

HETEROCYCLES, Vol. 95, No. 1, 2017, pp. 547-556. © 2017 The Japan Institute of Heterocyclic Chemistry  
Received, 8th July, 2016, Accepted, 6th September, 2016, Published online, 19th October, 2016  
DOI: 10.3987/COM-16-S(S)16

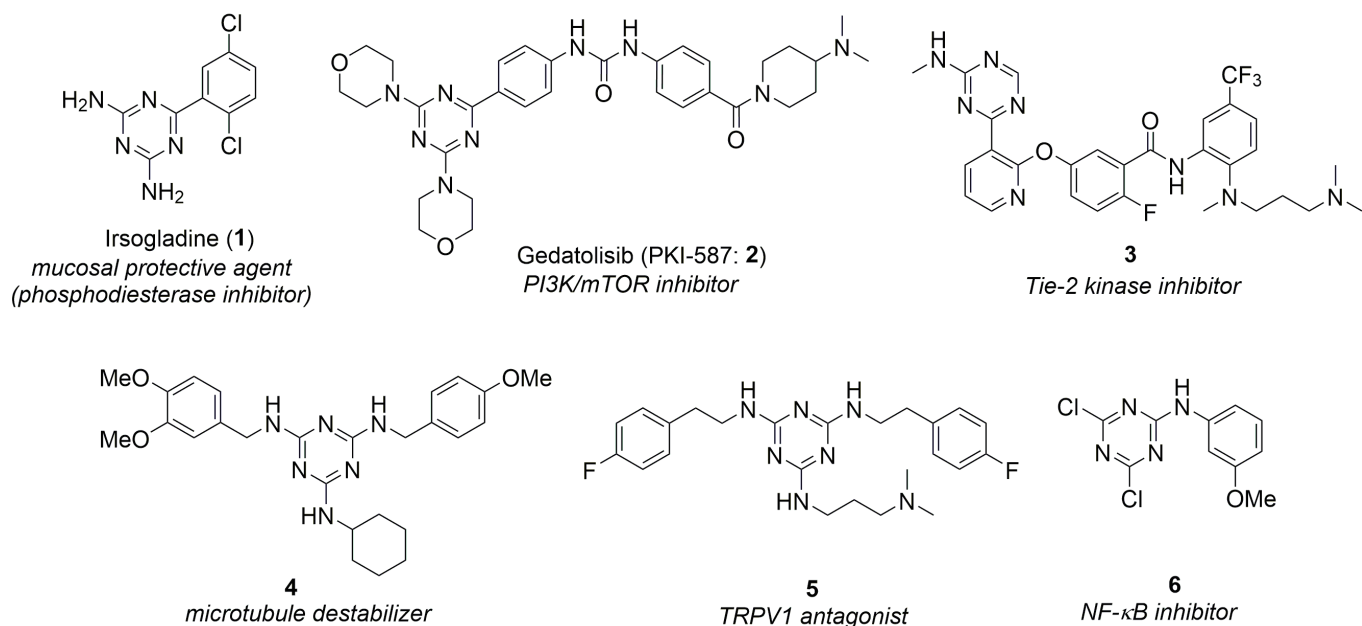
## DESIGN AND SYNTHESIS OF 1,3,5-TRIAZINE DERIVATIVES AS NOVEL INVERSE AGONISTS OF NUCLEAR RETINOIC ACID RECEPTOR-RELATED ORPHAN RECEPTOR- $\gamma$

Kazuma Kaitoh, Hirozumi Toyama, Yuichi Hashimoto, and Shinya Fujii\*

Institute of Molecular and Cellular Biosciences, The University of Tokyo, 1-1-1 Yayoi, Bunko-ku, Tokyo 113-0032, Japan. E-mail: fujiis@iam.u-tokyo.ac.jp

**Abstract** – 1,3,5-Triazine structure is a versatile chemical species for development of functional molecules, including biologically active compounds. We report herein the design, synthesis and biological evaluation of novel inverse agonists of nuclear retinoic acid receptor-related orphan receptor- $\gamma$  (ROR $\gamma$ ), in which the 2-anilino-1,3,5-triazine moiety was used as a scaffold for structural development. Among the synthesized compounds, **13b** exhibited potent and selective inverse agonistic activity toward ROR $\gamma$ , being more potent than the lead compound T0901317 (**7**). The results suggest that the 2-anilino-1,3,5-triazine moiety is a useful scaffold for development of inhibitory ligands of nuclear receptors.

