

# Identification of Potent and Selective Diphenylpropanamide ROR $\gamma$ Inhibitors

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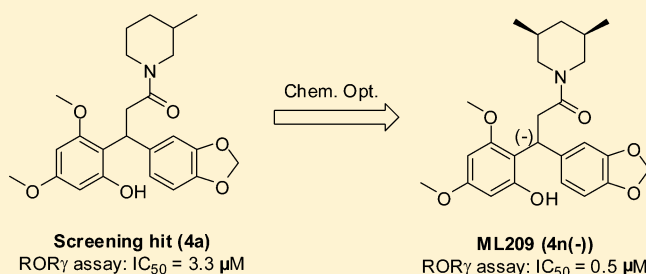
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## Supporting Information

**ABSTRACT:** Retinoic acid-related orphan receptor ROR $\gamma$ t plays a pivotal role in the differentiation of T<sub>H</sub>17 cells. Antagonizing ROR $\gamma$ t transcriptional activity is a potential means to treat T<sub>H</sub>17-related autoimmune diseases. Herein, we describe the identification of a series of diphenylpropanamides as novel and selective ROR $\gamma$  antagonists. Diphenylpropanamide **4n** inhibited the transcriptional activity of ROR $\gamma$ t, but not ROR $\alpha$ , in cells. In addition, it suppressed human T<sub>H</sub>17 cell differentiation at submicromolar concentrations.

**KEYWORDS:** retinoic acid-related orphan receptor, ROR $\gamma$  antagonist, diphenylpropanamide, T<sub>H</sub>17-related autoimmune diseases



Retinoic acid-related orphan receptor  $\gamma$  (ROR $\gamma$ ) is a member of the nuclear hormone receptor superfamily. Although some high-affinity ligands for ROR $\gamma$  have been identified, such as 7-hydroxy cholesterol, ROR $\gamma$  is still considered an orphan receptor.<sup>1,2</sup> A single gene encodes for two isoforms, ROR $\gamma$ 1 and ROR $\gamma$ t, generated by alternative initiation and splicing, which differ only in their amino terminal domains.<sup>3</sup> ROR $\gamma$ 1 is widely expressed in many tissues, including liver, adipose tissue, skeletal muscle, and kidney. ROR $\gamma$ t is expressed in CD4<sup>+</sup>/CD8<sup>+</sup> thymocytes, lymphoid tissue inducer cells, innate lymphoid cells that produce IL-17 and/or IL-22, and inflammatory T cells, including T<sub>H</sub>17 and a subset of TCR $\gamma$  $\delta$ -expressing T cells. T<sub>H</sub>17 cells are T lymphocytes that populate intestinal lamina propria and produce interleukin 17a (IL-17a), IL-17f, and IL-22.<sup>3</sup> ROR $\gamma$ t is a key transcription factor for the differentiation of T<sub>H</sub>17 cells,<sup>4</sup> which comprise one of the distinct effector T cell lineages involved in the regulation of host defense, particularly against extracellular microorganisms at mucosal barriers.<sup>5</sup> Recent studies indicate that T<sub>H</sub>17 cells play key pro-inflammatory roles in a variety of autoimmune diseases and in cancer.<sup>6,7</sup> For instance, mice lacking IL-17 or the p19 subunit of IL-23, which is required for the expansion and possibly the function of T<sub>H</sub>17 cells in vivo, are resistant to mouse autoimmune disease models, including experimental autoimmune encephalomyelitis, collagen-induced arthritis, and inflammatory bowel disease.<sup>8–10</sup> T<sub>H</sub>17 cells and the cytokines they produce appear to have essential functions in the

