (1H, d, $J=8.0$ Hz), 8.64 (1H, d, $J=8.0$ Hz), 8.72 (1H, s). HR-FAB-MS m/z : 357.1629 (Calcd for $\text{C}_{21}\text{H}_{19}\text{N}_5\text{O}$: (M) $^+$, 357.1590).

2-Benzyl-4-(4-cyanophenyl)-6-morpholino-1,3,5-triazine (15): $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 3.75–3.78 (4H, m), 3.90–4.00 (4H, m), 4.04 (2H, s), 7.24 (1H, t, $J=7.5$ Hz), 7.32 (2H, t, $J=7.5$ Hz), 7.42 (2H, d, $J=7.5$ Hz), 7.73 (2H, d, $J=8.5$), 8.51 (2H, d, $J=8.5$ Hz). HR-FAB-MS m/z : 357.1570 (Calcd for $\text{C}_{21}\text{H}_{19}\text{N}_5\text{O}$: (M) $^+$, 357.1590).

2-Benzyl-4-(2-fluorophenyl)-6-morpholino-1,3,5-triazine (16): $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 3.73–3.75 (4H, m), 3.88–3.97 (4H, m), 4.05 (2H, s), 7.14 (1H, dd, $J=7.5, 2.5$ Hz), 7.21–7.24 (2H, m),

7.31 (2H, d, $J=7.5$ Hz), 7.42–7.47 (3H, m), 8.09 (1H, td, $J=7.5, 2.5$ Hz). HR-FAB-MS m/z : 350.1527 (Calcd for $C_{20}H_{19}FN_4O$: (M)⁺, 350.1543).

2-Benzyl-4-(3-fluorophenyl)-6-morpholino-1,3,5-triazine (17): ¹H-NMR (500 MHz, CDCl₃) δ : 3.73–3.79 (4H, m), 3.90–4.00 (4H, m), 4.03 (2H, s), 7.18–7.25 (3H, m), 7.31 (2H, td, $J=8.0, 2.0$ Hz), 7.39–7.44 (3H, m), 8.01–8.09 (1H, m), 8.21 (1H, dd, $J=8.0, 2.0$ Hz). HR-FAB-MS m/z : 350.1521 (Calcd for $C_{20}H_{19}FN_4O$: (M)⁺, 350.1543).

2-Benzyl-4-(4-fluorophenyl)-6-morpholino-1,3,5-triazine (18): ¹H-NMR (500 MHz, CDCl₃) δ : 3.73–3.79 (4H, m), 3.86–3.99 (4H, m), 4.06 (2H, s), 7.15 (2H, t, $J=7.5$ Hz), 7.23 (1H, td, $J=8.0, 2.0$ Hz), 7.31 (2H, td, $J=8.0, 2.0$ Hz), 7.42 (2H, d, $J=7.5$ Hz), 8.43 (2H, td, $J=8.0, 2.0$ Hz). HR-FAB-MS m/z : 350.1578 (Calcd for $C_{20}H_{19}FN_4O$: (M)⁺, 350.1543).

2-Benzyl-4,6-dichloro-1,3,5-triazine (20): ¹H-NMR (500 MHz, CDCl₃) δ : 4.18 (2H, s), 7.29 (1H, d, $J=7.0$ Hz), 7.33–7.41 (4H, m). MS (FAB) m/z 240 (M+H)⁺.

2-Benzyl-4-chloro-6-morpholino-1,3,5-triazine (21): ¹H-NMR (500 MHz, CDCl₃) δ : 3.71–3.73 (4H, m), 3.81–3.87 (4H, m), 3.93 (2H, s), 7.24, (1H, t, $J=7.3$ Hz), 7.31 (2H, t, $J=7.3$ Hz), 7.35 (2H, d, $J=7.3$ Hz). MS (FAB) m/z 291 (M+H)⁺.

2-Chloro-4,6-bis(morpholin-4-yl)-1,3,5-triazine (22): ¹H-NMR (500 MHz, CDCl₃) δ : 3.65–3.85 (16H, m).

19. N. Ishii, K. Watashi, T. Hishiki, K. Goto, D. Inoue, M. Hijikata, T. Wakita, N. Kato, and K. Shimotohno, *J. Virol.*, 2006, **80**, 4510.