From ROR γ t Agonist to Two Types of ROR γ t Inverse Agonists

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Supporting Information

ABSTRACT: Biaryl amides as new ROR γ t modulators were discovered. The crystal structure of biaryl amide agonist **6** in complex with ROR γ t ligand binding domain (LBD) was resolved, and both “short” and “long” inverse agonists were obtained by removing from **6** or adding to **6** a proper structural moiety. While “short” inverse agonist (**8**) recruits a corepressor peptide and dispels a coactivator peptide, “long” inverse agonist (**9**) dispels both. The two types of inverse agonists can be utilized as potential tools to study mechanisms of Th17 transcriptional network inhibition and related disease biology.

KEYWORDS: ROR γ t, agonist, inverse agonist, cocrystal structure, Th17 cell differentiation, biaryl amides

Retinoic acid receptor-related orphan receptor γ -t (ROR γ t), a member of the nuclear receptor superfamily, is the master regulator of T helper 17 (Th17) cell differentiation, which plays a key role in the pathology of several inflammatory and autoimmune diseases.^{1–6} The functional activities of ROR γ t can be achieved by the recruitment of transcriptional coactivators or corepressors as a result of the ligand binding to its ligand binding domain (LBD).⁷ Thus, ROR γ t small molecular inhibitors suppress Th17 cell differentiation and can be used as medical agents for Th17 cell-mediated diseases.^{7–14} Since the ROR γ t inhibitors (inverse agonists or antagonists) such as digoxin,¹⁵ SR1001,¹⁶ and ursolic acid¹⁷ were first reported in 2011, a number of small molecular ROR γ t inhibitors have been disclosed,^{18–20} a few of which exhibited the suppression activity of Th17 cell differentiation and efficacy in autoimmune disease animal models.

Previously, we reported the identification of a ROR γ t inverse agonist HTS hit (**1**) from which quite a few of new ROR γ t inverse agonists such as thiazole ketones (e.g., **2**)^{21,22} and thiazole ethers²³ were discovered (Figure 1). Thiazole ring replacement with a phenyl ring and subsequent optimization led to the identification of a *tert*-amine (**3a**) as an ROR γ t agonist, evidenced by a dual fluorescence resonance energy transfer (dual FRET) assay which is able to measure activities of both agonists and inverse agonists according to the ROR γ t basal level activity changes (see the Supporting Information).²⁴ The cocrystal structure of **3a** with ROR γ t LBD revealed that the left-hand side (LHS) phenyl of **3a** lies in the hydrophobic pocket close to activation function 2 (AF2) domain (helix 12),

Figure 1. Structures of ROR γ t agonists (**3a** and **4a**) and inverse agonists (**1**, **2**, **3b**, and **4b**).

which is attributed to the activation of ROR γ t by stabilizing the AF2 domain toward recruitment of steroid receptor coactivator (SRC).²⁴ According to the binding mode of **3a**, we designed and synthesized a series of ROR γ t inverse agonists (e.g., **3b**) by introducing substituents to the *para*-position of the LHS phenyl ring of **3a** to interfere with the AF2 domain. For the first time, the relationship between structural disruption of ligand/AF2 domain and the level of ROR γ t inhibition was then established.²⁴ Later, scientists from Genentech and Argenta reported a similar finding that a small structural change to their *tert*-sulfonamides led to opposite mechanisms of action (MOA)

Received: November 17, 2017

Accepted: January 22, 2018

Published: January 22, 2018

with ROR γ t.²⁵ Optimized phenylsulfonamides (e.g., **4a**) were identified as ROR γ t agonists, while benzylsulfonamides (e.g., **4b**) exhibited potent inverse agonist activity. Structurally, both **3b** and **4b** are considered as “long” inverse agonists compared to the size of their corresponding agonists **3a** and **4a**. Interestingly, when docking our inverse agonists **1** and **2** to the pocket of ROR γ t LBD, it was found that the LHS moiety of amides is somewhat short and unable to reach the hydrophobic pocket near AF2 domain. Do these “short” inverse agonists behave the same as the “long” ones? In this paper, we report identification of “long” and “short” inverse agonists from a single biaryl amide agonist such as **6** using structure-based design.

Docking the thiazole ketone amides into ROR γ t LBD revealed that the *ortho*-position of the ketone phenyl points to the AF2 domain. It was our hypothesis that certain sizes of substituents at the *ortho*-position of the ketone phenyl ring could reach and stabilize the AF2 domain and thus could convert the ROR γ t inverse agonist to a ROR γ t agonist. To test this hypothesis, we designed and synthesized a series of thiazole ketone amides with different sizes of substituents at the *ortho*-position of the ketone phenyl ring (**5a–e**) and evaluated them in FRET and dual FRET assays (Table 1).^{24,26} As predicted,

Table 1. SAR of *Ortho*-Substitution at Ketone Phenyl of Amides

The chemical structure shows a thiazole ring substituted with a phenyl group at the 2-position and a ketone group at the 4-position. The ketone group is further substituted with a phenyl ring at the *ortho*-position, which has a substituent R. The thiazole ring is also substituted with an amide group at the 5-position, which is further substituted with a phenyl ring at the *ortho*-position, which has a substituent R. The amide group is further substituted with a phenyl ring at the *ortho*-position, which has a substituent R.

Compd	R	ROR γ FRET ^a pIC ₅₀ (% max) ^b	ROR γ dual FRET ^a pXC ₅₀ (% max)
5a	H	7.4±0.06 (98)	8.0±0.04 (51) ^c
5b	Me	7.8±0.09 (99)	8.0±0.03 (51) ^c
5c		< 5.6	6.9±0.38 (94) ^d
5d		< 4.6	7.6±0.08 (157) ^d
5e		< 4.6	7.4±0.21 (206) ^d

^apIC₅₀ value or pXC₅₀ value is the mean of at least two determinations, the error is expressed by $\pm$ SEM. ^b% max inhibition measured against activation by a surrogate agonist. ^cpIC₅₀ (% max inhibition). ^dpEC₅₀ (% max activation).

while compounds with no substituent (**5a**) or smaller substituents such as methyl (**5b**) exhibited inverse agonist activities, the ones with larger substituents (**5c–e**) showed agonist activities. Furthermore, the level of activation (% max) becomes greater as size of the *ortho*-substituents increases (**5e** > **5d** > **5c**).

To confirm the binding mode, we conducted cocrystallization of ROR γ t LBD with thiazole ketone amides. Luckily, a crystal structure of agonist **5d** in complex with ROR γ t LBD was resolved (resolution: 2.65 Å, PDB code: SYP5; see the Supporting Information) (Figure 2a). The overall binding motif of **5d** in ROR γ t LBD is similar to that of **3a** (see Figure 1S in the Supporting Information). There are H-bondings

Figure 2. (a) Co-crystal structure of agonist **5d** (magenta stick) and ROR γ t LBD. (b) Overlay of agonist **5d** (magenta stick) and inverse agonist **5b** (gray stick). Residues involved in key molecular interactions with **5d** are highlighted and labeled.

between the sulfone moiety and Arg367/Arg364. The other H-bondings are between the linker amide NH and a backbone carbonyl of Phe377 and between amide carbonyl and His323 through a water molecule. One phenyl ring forms π – π stacking with Phe377 and the other with Phe388. The thiazole ring forms π – π stacking with Phe378. The isobutyl moiety at the *ortho*-position of the phenyl ring occupies the hydrophobic pocket close to the AF2 domain, contributing to the activation of ROR γ t through stabilizing the AF2 domain to SRC recruitment. Clearly, small substituents like methyl could not reach the hydrophobic pocket close to the AF2 domain as indicated in a docking overlay of **5b** with **5d** (Figure 2b) and, thus, possibly is not able to stabilize the AF2 domain, which makes **5b** an inverse agonist.²⁷ Obviously, **5b** is a “short” inverse agonist compared to the size of agonist **5d**.

We previously converted the *tert*-amine agonist **3a** to a series of “long” inverse agonists such as **3b** by adding a substituent to LHS phenyl of **3a**.²⁴ Here we identified a series of thiazole ketone amides as “short” inverse agonists which can be derived from the corresponding agonists such as **5d** by reducing the size of substituents at *ortho*-position of ketone phenyl ring. It is our desire to have a single chemical scaffold that allows us to design agonists as well as both “long” and “short” inverse agonists from. However, the *tert*-amine series or thiazole ketone series is not an ideal chemical scaffold on which both “long” and “short” inverse agonists can be properly designed and easily synthesized. During LHS optimization of thiazole amide **1**, we

identified the biaryl amide **6** as a ROR γ t agonist, which showed a pEC₅₀ of 7.8 and max activation of 191% in dual FRET assay. Fortunately enough, a cocrystal structure of **6** with ROR γ t LBD was resolved (resolution: 2.2 Å, PDB code: SYP6; see Supporting Information) (Figure 3). The mode of binding of

Figure 3. Co-crystal structure of agonist **6** (magenta stick) and ROR γ t LBD. Residues involved in key molecular interactions with **6** are highlighted and labeled.

6 in ROR γ t LBD is similar to that of **3a** and **5d**: H-bondings (sulfone moiety with Arg367/Arg364, amide NH with a Phe377, amide carbonyl with His323 through a water molecule) and three π - π stacking interactions (three phenyls with Phe377, Arg378 and Arg388). The isobutyl group at the *para*-position of the LHS phenyl ring lies in the hydrophobic pocket close to AF2 domain, contributing to the activation of ROR γ t through stabilizing the AF2 domain to SRC recruitment. With its synthetic accessibility, the biaryl amide series is considered an ideal chemical scaffold on which both “long” and “short” inverse agonists can be easily obtained.²⁸

Based on the binding mode of **6**, we designed and synthesized a series of biaryl amides with LHS aryl moieties of different sizes, some larger than **6** and some smaller than **6** (Table 2). In a FRET assay that has a surrogate agonist added, agonist **6** did not give an activity value (pIC₅₀ < 4.6) as expected. Replacing LHS 3-CN-4-^tBu-Ph moiety with the smaller 3-CN-Ph (**7c**), the ROR γ t agonist **6** become a “short” antagonist, as evidenced by the FRET assay (pIC₅₀ = 7.5) and the dual FRET assay (pIC₅₀ < 5). Further reducing the size of LHS to Ph (**7b**) and ^tPr (**7a**), agonist **6** turns into “short” inverse agonists with increased maximum percentage of inhibition (from 40% to 64% in dual FRET assay). On the other hand, replacing the isobutyl moiety with a larger cyclohexylmethyl (**7d**), agonist **6** becomes a “long” antagonist, indicated by the FRET assay (pIC₅₀ = 7.1) and the dual FRET assay (pIC₅₀ < 5). Further increasing the size of LHS to (1-acetylpiperidin-4-yl)-methyl (**7e**) and (1-pivaloylpiperidin-4-yl)-methyl (**7f**), agonist **6** turns into “long” inverse agonists with increased maximum percentage of inhibition (from 35% to 121% in dual FRET assay). Interestingly, the size of LHS did not have much impact on ROR γ t potency (pXC₅₀ values).

Are “short” inverse agonists different from “long” inverse agonists in terms of ROR γ t activities and coactivator/corepressor peptide recruitment? To answer this question, we selected representative “short” inverse agonist **8** and “long” inverse agonist **9** previously discovered in the same biaryl series (Figure 4)^{28,29} and evaluated them in FRET and dual FRET assays. Both **8** and **9** showed inhibitory activity against ROR γ t

Table 2. LHS SAR of Biaryl Amides

Compd	R	ROR γ FRET ^a pIC ₅₀ (% max) ^b	ROR γ dual FRET ^a pXC ₅₀ (% max)
7a		6.7±0.05 (114)	7.0±0.22 (64) ^c
7b		7.5±0.13 (97)	7.5±0.27 (40) ^c
7c		7.5±0.18 (58)	< 5
6		< 4.6	7.7±0.04 (199) ^d
7d		7.1±0.04 (80)	< 5
7e		6.9±0.07 (95)	7.2±0.03 (35) ^c
7f		7.0±0.06 (120)	7.3±0.06 (121) ^c

^apIC₅₀ value or pXC₅₀ value is the mean of at least two determinations, the error is expressed by ± SEM. ^b% max inhibition measured against activation by the surrogate agonist. ^cpIC₅₀ (% max inhibition). ^dpEC₅₀ (% max activation).

Figure 4. Structures of ROR γ t agonist (**6**) and inverse agonists (**8** and **9**).

with similar potency in FRET and dual FRET assays (Table 3). Furthermore, both **8** and **9** inhibited Th17 cell differentiation.²⁴ However, while “long” inverse agonist **9** showed similar

Table 3. ROR γ t Activities of Biaryl Amides **8** and **9**

compd	ROR γ FRET ^a pIC ₅₀ (% max) ^b	ROR γ dual FRET ^a pIC ₅₀ (% max)	IL-17 ELISA pIC ₅₀
8	7.8 ± 0.11 (104)	8.1 ± 0.09 (45)	6.7 ± 0.09
9	7.5 ± 0.21 (118)	7.5 ± 0.03 (86)	7.6 ± 0.31

^apIC₅₀ value is the mean of at least two determinations; the error is expressed by ± SEM. ^b% max inhibition measured against activation by the surrogate agonist.

potency in both Th17 and FRET assays, the “short” inverse agonist **8** exhibited about one log unit lower potency in the Th17 assay than in the FRET assay. A dual FRET assay based peptide profiling study showed that coactivator peptide [e.g., steroid receptor coactivator 1 (SRC1)] was recruited while binding of **6** to ROR γ t LBD, whereas corepressor peptide [e.g., nuclear receptor corepressor 2 (NCOR2)] was not (Figure 5,

Figure 5. Peptide recruitment profiling for agonist **6** and inverse agonists **8** and **9**.

see the Supporting Information).²⁴ Interestingly, while “short” inverse agonists such as **8** did the opposite (recruiting corepressor peptide NCOR2 and dispelling coactivator peptide SRC1), “long” inverse agonists such as **9** did not recruit either NCOR2 or SRC1 peptide. This indicates that the “short” inverse agonists behave differently from the “long” ones in terms of peptide recruitment. The two types of inverse agonists might inhibit Th17 cell transcriptional network by different mechanism,³⁰ which is under further investigation.

In summary, using structure-based design, we have identified a key position in thiazole ketone amides (**5**) to modulate their ROR γ t activities by introducing different size of substituents. Furthermore, we have discovered a biaryl amide agonist (**6**) and resolved its crystal structure in complex with ROR γ t LBD, from which we were able to obtain both “short” and “long” inverse agonists by removing from or adding to a proper structural moiety. While “short” inverse agonist (**8**) recruits a corepressor peptide and dispels a coactivator peptide, “long” inverse agonist (**9**) dispels both. The two types of inverse

agonists might behave differently in terms of MOA, which is under further investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.7b00476.

Synthetic experimental and compound characterization, crystallography studies, assay descriptions, and molecular docking studies (PDF)

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Funding

This research was supported by GlaxoSmithKline and by the National Science Foundation of China (Grant No. 81573276).

Notes

The authors declare no competing financial interest.

Studies in this manuscript were conducted in accordance with the GSK Policy on the Care, Welfare and Treatment of Laboratory Animals and were reviewed by the Institutional Animal Care and Use Committee either at GSK or by the ethical review process at the institution where the work was performed.

■ ACKNOWLEDGMENTS

We thank Mingming Gao, Wei Zhang, Jing Zhang, Gang An, Melanie Huxdorf, Justin Liao, Yaobang Cheng, Hui Lei, Hongtao Lu, and Zhong Zhong for their help and discussions.

■ REFERENCES

- (1) Rich, P.; Sigurgeirsson, B.; Thaci, D.; Ortonne, J.-P.; Paul, C.; Schopf, R. E.; Morita, A.; Roseau, K.; Harfst, E.; Guettner, A.; Machacek, M.; Papavassilis, C. Secukinumab induction and maintenance therapy in moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled, phase II regimen-finding study. *Br. J. Dermatol.* **2013**, *168*, 402–411.
- (2) Lock, C.; Hermans, G.; Pedotti, R.; Brendolan, A.; Schadt, E.; Garren, H.; Langer-Gould, A.; Strober, S.; Cannella, B.; Allard, J.; Klonowski, P.; Austin, A.; Lad, N.; Kaminski, N.; Galli, S. J.; Oksenberg, J. R.; Raine, C. S.; Heller, R.; Steinman, L. Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis. *Nat. Med.* **2002**, *8*, S00–S08.
- (3) Chabaud, M.; Durand, J. M.; Buchs, N.; Fossiez, F.; Page, G.; Frappart, L.; Miossec, P. Human interleukin-17: A T cell-derived proinflammatory cytokine produced by the rheumatoid synovium. *Arthritis Rheum.* **1999**, *42*, 963–970.
- (4) Fujino, S.; Andoh, A.; Bamba, S.; Ogawa, A.; Hata, K.; Araki, Y.; Bamba, T.; Fujiyama, Y. Increased expression of interleukin 17 in inflammatory bowel disease. *Gut* **2003**, *52*, 65–70.
- (5) Ivanov, I. I.; McKenzie, B. S.; Zhou, L.; Tadokoro, C. E.; Lepelley, A.; Lafaille, J. J.; Cua, D. J.; Littman, D. R. The orphan

nuclear receptor ROR γ directs the differentiation program of proinflammatory IL-17⁺ T helper cells. *Cell* **2006**, 126, 1121–1133.

(6) Matusiewicz, D.; Kivisäkk, P.; He, B.; Kostulas, N.; Ozenci, V.; Fredrikson, S.; Link, H. Interleukin-17 mRNA expression in blood and CSF mononuclear cells is augmented in multiple sclerosis. *Mult. Scler.* **1999**, 5, 101–104.

(7) Solt, L. A.; Burris, T. P. Action of RORs and their ligands in (patho)physiology. *Trends Endocrinol. Metab.* **2012**, 23, 619–627.

(8) Huh, J. R.; Littman, D. R. Small molecule inhibitors of ROR γ t: targeting Th17 cells and other applications. *Eur. J. Immunol.* **2012**, 42, 2232–2237.

(9) Burris, T. P.; Busby, S. A.; Griffin, P. R. Targeting orphan nuclear receptors for treatment of metabolic diseases and autoimmunity. *Chem. Biol.* **2012**, 19, 51–59.

(10) Murali Dhar, T. G.; Zhao, Q.; Markby, D. W. Targeting the nuclear hormone receptor ROR γ t for the treatment of autoimmune and inflammatory disorders. *Annu. Rep. Med. Chem.* **2013**, 48, 169–182.

(11) Yang, J.; Sundrud, M. S.; Skepner, J.; Yamagata, T. Targeting Th17 cells in autoimmune diseases. *Trends Pharmacol. Sci.* **2014**, 35, 493–500.

(12) Isono, F.; Fujita-Sato, S.; Ito, S. Inhibiting ROR γ t/Th17 axis for autoimmune disorders. *Drug Discovery Today* **2014**, 19, 1205–1211.

(13) Dong, C. Targeting Th17 cells in immune diseases. *Cell Res.* **2014**, 24, 901–903.

(14) Zhang, Y.; Luo, X.-y.; Wu, D.-h.; Xu, Y. ROR nuclear receptors: structures, related diseases, and drug discovery. *Acta Pharmacol. Sin.* **2015**, 36, 71–87.

(15) Huh, J. R.; Leung, M. W. L.; Huang, P.; Ryan, D. A.; Krout, M. R.; Malapaka, R. R. V.; Chow, J.; Manel, N.; Ciofani, M.; Kim, S. V.; Cuesta, A.; Santori, F. R.; Lafaille, J. J.; Xu, H. E.; Gin, D. Y.; Rastinejad, F.; Littman, D. R. Digoxin and its derivatives suppress TH17 cell differentiation by antagonizing ROR γ t activity. *Nature* **2011**, 472, 486–490.

(16) Solt, L. A.; Kumar, N.; Nuhant, P.; Wang, Y.; Lauer, J. L.; Liu, J.; Istrate, M. A.; Kamenecka, T. M.; Roush, W. R.; Vidovic, D.; Schürer, S. C.; Xu, J.; Wagoner, G.; Drew, P. D.; Griffin, P. R.; Burris, T. P. Suppression of TH17 differentiation and autoimmunity by a synthetic ROR ligand. *Nature* **2011**, 472, 491–494.

(17) Xu, T.; Wang, X.; Zhong, B.; Nurieva, R. I.; Ding, S.; Dong, C. Ursolic acid suppresses interleukin-17 (IL-17) production by selectively antagonizing the function of ROR γ t protein. *J. Biol. Chem.* **2011**, 286, 22707–22710.

(18) Fauber, B. P.; Magnuson, S. Modulators of the nuclear receptor retinoic acid receptor-related orphan receptor- γ (ROR γ or RORc). *J. Med. Chem.* **2014**, 57, 5871–5892.

(19) Cyr, P.; Bronner, S. M.; Crawford, J. J. Recent progress on nuclear receptor ROR γ modulators. *Bioorg. Med. Chem. Lett.* **2016**, 26, 4387–4393.

(20) Bronner, S. M.; Zbieg, J. R.; Crawford, J. J. ROR γ antagonists and inverse agonists: a patent review. *Expert Opin. Ther. Pat.* **2017**, 27, 101–112.

(21) Wang, Y.; Cai, W.; Zhang, G.; Yang, T.; Liu, Q.; Cheng, Y.; Zhou, L.; Ma, Y.; Cheng, Z.; Lu, S.; Zhao, Y.-G.; Zhang, W.; Xiang, Z.; Wang, S.; Yang, L.; Wu, Q.; Orband-Miller, L. A.; Xu, Y.; Zhang, J.; Gao, R.; Huxdorf, M.; Xiang, J.-X.; Zhong, Z.; Elliott, J. D.; Leung, S.; Lin, X. Discovery of novel N-(5-(arylcarbonyl)thiazol-2-yl)amides and N-(5-(arylcarbonyl)thiophen-2-yl)amides as potent ROR γ t inhibitors. *Bioorg. Med. