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Letter

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Identification of Potent and Selective Diphenylpropanamide RORγ Inhibitors

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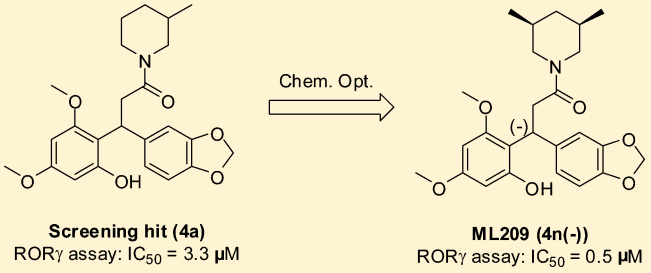
Supporting Information

ABSTRACT: Retinoic acid-related orphan receptor RORγt plays a pivotal role in the differentiation of T_H17 cells. Antagonizing RORγt transcriptional activity is a potential means to treat T_H17-related autoimmune diseases. Herein, we describe the identification of a series of diphenylpropanamides as novel and selective RORγ antagonists. Diphenylpropanamide **4n** inhibited the transcriptional activity of RORγt, but not RORα, in cells. In addition, it suppressed human T_H17 cell differentiation at submicromolar concentrations.



Screening hit (4a)
RORγ assay: IC_{50} = 3.3 μM

ML209 (4n(-))
RORγ assay: IC_{50} = 0.5 μM

KEYWORDS: *retinoic acid-related orphan receptor, RORγ antagonist, diphenylpropanamide, T_H17-related autoimmune diseases*

Retinoic acid-related orphan receptor γ (RORγ) is a member of the nuclear hormone receptor superfamily. Although some high-affinity ligands for RORγ have been identified, such as 7-hydroxy cholesterol, RORγ is still considered an orphan receptor.[1,2] A single gene encodes for two isoforms, RORγ1 and RORγt, generated by alternative initiation and splicing, which differ only in their amino terminal domains.[3] RORγ1 is widely expressed in many tissues, including liver, adipose tissue, skeletal muscle, and kidney. RORγt is expressed in $CD4^+/CD8^+$ thymocytes, lymphoid tissue inducer cells, innate lymphoid cells that produce IL-17 and/or IL-22, and inflammatory T cells, including T_H17 and a subset of TCRγδ-expressing T cells. T_H17 cells are T lymphocytes that populate intestinal lamina propria and produce interleukin 17a (IL-17a), IL-17f, and IL-22.[3] RORγt is a key transcription factor for the differentiation of T_H17 cells,[4] which comprise one of the distinct effector T cell lineages involved in the regulation of host defense, particularly against extracellular microorganisms at mucosal barriers.[5] Recent studies indicate that T_H17 cells play key pro-inflammatory roles in a variety of autoimmune diseases and in cancer.[6,7] 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_H17 cells in vivo, are resistant to mouse autoimmune disease models, including experimental autoimmune encephalomyelitis, collagen-induced arthritis, and inflammatory bowel disease.[8−10] T_H17 cells and the cytokines they produce appear to have essential functions in the pathogenesis of psoriasis as well.[11] 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.[9] Despite the potential of RORγ as a therapeutic target for these diseases, there are relatively few selective small-molecule RORγ antagonists disclosed in the literature (Figure 1). Digoxin (**1**) selectively antagonizes RORγ with an IC_{50} of 2.0 μM. Because of the cytotoxicity associated with digoxin, several less toxic analogues were synthesized and shown to retain RORγ inhibitory activity.[12] Ursolic acid (**2**), an active component in many herbs, selectively inhibited RORγ,[13,14] and recently SR2211 (**3**) was reported as a selective RORγ antagonist.[15] In this letter, we report the discovery and preliminary SAR (structure−activity relationship) studies of a novel series of potent and selective RORγ antagonists.