The aromatic nitrogen heterocycle 1,3,5-triazine (*s*-triazine) is a versatile functionality or core scaffold of a wide variety of functional molecules.<sup>1</sup> For instance, 2,4,6-trisubstituted-1,3,5-triazine derivatives such as DMT-MM<sup>2</sup> and TriBOT<sup>3</sup> are synthetically convenient and useful reagents for organic reactions. Triazines have also been widely utilized in medicinal chemistry. For example, triazine-based phosphodiesterase inhibitor irsogladine (**1**) is clinically used as a mucosal protective agent,<sup>4</sup> and kinase inhibitors such as phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) inhibitor gedatolisib (**2**)<sup>5</sup> and Tie-2 kinase inhibitor **3**<sup>6</sup> have been developed. Introduction of three arbitrary substructures into the 1,3,5-triazine core is a facile method not only to prepare chemical libraries, but also to investigate structure-activity relationships (SARs). This approach has yielded several biologically active compounds, such as microtubule destabilizer **4**<sup>7</sup> and transient receptor potential vanilloid 1 (TRPV1) blocker **5**.<sup>8</sup> We have also recently developed novel triazine-based NF- $\kappa$ B inhibitors such as **6**<sup>9</sup> (Figure 1).

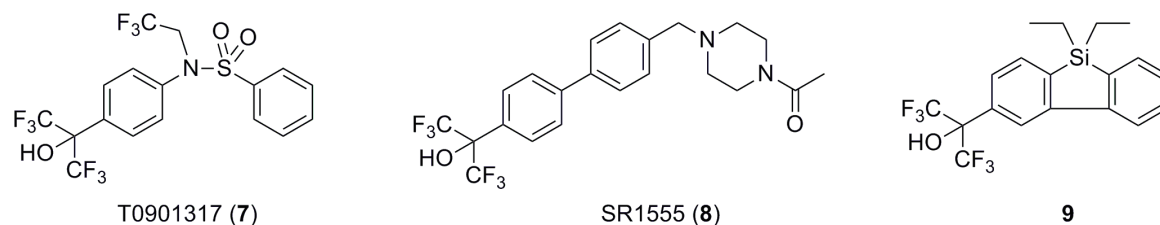


**Figure 1.** Examples of biologically active compounds bearing a 1,3,5-triazine moiety

To expand the utility of the 1,3,5-triazine substructure in the field of drug discovery, we have investigated application of the triazine moiety as a part of a novel multi-template. The foundation of the multi-template approach is that the number of three-dimensional spatial structures (fold structures) of human proteins is only approximately 1000, which is much smaller than the number of human proteins, estimated to be 50,000-70,000.<sup>10-12</sup> The multi-template approach is a promising strategy to develop novel drug candidates, and we have previously employed multi-templates such as thalidomide<sup>13</sup> and diphenylmethane<sup>14</sup> to obtain various biologically active compounds. In this paper, we report the design and synthesis of transcription modulators based on a novel template structure incorporating a 1,3,5-triazine moiety.

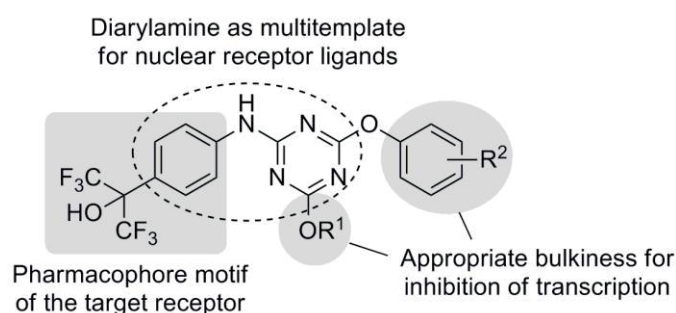
Here, we focused on inverse agonistic activity towards retinoic acid receptor-related orphan receptor- $\gamma$  (ROR $\gamma$ ). ROR $\gamma$  is a member of the nuclear receptor superfamily of ligand-dependent factors that regulate DNA transcription.<sup>15</sup> Increased transcriptional activation of ROR $\gamma$  is thought to be involved in autoimmune diseases,<sup>16</sup> and therefore ROR $\gamma$  inverse agonists, which inhibit the constitutive activity of ROR $\gamma$ , would be candidate drugs for treatment of these diseases. A sulfonamide derivative T0901317 (7, Figure 2) bearing a (1,1,1,3,3,3-hexafluoro-2-hydroxypropyl)phenyl moiety, which was originally developed as a nuclear liver X receptor (LXR) agonist,<sup>17</sup> also shows ROR $\gamma$  inverse agonist activity.<sup>18</sup> Based on the structural motif of 7, we have developed several analogues, such as 8<sup>19</sup> and 9,<sup>20</sup> as ROR $\gamma$  inverse agonists (Figure 2). Those structural development studies suggested that the (1,1,1,3,3,3-hexafluoro-2-hydroxypropyl)phenyl moiety of 7 is an essential pharmacophore for ROR $\gamma$

inverse agonistic activity of these derivatives, and that small structural modifications can significantly affect the activity and selectivity.<sup>21</sup>



**Figure 2.** Examples of developed ROR $\gamma$  inverse agonists bearing a (1,1,1,3,3,3-hexafluoro-2-hydroxypropyl)phenyl moiety

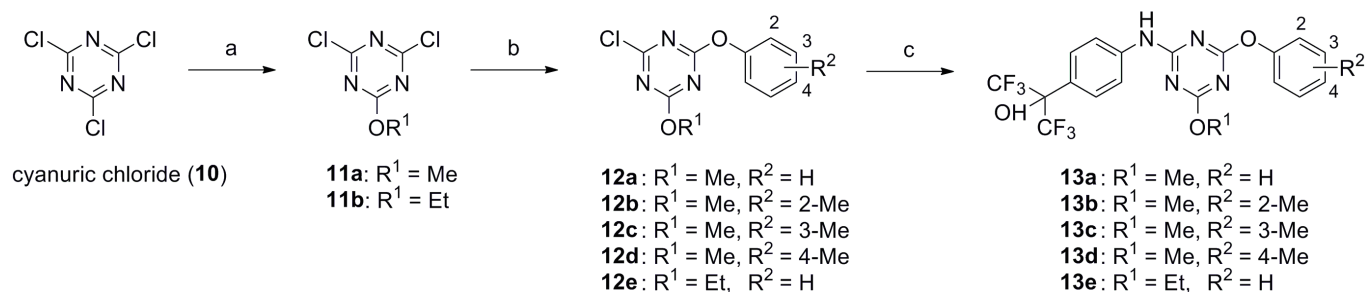
On the basis of these considerations, we planned to develop ROR $\gamma$  inverse agonists bearing a novel template structure that would enable facile investigation of SAR. For this purpose, we designed the 2-anilino-1,3,5-triazine scaffold shown in Figure 3. Diarylamine is an established multi-template for nuclear receptor ligands, and the (1,1,1,3,3,3-hexafluoro-2-hydroxypropyl)phenyl moiety is considered to be a pharmacophore motif of ROR $\gamma$  inverse agonists. The 4- and 6-positions of 1,3,5-triazine are available as points of structural modification. In order to exert inhibitory activity toward nuclear receptors, appropriate substituents on ligands are needed to induce the inactive conformation of the receptors. In addition, in the case of derivatives of 7, small structural modifications are known to alter the activity and selectivity, as mentioned above.<sup>21</sup> Therefore, we investigated the utility of the designed template structure and also carried out a pilot SAR study to examine the effect of small differences in structure (Figure 3).



**Figure 3.** Design scheme of novel ROR $\gamma$  inverse agonists

The designed 1,3,5-triazine derivatives were synthesized in three steps as illustrated in Scheme 1. We had initially intended to introduce the aniline moiety in the first step, but found that the following step of alkoxylation did not proceed in sufficient yield. Therefore firstly the alkoxy group and then phenoxy

groups were introduced, and the (1,1,1,3,3,3-hexafluoro-2-hydroxypropyl)phenylamino moiety was connected at the final step (Scheme 1).



**Scheme 1.** Synthesis of the designed 2-anilino-1,3,5-triazine derivatives. Reagents and conditions: (a) NaHCO<sub>3</sub>, MeOH or EtOH, 0 °C, 74% (**11a**), 25% (**11b**); (b) R<sup>2</sup>C<sub>6</sub>H<sub>4</sub>OH, *i*-Pr<sub>2</sub>EtN, CH<sub>2</sub>Cl<sub>2</sub>, rt, 68-84%; (c) 4-HO(CF<sub>3</sub>)<sub>2</sub>C-C<sub>6</sub>H<sub>4</sub>NH<sub>2</sub>, *i*-Pr<sub>2</sub>EtN, DMSO, 100 °C, 8-77%.

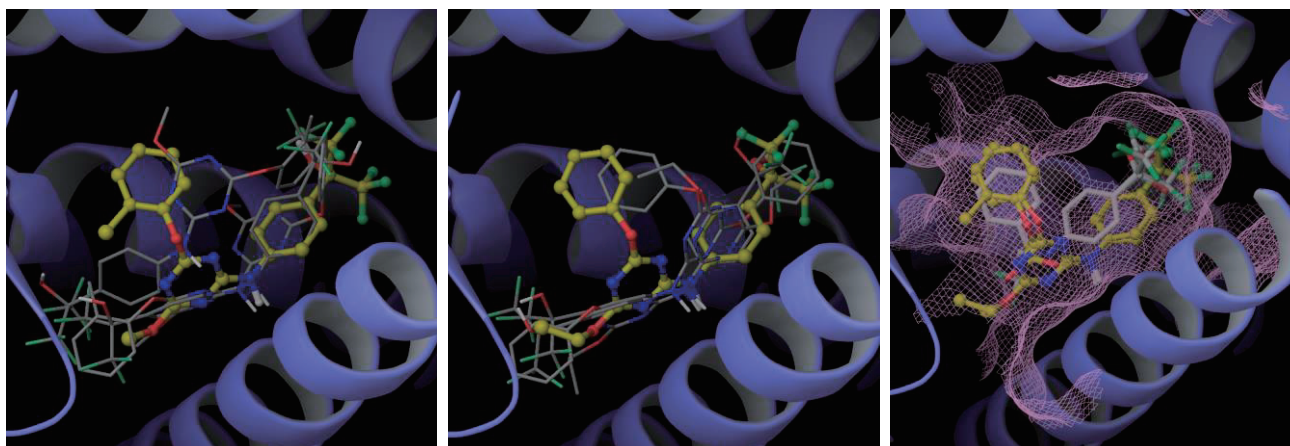
**Table 1.** Biological activity of **7** and synthesized compounds **13a-e**. N.A.; No activity was observed at the concentration of 10 μM.