pathogenesis of psoriasis as well.<sup>11</sup> Treatment of mice with neutralizing anti-IL-17 antibodies ameliorates autoimmune inflammation of the central nervous system, whereas transfer of cells producing IL-17 exacerbates the disease phenotype.<sup>9</sup> Despite the potential of ROR $\gamma$  as a therapeutic target for these diseases, there are relatively few selective small-molecule ROR $\gamma$  antagonists disclosed in the literature (Figure 1). Digoxin (**1**) selectively antagonizes ROR $\gamma$  with an IC<sub>50</sub> of 2.0  $\mu$ M. Because of the cytotoxicity associated with digoxin, several less toxic analogues were synthesized and shown to retain ROR $\gamma$  inhibitory activity.<sup>12</sup> Ursolic acid (**2**), an active component in many herbs, selectively inhibited ROR $\gamma$ ,<sup>13,14</sup> and recently SR2211 (**3**) was reported as a selective ROR $\gamma$  antagonist.<sup>15</sup> In this letter, we report the discovery and preliminary SAR (structure–activity relationship) studies of a novel series of potent and selective ROR $\gamma$  antagonists.

To identify selective ROR $\gamma$  antagonists, we performed a quantitative high-throughput screen (qHTS)<sup>16</sup> of 310000 compounds (PubChem AID: 2604) using a cell-based ROR $\gamma$  gene reporter assay to detect ROR $\gamma$  transcriptional inhibitors and a VP16 gene reporter assay as a counterscreen to exclude nonspecific inhibitors.<sup>12</sup> ROR $\gamma$ -dependent activities from the qHTS were tested in the above assays as well as gene reporter assays using ROR $\alpha$  and DHR3<sup>12</sup> to confirm ROR $\gamma$  activity and

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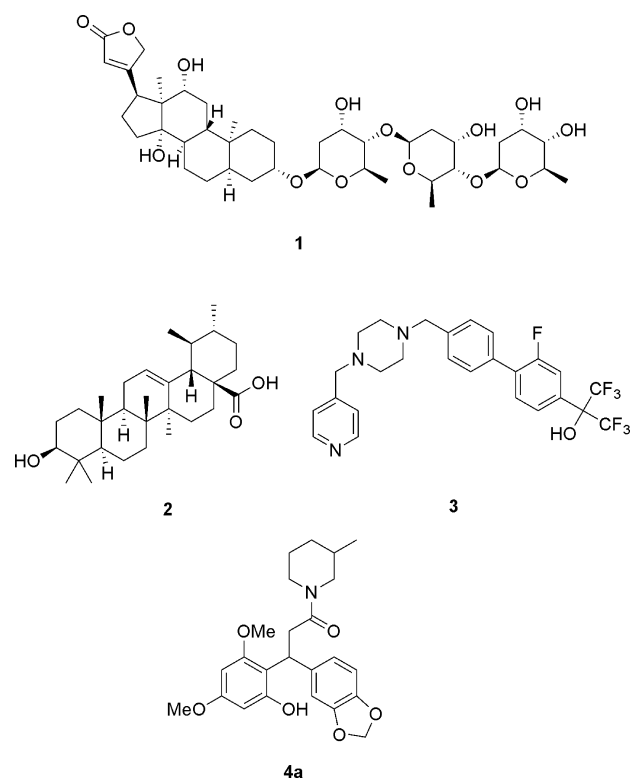
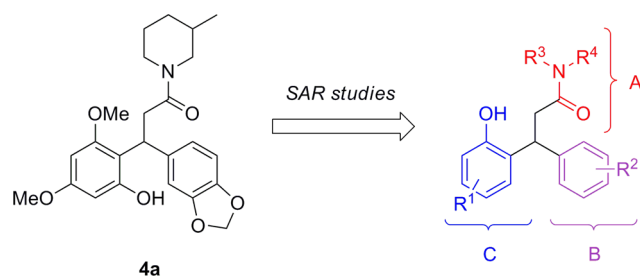
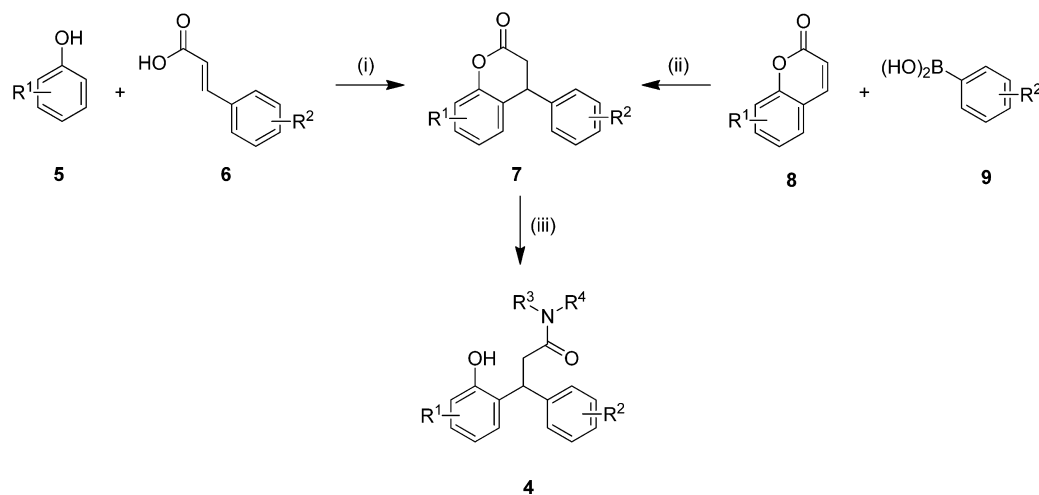
Figure 1. ROR $\gamma$  inhibitors.

Figure 2. SAR plan for 4a.

Scheme 1. Synthesis of Diphenylpropanamides<sup>a</sup>

<sup>a</sup>Reagents and conditions: (i) TFA, 3–12 h, 60–80 °C. (ii) 2,2'-Bipyridine, Pd(OAc)<sub>2</sub>, HOAc, DMA, 110 °C, 12 h. (iii) Method A: NHR<sup>3</sup>R<sup>4</sup>, DMA, 2–16 h, 80 °C; method B: NHR<sup>3</sup>R<sup>4</sup>, Me<sub>3</sub>Al, r.t. to 60 °C, 6 h.

Table 1. SAR of Region A

Entry	Compd	NR <sup>3</sup> R <sup>4</sup>	IC <sub>50</sub> (μM) (ROR $\gamma$ )	Entry	Compd	NR <sup>3</sup> R <sup>4</sup>	IC <sub>50</sub> (μM) <sup>*</sup> (ROR $\gamma$ )
1	4a		3.3±0.7	8	4h		24.4±7.9
2	4b		> 50	9	4i		12.8±3.4
3	4c		15.7±5.5	10	4j		4.7±0.4
4	4d		22.5±6.3	11	4k		inactive
5	4e	NEt <sub>2</sub>	> 50	12	4l		0.8±0.3
6	4f	NHBu	29.0±7.3	13	4m		inactive
7	4g		> 50	14	4n		1.1±0.2

<sup>\*</sup>Values of IC<sub>50</sub> are the mean of four replicates from two independent experiments. All tested analogues showed no cytotoxicity in the ROR $\gamma$  assay up to 96 μM.

selectivity. In agreement with results from two recent publications,<sup>12,14</sup> digoxin and ursolic acid were identified as selective antagonists in this screen. We chose to focus on a series of diphenylpropanamides, where the most potent member, 4a (Figure 1), had an IC<sub>50</sub> value of 3.3 μM in the ROR $\gamma$  assay and showed no activity in the VP16, ROR $\alpha$ , and DHR3 assays up to 96 μM. More importantly, 4a inhibited mouse T<sub>H</sub>17 cell differentiation by 84% and had no effect on Th1 cell differentiation at 20 μM (data not shown). Thus, 4a was selected as the lead for SAR studies.

Three regions within 4a were probed for the SAR studies: the amide region A, aryl substitution of B, and aryl substitution of C (Figure 2). As described in Scheme 1, chromanone 7 was

Table 2. SAR of Regions B and C

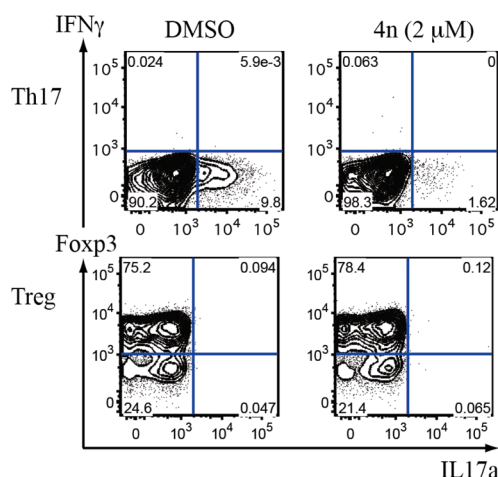
Entry	Compd	NR <sup>3</sup> R <sup>4</sup>	R <sup>2</sup>	R <sup>1</sup>	IC <sub>50</sub> (μM) <sup>a</sup> (RORγ)
1	4o				3.3±0.7
2	4p				30.0±7.2
3	4q				6.6±1.5
4	4r				4.0±1.1
5	4s				0.8±0.2
6	4t				1.0±0.3
7	4u				0.8±0.2
8	4v				1.7±0.6
9	4w				2.5±0.7
10	4x				1.0±0.5

<sup>a</sup>Values of IC<sub>50</sub> are the mean of four replicates from two independent experiments. All tested analogues showed no cytotoxicity in the RORγ assay up to 96 μM.

prepared either by reaction of phenol **5** with cinnamic acid **6**<sup>17–19</sup> or by reaction of coumarin **8** with boronic acid **9**.<sup>20</sup> Reaction of chromanone **7** with amine NHR<sup>3</sup>R<sup>4</sup> gave amide **4**. All analogues were evaluated in the RORγ, VP16, RORα, and DHR3 assays.

Primary, secondary, and aromatic amines were explored in region A. Compounds **4a–4n** were selected from over 40 compounds synthesized for SAR analysis of this area (Table 1). Secondary (**4f**) or aromatic amides (**4g**) showed weak or no activity. The pyrrolidine (**4b**), morpholine (**4k**), and acyclic tertiary amides (**4e**) showed no activity, while the unsubstituted piperidine (**4c**) and the azepane (**4d**) had weak potency. The 3-methyl piperidine (**4a**) was superior to 2-methyl (**4h**) and 4-methyl (**4i**) piperidines. The 3-methyl (**4a**) and 3,3-dimethyl (**4j**) substitutions had similar potency. Two analogues derived from meso amines, *cis*-3,5-dimethylpiperidine (**4n**) and *cis*-3,5-dimethylmorpholine (**4l**), were about 3–4-fold more potent than the lead (**4a**), while *cis*-3,5-dimethylpiperazine (**4m**) was inactive.

The SAR study was also investigated for regions B and C (Table 2). In region C, there were negligible changes in potency by removal of the 4-methoxy substituent (**4o**) or methylation of the phenol (**4r**). However, when the 6-methoxy

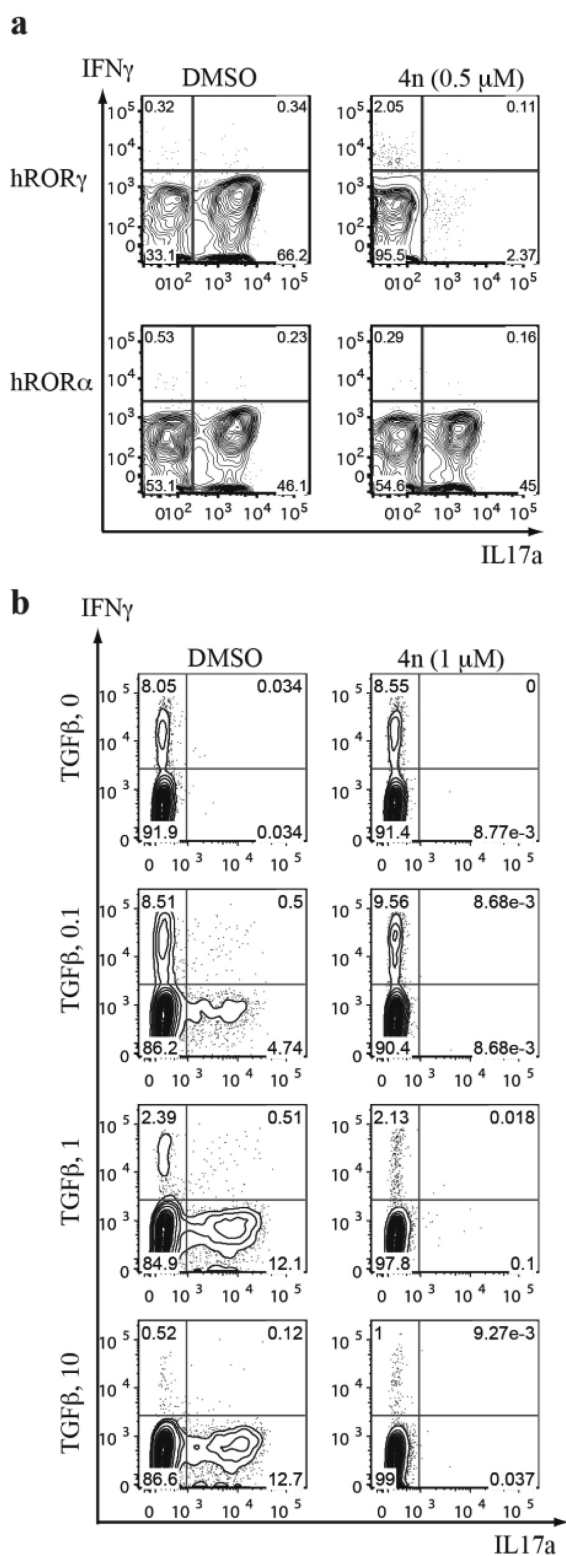


**Figure 3.** Inhibition of mouse Th17 cell differentiation with **4n**. Flow cytometry of intracellular staining for IL-17a and IFN-γ (top) or IL-17a and FoxP3 (bottom) in sorted naïve T cell populations activated and expanded in Th17 or Treg polarizing culture conditions. DMSO or 2 μM compound **4n** was added on day 1, and analysis was done on day 5. The staining control of FoxP3 staining in cells that do not express FoxP3 is provided in Figure 2b in the Supporting Information.

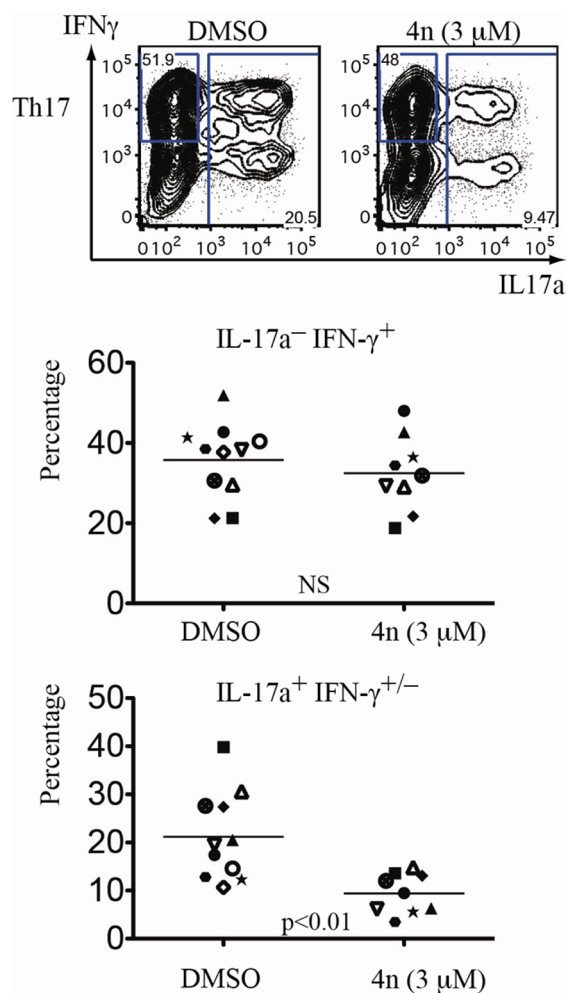
substituent was removed (**4p**), a significant loss in potency was observed. A phenyl group at the 5-position (**4q**) resulted in about a 2-fold loss of activity in comparison to the lead (**4a**). Electron-withdrawing groups, such as 4-CF<sub>3</sub> (**4s**), 4-Cl (**4t**), and 3-MeO (**4v**), as well as electron-donating groups, such as 4-MeO (**4x**) and 4-Me (**4u**), were tolerated. All tested analogues showed no antagonistic activity in the VP16, RORα, and DHR3 assays up to 96 μM.

Diphenylpropanamides have been reported as T-type calcium channel blockers<sup>21</sup> and glucocorticoid receptor (GR) modulators.<sup>22</sup> The benzylic stereocenter is known to affect the biological activities of GR modulators. The enantiomers of **4n** were separated by chiral HPLC to afford **4n**(–) and **4n**(+), assigned according to their optical rotation. Compound **4n**(–) was >20-fold more potent (IC<sub>50</sub> = 0.5 μM) than **4n**(+) (IC<sub>50</sub> = 10.5 μM), demonstrating that the chiral center affects potency. Compound **4n**(–) was inactive against RORα, VP16, and DHR3 at concentrations up to 96 μM, indicating that it is a highly selective RORγ transcriptional inhibitor. In addition, a profiling of **4n**(–) for antagonistic activity in a panel of 20 nuclear receptors was carried out in human embryonic kidney 293t (HEK293t) cells, which showed that **4n**(–) had only weak activities against ERRα (IC<sub>50</sub> = 14 μM), LXRα (IC<sub>50</sub> = 10 μM), TRα (IC<sub>50</sub> = 4.5 μM), and TRβ (IC<sub>50</sub> = 13 μM) (Table 2 in the Supporting Information). On the contrary, **4n**(–) showed no activity against other nuclear receptors including GR. Compound **4n** inhibited RORγ transcriptional activity with an IC<sub>50</sub> value of 300 nM when assayed in HEK293t cells.<sup>12</sup>

We examined next whether these diphenylpropanamides target RORγ directly. Fluorescein-labeled 25-hydroxycholesterol binds to the RORγ ligand binding domain (LBD) with a K<sub>d</sub> of 109 nM.<sup>12</sup> Compounds **4a** or **4n** inhibited fluoroprobe binding to RORγ with IC<sub>50</sub> values of 680 and 110 nM, respectively. Compound **4k**, an inactive derivative, failed to displace hydroxycholesterol (Figure 1 in the Supporting Information). In accordance with the cell-based RORγ gene reporter assay, compound **4n**(–) was 12-fold more potent (IC<sub>50</sub> = 51 nM) than compound **4n**(+) (IC<sub>50</sub> = 605 nM) in the competition assays (Figure 1 in the Supporting Information).



**Figure 4.** Compound **4n** inhibits human Th17 cell differentiation. (a) FACS-sorted naïve human CD4<sup>+</sup> T cells were transduced with lentiviral vectors encoding human ROR $\alpha$ -IRES-GFP or ROR $\gamma$ -IRES-GFP on day 1 (16 h after TCR stimulation), and GFP expressing cells were gated for analysis on day 6. DMSO or 0.5  $\mu$ M compound **4n** was added 6 h after transduction. (b) Flow cytometry of the production of IL-17A and IFN- $\gamma$  by human naïve cord blood T cells cultured for 6 days in the presence of IL-2, IL-23, and IL-1 $\beta$  with various concentrations of TGF- $\beta$  (ng/mL).



**Figure 5.** Inhibition of IL-17 expression from human memory Th17 cells. Human memory (CD45RO<sup>+</sup>CD45RA<sup>-</sup>CD3<sup>+</sup>CD4<sup>+</sup>CCR6<sup>+</sup>CD161<sup>+</sup>) cells were purified from healthy donor peripheral blood samples and were cultured in the presence of IL-1 $\beta$ , IL-23, and IL-2 for 6 days with or without 3  $\mu$ M compound **4n**. Intracellular staining for IFN- $\gamma$  or IL-17A in memory CD4<sup>+</sup> T cells from multiple donors ( $n = 11$  or  $n = 9$ ) performed on day 6. (Top) Representative FACS plots from one donor are shown. (Bottom) Each symbol indicates a separate donor. Statistical analysis was done by a two-tailed unpaired Student's  $t$  test; IL-17A<sup>-</sup>IFN- $\gamma$ <sup>+</sup>, not significant; and IL-17A<sup>+</sup>IFN- $\gamma$ <sup>+</sup>,  $p < 0.01$ .

These results indicate that the diphenylpropanamide antagonists directly interact with the ROR $\gamma$  LBD.

Because ROR $\gamma$ t is a key regulator for Th17 cell polarization, compound **4n** was evaluated further for antagonistic activity in Th17 differentiation assays. Compound **4n** selectively inhibited murine Th17 cell differentiation (Figure 3 and Figure 2a in the Supporting Information) without affecting the differentiation of naïve CD4<sup>+</sup> T cells into other lineages, including Th1 and regulatory T cells (data not shown and Figure 3). Moreover, compound **4n** inhibited ROR $\gamma$ t-directed expression of IL-17A in human T cells but had no effect on expression induced by the closely related ROR $\alpha$  (Figure 4a), confirming its selectivity for ROR $\gamma$ . We showed previously that ROR $\gamma$ t activity is important both for induction and for maintenance of human Th17 cells.<sup>12</sup> Indeed, compound **4n** significantly reduced induction of IL-17A expression upon in vitro differentiation of naïve cord blood CD4<sup>+</sup> T cells (Figure 4b) and maintenance

of IL-17A in ex vivo-isolated memory human Th17 cells, with little effect on IFN- $\gamma$  expressing cells (Figure 5).

In summary, we have identified a series of diphenylpropanamides as novel and selective ROR $\gamma$  antagonists. Preliminary SAR studies of the active compound identified in the initial screen, **4a**, led to the identification of **4n(-)**,<sup>23</sup> which can serve as a valuable pharmacological tool for studying various cellular activities controlled by ROR $\gamma$ .<sup>24</sup> Further lead optimization and in vivo studies are currently ongoing and will be reported in due course.

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

ROR $\gamma$ , VP16, ROR $\alpha$ , and DHR3 assays description; NR profiling data; in vitro ROR $\gamma$  binding assay; in vitro mouse T cell and human T cell assays; synthetic procedures; and analytical data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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J.R.H., J.L., C.P.A., F.R., R.L.J., W.H., and D.R.L. designed the experiments. J.R.H., E.E.E., W.H., and D.R.L. wrote the manuscript with input from the coauthors. J.R.H., E.E.E., H.W., P.H., R.L.J., and W.H. performed experiments. J.R.H., J.L., R.H., R.L.J., W.H., and D.R.L. analyzed the data.

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### Notes

The authors declare no competing financial interest.

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