To identify selective RORγ antagonists, we performed a quantitative high-throughput screen (qHTS)[16] of 310000 compounds (PubChem AID: 2604) using a cell-based RORγ gene reporter assay to detect RORγ transcriptional inhibitors and a VP16 gene reporter assay as a counterscreen to exclude nonspecific inhibitors.[12] RORγ-dependent actives from the qHTS were tested in the above assays as well as gene reporter assays using RORα and DHR3[12] to confirm RORγ activity and

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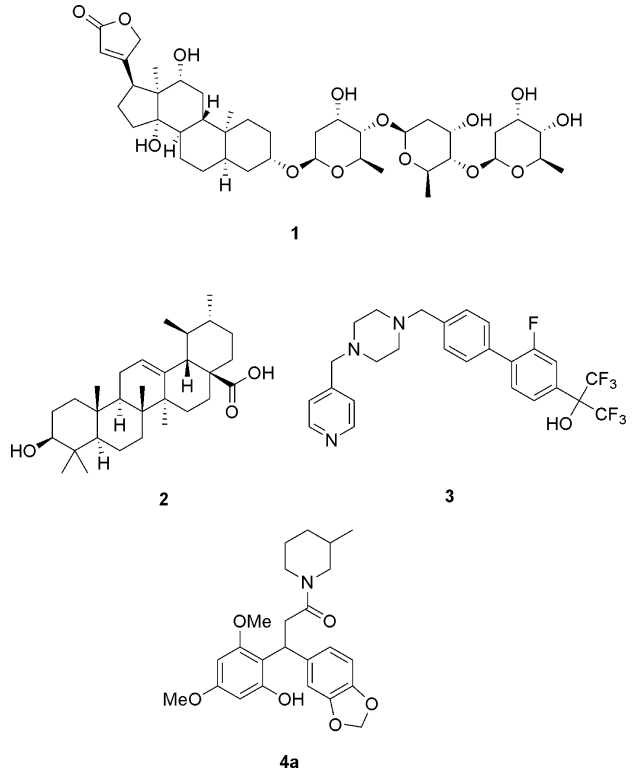


Figure 1. RORγ inhibitors.

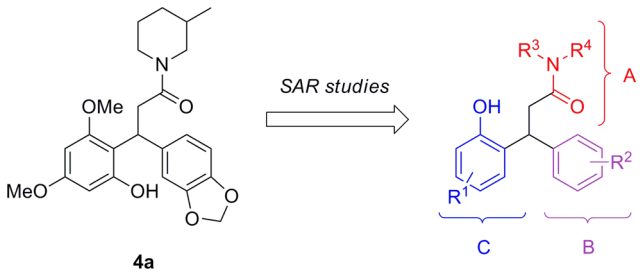
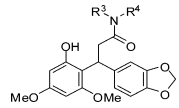


Figure 2. SAR plan for **4a**.

Table 1. SAR of Region A



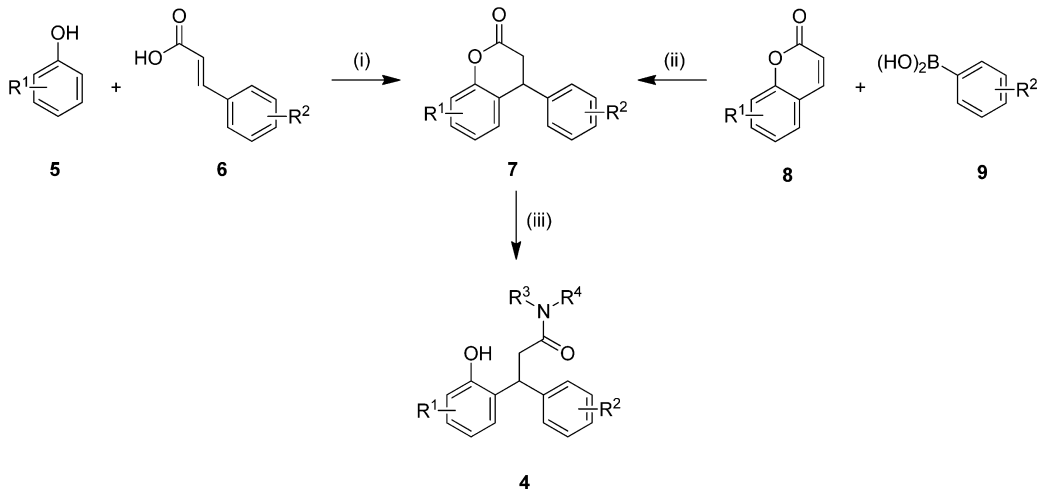
Entry	Compd	NR^3R^4	IC_{50} (μM) (RORγ)	Entry	Compd	NR^3R^4	IC_{50} (μM)* (RORγ)
1	**4a**		3.3±0.7	8	**4h**		24.4±7.9
2	**4b**		> 50	9	**4i**		12.8±3.4
3	**4c**		15.7±5.5	10	**4j**		4.7±0.4
4	**4d**		22.5±6.3	11	**4k**		inactive
5	**4e**	NEt_2	> 50	12	**4l**		0.8±0.3
6	**4f**	NHBu	29.0±7.3	13	**4m**		inactive
7	**4g**		> 50	14	**4n**		1.1±0.2

*Values of IC_{50} are the mean of four replicates from two independent experiments. All tested analogues showed no cytotoxicity in the RORγ assay up to 96 μM.

selectivity. In agreement with results from two recent publications,[12,14] 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_{50} value of 3.3 μM in the RORγ assay and showed no activity in the VP16, RORα, and DHR3 assays up to 96 μM. More importantly, **4a** inhibited mouse T_H17 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

Scheme 1. Synthesis of Diphenylpropanamides[a]



[a]Reagents and conditions: (i) TFA, 3−12 h, 60−80 °C. (ii) 2,2′-Bipyridine, $Pd(OAc)_2$, HOAc, DMA, 110 °C, 12 h. (iii) Method A: NHR^3R^4, DMA, 2−16 h, 80 °C; method B: NHR^3R^4, Me_3Al, r.t. to 60 °C, 6 h.

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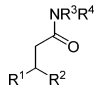
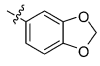
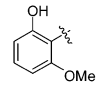
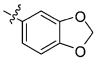
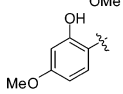
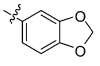
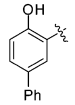
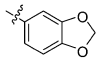
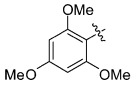
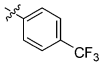
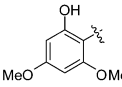
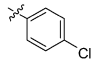
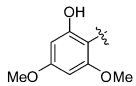
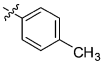
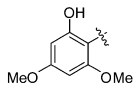
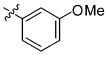
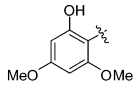
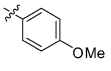
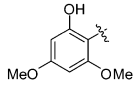
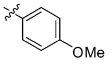
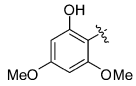
Table 2. SAR of Regions B and C



Entry	Compd	NR^3R^4	R^2	R^1	IC_{50} (μM)* ($ROR\gamma$)
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

*Values of IC_{50} 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**[17−19] or by reaction of coumarin **8** with boronic acid **9**.[20] Reaction of chromanone **7** with amine NHR^3R^4 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

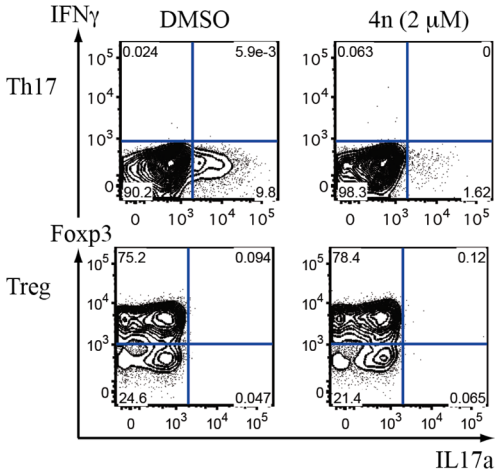


Figure 3. Inhibition of mouse Th17 cell differentiation with **4n**. Flow cytometry of intracellular staining for IL-17a and IFN-γ (top) or IL-17a and FoxP3 (bottom) in sorted naïve T cell populations activated and expanded in Th17 or Treg polarizing culture conditions. DMSO or 2 μM compound **4n** was 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_3 (**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[21] and glucocorticoid receptor (GR) modulators.[22] 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_{50} = 0.5 μM) than **4n**(+) (IC_{50} = 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_{50} = 14 μM), LXRα (IC_{50} = 10 μM), TRα (IC_{50} = 4.5 μM), and TRβ (IC_{50} = 13 μM) (Table 2 in the Supporting Information). On the contrary, **4n**(−) showed no activity against other nuclear receptors including GR. Compound **4n** inhibited RORγt transcriptional activity with an IC_{50} value of 300 nM when assayed in HEK293t cells.[12]

We examined next whether these diphenylpropanamides target RORγ directly. Fluorescein-labeled 25-hydroxycholesterol binds to the RORγ ligand binding domain (LBD) with a K_d of 109 nM.[12] Compounds **4a** or **4n** inhibited fluoroprobe binding to RORγ with IC_{50} 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_{50} = 51 nM) than compound **4n**(+) (IC_{50} = 605 nM) in the competition assays (Figure 1 in the Supporting Information).

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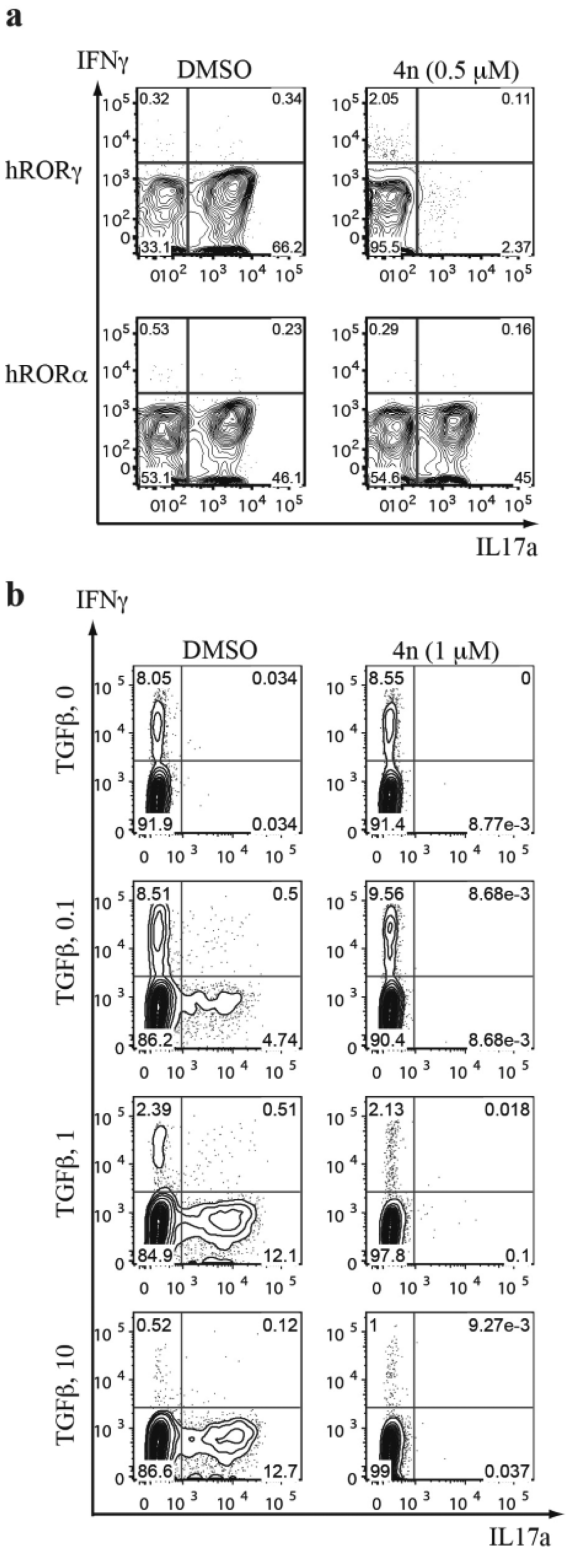

Figure 4. Compound **4n** inhibits human Th17 cell differentiation. (a) FACS-sorted naïve human CD4$^+$ T cells were transduced with lentiviral vectors encoding human RORα-IRES-GFP or RORγt-IRES-GFP on day 1 (16 h after TCR stimulation), and GFP expressing cells were gated for anyalsis on day 6. DMSO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

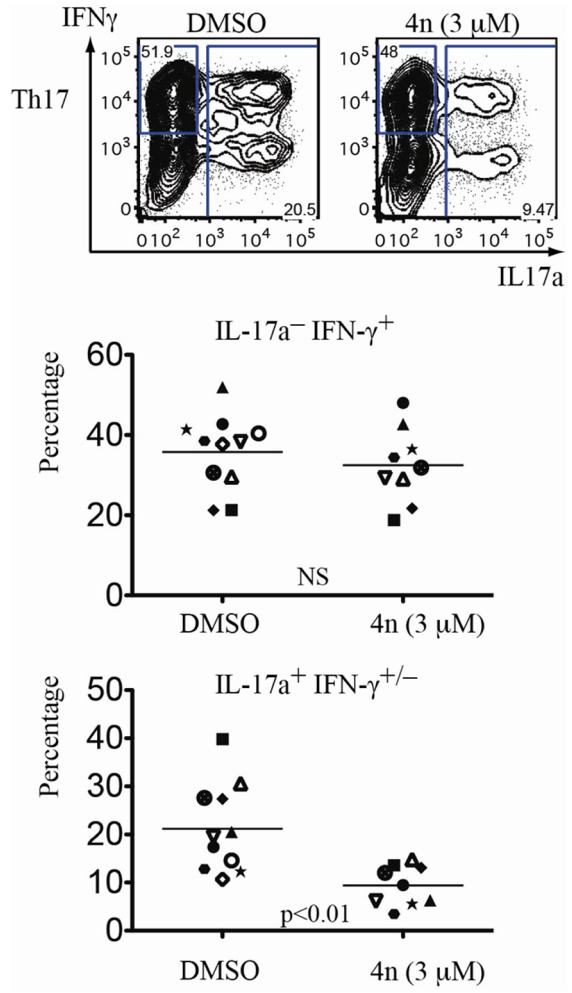

Figure 5. Inhibition of IL-17 expression from human memory Th17 cells. Human memory (CD45RO$^+$CD45RA$^-$CD3$^+$CD4$^+$-CCR6$^+$CD161$^+$) cells were purified from healthy donor peripheral blood samples and were cultured in the presence of IL-1β, IL-23, and IL-2 for 6 days with or without 3 μM compound **4n**. Intracellular staining for IFN-γ or IL-17A in memory CD4$^+$ 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$^-$IFN-γ^+, not significant; and IL-17A$^+$IFN-$\gamma^{\pm}$, $p < 0.01$.

These results indicate that the diphenylpropanamide antagonists directly interact with the RORγ LBD.

Because RORγt 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$^+$ T cells into other lineages, including Th1 and regulatory T cells (data not shown and Figure 3). Moreover, compound **4n** inhibited RORγt-directed expression of IL-17A in human T cells but had no effect on expression induced by the closely related RORα (Figure 4a), confirming its selectivity for RORγ. We showed previously that RORγt activity is important both for induction and for maintenance of human Th17 cells.[12] Indeed, compound **4n** significantly reduced induction of IL-17A expression upon in vitro differentiation of naïve cord blood CD4$^+$ T cells (Figure 4b) and maintenance

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

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

■ ASSOCIATED CONTENT

Supporting Information

RORγ, VP16, RORα, and DHR3 assays description; NR profiling data; in vitro RORγ 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.I., 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.I., 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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