Compound	R <sup>1</sup>	R <sup>2</sup>	inverse agonist		agonist		
			hROR <sub>γ</sub> IC <sub>50</sub> (μM)	hLXR <sub>α</sub> EC <sub>50</sub> (μM)	hLXR <sub>β</sub> EC <sub>50</sub> (μM)	hPXR EC <sub>50</sub> (μM)	hFXR EC <sub>50</sub> (μM)
<b>7</b>	-	-	8.9	0.26	1.0	3.4	0.21
<b>13a</b>	Me	H	5.8	N.A.	N.A.	N.A.	N.A.
<b>13b</b>	Me	2-Me	3.3	N.A.	N.A.	N.A.	N.A.
<b>13c</b>	Me	3-Me	9.0	N.A.	N.A.	N.A.	N.A.
<b>13d</b>	Me	4-Me	4.7	N.A.	N.A.	N.A.	N.A.
<b>13e</b>	Et	H	3.6	N.A.	N.A.	N.A.	N.A.

The biological activities of synthesized compounds **13a-e** and the lead compound **7** were evaluated by luciferase reporter gene assay in HEK293 cells. Since compound **7** exhibits agonistic activity toward LXR<sub>α</sub> and β,<sup>17</sup> FXR<sup>21</sup> and PXR (SXR),<sup>23</sup> as well as inverse agonistic activity toward ROR<sub>α</sub> and γ, we evaluated not only inverse agonistic activity toward hROR<sub>γ</sub>, but also agonistic activities toward hLXR<sub>α</sub>, hLXR<sub>β</sub>, hFXR, and hPXR. The results of reporter gene assays are summarized in Table 1. Compound **7** exhibited activity toward all tested nuclear receptors, as reported. On the other hand, the synthesized compounds **13a-e** exhibited significant hROR<sub>γ</sub> inverse agonistic activity, but did not exhibit agonistic activity toward the other tested nuclear receptors. The results suggested that the designed template

structure is a reasonable scaffold for ROR $\gamma$  inverse agonists, and the developed compounds show selectivity for ROR $\gamma$  over other receptors. Regarding hROR $\gamma$  inverse agonistic activity, each compound exhibited significant activity. It is suggested that introduction of an *ortho*-substitution at the phenoxy moiety and elongation of the alkoxy group could enhance the potency in comparison to that of the parent compound **13a**, and compounds **13b** and **13e** were more potent than **7** (Table 1).



**Figure 4.** Docking simulations of novel triazine derivatives and hROR $\gamma$ . Binding modes of **13b** (left), **13e** (center), and overlay of the common conformation of the two compounds and **7** (right). The common conformation is indicated with ball-and-stick models (carbon in yellow) and **7** is displayed with carbon in gray. The protein surface is displayed as a mesh.

In order to elucidate the SAR, we conducted docking simulations of the compounds using AutoDock 4.2.<sup>24</sup> Compounds **13b**, **13c** and **13e** were docked with the X-ray crystal structure of hROR $\gamma$  ligand-binding domain (PDB ID: 4NB6).<sup>21</sup> The calculation generated multiple docked conformations of the compounds, and we compared the four conformations of each compound with lowest energy. In the calculated structures, each compound occupies the ligand-binding pocket at which **7** is located in the X-ray structure. Regarding the potent compounds **13b** and **13e**, one conformation among the four of **13b** is almost identical to one of the four of **13e** (Figures 4a, 4b and 4c). On the other hand, the less potent **13c** did not show a similar low-energy conformation. Therefore, the conformation common to **13b** and **13e** might be an active conformation of the developed triazine derivatives. In this putative active conformation, the 2-anilino-4-phenoxytriazine scaffold mimics the synclinal bended conformation of sulfonamide **7** (Figure 4c). The calculated structure also suggests that the *ortho*-methyl group of **13b** and ethyl group of **13e** are located in the proximal region, and increase of hydrophobic interaction in this region might enhance the activity of the compounds.

In conclusion, we have developed novel ROR $\gamma$  inverse agonists by utilizing the 2-anilino-1,3,5-triazine scaffold as a template structure. The designed template structure is useful for facile SAR investigation.

Among the compounds synthesized, **13b** exhibited potent and selective ROR $\gamma$  inverse agonistic activity, being approximately three times more potent than the known compound **7**. The SAR information obtained here should be useful for further structural development of ROR $\gamma$  inverse agonists. Furthermore, the designed template structure could also be useful as a novel multi-template for development of ligands of other nuclear receptors.

## EXPERIMENTAL

### Chemistry

**General remarks.**  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on a JEOL JNM-GX500 spectrometer. Chemical shifts are expressed in  $\delta$  (ppm) values with tetramethylsilane (TMS) as a reference. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra were collected on a Bruker Daltonics micrOTOF-II in the negative ion modes. All melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected.

**2,4-Dichloro-6-methoxy-1,3,5-triazine (11a).** Cyanuric chloride (9.23 g, 50.0 mmol) was added to a solution of sodium hydrogen carbonate (4.20 g, 50.0 mmol) in MeOH (200 mL) at 0 °C. The mixture was stirred for 20 min at 0 °C, then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by recrystallization from *n*-hexane to afford 6.67 g (74%) of **11a** as colorless crystals.  $^1\text{H}$ -NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.14 (3H, s);  $^{13}\text{C}$ -NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  172.70, 171.63, 57.09.

**2,4-Dichloro-6-ethoxy-1,3,5-triazine (11b).** Cyanuric chloride (1.86 g, 10.1 mmol) was added to a solution of sodium hydrogen carbonate (843 mg, 10.0 mmol) in EtOH (40 mL) at 0 °C. The mixture was stirred for 25 min at 0 °C, then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by recrystallization from *n*-hexane to afford 493 mg (2.54 mmol, 25%) of **11b** as colorless crystals.  $^1\text{H}$ -NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.57 (2H, q,  $J = 7.3$  Hz), 1.47 (3H, t,  $J = 7.2$  Hz);  $^{13}\text{C}$ -NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  172.64, 171.07, 66.75, 14.09.

### General procedure for the synthesis of compounds 12a-12e.

The appropriate phenol (1.0 eq.) in  $\text{CH}_2\text{Cl}_2$  (5 mL) and *N,N*-diisopropylethylamine (1.0 eq.) in  $\text{CH}_2\text{Cl}_2$  (5 mL) were added dropwise to a solution of **11a** or **11b** (1 eq.) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at room temperature. The mixture was stirred for 30 min at room temperature. The reaction mixture was washed with dilute hydrochloric acid and brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel chromatography (eluent: *n*-hexane/EtOAc 10:1 or 5:1).

**2-Chloro-4-methoxy-6-phenoxy-1,3,5-triazine (12a).** Colorless solid (Yield: 69%);  $^1\text{H}$ -NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44 (2H, t,  $J = 7.2$  Hz), 7.30 (1H, t,  $J = 7.4$  Hz), 7.18 (2H, m), 4.02 (3H, s);  $^{13}\text{C}$ -NMR (125

MHz, CDCl<sub>3</sub>)  $\delta$  173.41, 172.91, 172.36, 151.51, 129.86, 126.62, 121.41, 56.36.

**2-Chloro-4-methoxy-6-(2-methylphenoxy)-1,3,5-triazine (12b).** Colorless solid (Yield: 74%); <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.28 (1H, dd,  $J = 7.4, 1.7$  Hz), 7.24 (1H, dt,  $J = 7.3, 1.7$  Hz), 7.21 (1H, dt,  $J = 7.3, 1.3$  Hz), 7.07 (1H, dd,  $J = 7.7, 1.4$  Hz), 4.00 (3H, s), 2.19 (3H, s); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  173.46, 172.95, 172.17, 150.19, 131.59, 130.08, 127.32, 126.74, 121.49, 56.30, 16.32.

**2-Chloro-4-methoxy-6-(3-methylphenoxy)-1,3,5-triazine (12c).** Colorless solid (Yield: 73%); <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.31 (1H, dt,  $J = 7.4, 1.1$  Hz), 7.10 (1H, d,  $J = 7.4$  Hz), 6.97 (1H, s), 6.96 (1H, d,  $J = 6.9$  Hz), 4.02 (3H, s), 2.39 (3H, s); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  173.38, 172.90, 172.42, 151.47, 140.15, 129.52, 127.40, 121.85, 118.35, 56.33, 21.51.

**2-Chloro-4-methoxy-6-(4-methylphenoxy)-1,3,5-triazine (12d).** Colorless solid (Yield: 68%); <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.22 (2H, d,  $J = 8.0$  Hz), 7.05 (2H, td,  $J = 3.2, 5.6$  Hz), 4.02 (3H, s), 2.37 (3H, s).

**2-Chloro-4-ethoxy-6-phenoxy-1,3,5-triazine (12e).** Colorless solid (Yield: 84%); <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.43 (2H, tt,  $J = 2.3, 8.0$  Hz), 7.30 (1H, t,  $J = 7.4$  Hz), 7.17 (2H, dt,  $J = 2.3, 8.0$  Hz), 4.44 (2H, q,  $J = 5.9$  Hz), 1.39 (3H, t,  $J = 7.2$  Hz).

#### General procedure for the synthesis of compounds 13a-e.

To a solution of **12a-e** in DMSO (500  $\mu$ L) were added 4-(hexafluoro-2-hydroxyisopropyl)aniline (2 eq.) and *N,N*-diisopropylethylamine (2 eq.) at room temperature. The mixture was stirred for 15 min at 100 °C, then poured into dilute hydrochloric acid and extracted with EtOAc. The organic layer washed with brine, dried over sodium sulfate and concentrated. The residue was purified by recrystallization from MeOH.

**2-{4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropyl)anilino}-4-methoxy-6-phenoxy-1,3,5-triazine (13a).** Colorless solid (Yield: 27%); mp 145.7-147.6 °C; <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.60 (4H, br), 7.44 (2H, t,  $J = 8.0$  Hz), 7.38 (1H, s), 7.30 (1H, t,  $J = 7.4$  Hz), 7.20 (2H, d,  $J = 7.4$  Hz), 4.01 (3H, s), 3.59 (1H, s); HRMS (ESI-)  $m/z$  459.0905 [(M-H)<sup>-</sup>]: calcd. for C<sub>19</sub>H<sub>14</sub>F<sub>6</sub>N<sub>4</sub>O<sub>3</sub>, 459.0886].

**2-{4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropyl)anilino}-4-methoxy-6-(2-methylphenoxy)-1,3,5-triazine (13b).** Colorless solid (Yield: 8%); mp 201.8-203.5 °C; <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.66 (4H, br), 7.30 (1H, s), 7.29 (1H, d,  $J = 7.4$  Hz), 7.25 (1H, t,  $J = 8.9$  Hz), 7.22 (1H, t,  $J = 6.9$  Hz), 7.11 (1H, dd,  $J = 1.4, 7.7$  Hz), 4.01 (3H, s), 3.54 (1H, s), 2.21 (3H, s); HRMS (ESI-)  $m/z$  473.1048 [(M-H)<sup>-</sup>]: calcd. for C<sub>20</sub>H<sub>16</sub>F<sub>6</sub>N<sub>4</sub>O<sub>3</sub>, 473.1043].

**2-{4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropyl)anilino}-4-methoxy-6-(3-methylphenoxy)-1,3,5-triazine (13c).** Colorless solid (Yield: 77%); mp 167.1-168.8 °C; <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.60 (4H, br), 7.35 (1H, s), 7.31 (1H, t,  $J = 7.7$  Hz), 7.11 (1H, d,  $J = 7.4$  Hz), 7.01 (1H, s), 7.00 (1H, d,  $J = 8.0$  Hz), 4.01 (3H, s), 3.52 (1H, s), 2.39 (3H, s); HRMS (ESI-)  $m/z$  473.1041 [(M-H)<sup>-</sup>]: calcd. for C<sub>20</sub>H<sub>16</sub>F<sub>6</sub>N<sub>4</sub>O<sub>3</sub>, 473.1043].

**2-{4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropyl)anilino}-4-methoxy-6-(4-methylphenoxy)-1,3,5-triazine (13d).** Colorless solid (Yield: 69%); mp 207.3-208.2 °C; <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.60 (4H, br), 7.31 (1H, s), 7.22 (2H, d, *J* = 8.0 Hz), 7.07 (2H, td, *J* = 3.4, 5.4 Hz), 4.01 (3H, s), 3.53 (1H, s), 2.39 (3H, s); HRMS (ESI-) *m/z* 473.1054 [(M-H)<sup>-</sup> :calcd. for C<sub>20</sub>H<sub>16</sub>F<sub>6</sub>N<sub>4</sub>O<sub>3</sub>, 473.1043].

**4-Ethoxy-2-{4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropyl)anilino}-6-phenoxy-1,3,5-triazine (13e).** Colorless solid (Yield: 69%); mp 164.8-165.6 °C; <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 7.57 (4H, br), 7.43 (2H, t, *J* = 8.0 Hz), 7.35 (1H, s), 7.30 (1H, t, *J* = 7.2 Hz), 7.20 (2H, d, *J* = 8.0 Hz), 4.43 (2H, q, *J* = 7.1 Hz), 3.57 (1H, s), 1.40 (3H, t, *J* = 6.9 Hz); HRMS (ESI-) *m/z* 473.1049 [(M-H)<sup>-</sup> :calcd. for C<sub>20</sub>H<sub>16</sub>F<sub>6</sub>N<sub>4</sub>O<sub>3</sub>, 473.1043].

### Reporter gene assay

pcDNA3.1(-)-hRORα1, pcDNA3.1(-)-hRORβ1, pcDNA3.1(-)-hRORγ1 and RORE-TK-Luc were provided by Itsuu Laboratory. CMX-β-GAL was provided by Professor Dr. Makoto Makishima (Nihon University School of Medicine). pVP16-PXR was kind gift from Professor Dr. Hitoshi Shirakawa (Graduate School of Agricultural Science, Tohoku University). HEK 293 cells were cultured in DMEM containing 5% FBS, penicillin and streptomycin mixture at 37 °C in a humidified atmosphere of 5% CO<sub>2</sub> in air. Cells were seeded at a density of 20% confluence/96-well plate 24 h prior to transfection. Cells in each well were cotransfected with 150 ng of a nuclear receptor expression plasmid, 500 ng of a luciferase reporter and 10 ng of CMX-β-GAL expression vector. Transfections were performed by the calcium phosphate co-precipitation method. After 24 h, transfected cells were treated with test compounds or DMSO for 24 h. Treated cells were assayed for luciferase activity with a Wallac ARVO SX 1420 Multilabel Counter (PerkinElmer). The luciferase activity of each sample was normalized by the level of β-galactosidase activity. Each transfection was carried out in triplicate.

### Docking simulation

The structure of the LBD of RORγ was prepared from the Protein Data Bank accession 4NB6. Polar hydrogens were added, and partial atomic charges were assigned using AutoDockTools (ADT). Molecular docking was performed using AutoDock 4.2 with Genetic Algorithm.

### ACKNOWLEDGEMENTS

We thank Professor Dr. Hitoshi Shirakawa (Graduate School of Agricultural Science, Tohoku University) and Dr. Shoko Sato (Department of Biological Science and Technology, Tokyo University of Science) for providing pVP16-PXR plasmid. This work was partially supported by Platform for Drug Discovery, Informatics, and Structural Life Science, and the JSPS KAKENHI (Grant No. 26293025 (Y.H.), No. 25460146 (S.F.)).

## REFERENCES

1. G. Giacomelli and A. Porcheddu, 1,3,5-Triazine, Chapter 3, pp. 197-290, ed. by A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, and R. J. K. Taylor, 'Comprehensive Heterocyclic Chemistry III, 3rd Ed. Vol. 9, Six-membered Rings with Three or more Heteroatoms, and their Fused Carbocyclic Derivatives', Elsevier, Amsterdam, 2008.
2. M. Kunishima, C. Kawachi, F. Iwasaki, K. Terao, and S. Tani, [Tetrahedron Lett.](#), 1999, **40**, 5327; M. Kunishima, C. Kawachi, K. Hioki, K. Terao, and S. Tani, [Tetrahedron](#), 2001, **57**, 1551.
3. K. Yamada, H. Fujita, and M. Kunishima, [Org. Lett.](#), 2012, **14**, 5026; H. Fujita, N. Hayakawa, and M. Kunishima, [J. Org. Chem.](#), 2015, **80**, 11200.
4. F. Ueda, S. Aratani, K. Mimura, K. Kimura, A. Nomura, and H. Enomoto, *Arzneim.-Forsch.*, 1984, **34**, 474; F. Ueda, S. Aratani, K. Mimura, K. Kimura, A. Nomura, and H. Enomoto, *Arzneim.-Forsch.*, 1984, **34**, 478; T. Kyoji, M. Oka, K. Noda, and Y. Ukai, [Life Sci.](#), 2004, **75**, 1833.
5. A. M. Venkatesan, C. M. Dehnhardt, E. Delos Santos, Z. Chen, O. Dos Santos, S. Ayril-Kaloustian, G. Khafizova, N. Brooijmans, R. Mallon, I. Hollande, L. Feldberg, J. Lucas, K. Yu, J. Gibbons, R. T. Abraham, I. Chaudhary, and T. S. Mansour, [J. Med. Chem.](#), 2010, **53**, 2636.
6. B. L. Hodous, S. D. Geuns-Meyer, P. E. Hughes, B. K. Albrecht, S. Bellon, J. Bready, S. Caenepeel, V. J. Cee, S. C. Chaffee, A. Coxon, M. Emery, J. Fretland, P. Gallant, Y. Gu, D. Hoffman, R. E. Johnson, R. Kendall, J. L. Kim, A. M. Long, M. Morrison, P. R. Olivieri, V. F. Patel, A. Polverino, P. Rose, P. Tempest, L. Wang, D. A. Whittington, and H. Zhao, [J. Med. Chem.](#), 2007, **50**, 611.
7. H.-S. Moon, E. M. Jacobson, S. M. Khersonsky, M. R. Luzung, D. P. Walsh, W. Xiong, J. W. Lee, P. B. Parikh, J. C. Lam, T.-W. Kang, G. R. Rosania, A. F. Schier, and Y.-T. Chang, [J. Am. Chem. Soc.](#), 2002, **124**, 11608.
8. M. Vidal-Mosquera, A. Fernández-Carvajal, A. Moure, P. Valente, R. Planells-Cases, J. M. González-Ros, J. Bujons, A. Ferrer-Montiel, and A. Messeguer, [J. Med. Chem.](#), 2011, **54**, 7441.
9. S. Fujii, T. Kobayashi, A. Nakatsu, H. Miyazawa, and H. Kagechika, [Chem. Pharm. Bull.](#), 2014, **62**, 700.
10. N. V. Grishin, [J. Struct. Biol.](#), 2001, **134**, 167.
11. E. V. Koonin, Y. I. Wolf, and G. P. Karev, [Nature](#), 2002, **420**, 218.
12. M. A. Koch, L.-O. Wittenberg, S. Basu, D. A. Jeyaraj, E. Gourzoulidou, K. Reinecke, A. Odermatt, and H. Waldmann, [Proc. Natl. Acad. Sci. USA](#), 2004, **101**, 16721.
13. T. Noguchi-Yachide, A. Aoyama, M. Makishima, H. Miyachi, and Y. Hashimoto, [Bioorg. Med. Chem. Lett.](#), 2007, **17**, 3957; M. Tetsuhashi, M. Ishikawa, M. Hashimoto, Y. Hashimoto, and H. Aoyama, [Bioorg. Med. Chem.](#), 2010, **18**, 5323; K. Motoshima, K. Sugita, Y. Hashimoto, and M. Ishikawa, [Bioorg. Med. Chem. Lett.](#), 2011, **21**, 3041; K. Motoshima, M. Ishikawa, Y. Hashimoto,

- and K. Sugita, [Bioorg. Med. Chem.](#), 2011, **19**, 3156; T. Noguchi-Yachide, K. Sugita, and Y. Hashimoto, [Heterocycles](#), 2011, **83**, 2137.
14. S. Hosoda, A. Tanatani, K. Wakabayashi, M. Makishima, K. Imai, H. Miyachi, K. Nagasawa, and Y. Hashimoto, [Bioorg. Med. Chem.](#), 2006, **14**, 5489; M. Kainuma, J. Kasuga, S. Hosoda, K. Wakabayashi, A. Tanatani, K. Nagasawa, H. Miyachi, M. Makishima, and Y. Hashimoto, [Bioorg. Med. Chem. Lett.](#), 2006, **16**, 3213; S. Hosoda and Y. Hashimoto, [Bioorg. Med. Chem. Lett.](#), 2007, **17**, 5414; S. Hosoda, D. Matsuda, H. Tomoda, M. Hashimoto, H. Aoyama, and Y. Hashimoto, [Bioorg. Med. Chem. Lett.](#), 2009, **19**, 4228; K. Maruyama, T. Noguchi-Yachide, K. Sugita, Y. Hashimoto, and M. Ishikawa, [Bioorg. Med. Chem. Lett.](#), 2010, **20**, 6661.
15. D. J. Mangelsdorf, C. Thummel, M. Beato, P. Herrlich, G. Schütz, G. K. Umesono, B. Blumberg, P. Kastner, M. Mark, P. Chambon, and R. M. Evans, [Cell](#), 1995, **83**, 835.
16. B. P. Fauber and S. J. Magnuson, [J. Med. Chem.](#), 2014, **57**, 5871.
17. J. R. Schultz, H. Tu, A. Luk, J. J. Repa, J. C. Medina, L. Li, S. Schwendner, S. Wang, M. Thoolen, D. J. Mangelsdorf, K. D. Lustig, and B. Sham, [Genes Dev.](#), 2000, **14**, 2831.
18. N. Kumar, L. A. Solt, J. J. Conkright, Y. Wang, M. A. Istrate, S. A. Busby, R. D. Garcia-Ordenez, T. P. Burris, and P. R. Griffin, [Mol. Pharmacol.](#), 2010, **77**, 228.
19. L. A. Solt, N. Kumar, Y. He, T. M. Kamenecka, P. R. Griffin, and T. P. Burris, [ACS Chem. Biol.](#), 2012, **7**, 1515.
20. H. Toyama, M. Nakamura, Y. Hashimoto, and S. Fujii, [Bioorg. Med. Chem.](#), 2015, **23**, 2982.
21. Y. Xue, E. Chao, W. J. Zuercher, T. M. Willson, J. L. Collins, and M. R. Redinbo, [Bioorg. Med. Chem.](#), 2007, **15**, 2156; B. P. Fauber, G. de Leon Boenig, B. Burton, C. Eidenschenk, C. Everett, A. Gobbi, S. G. Hymowitz, A. R. Johnson, M. Liimatta, P. Lockey, M. Norman, W. Ouyang, O. René, and H. Wong, [Bioorg. Med. Chem. Lett.](#), 2013, **23**, 6604.
22. K. A. Houck, K. M. Borchert, C. D. Hepler, J. S. Thomas, K. S. Bramlett, L. F. Michael, and T. P. Burris, [Mol. Genet. Metab.](#), 2004, **83**, 184.
23. S. J. Langmade, S. E. Gale, A. Frolov, I. Mohri, K. Suzuki, S. H. Mellon, S. U. Walkley, D. F. Covey, J. E. Schaffer, and D. S. Ory, [Proc. Natl. Acad. Sci. USA](#), 2006, **103**, 13807.
24. G. M. Morris, R. Huey, W. Lindstrom, M. F. Sanner, R. K. Belew, D. S. Goodsell, and A. J. Olson, [J. Comput. Chem.](#), 2009, **16**, 2785.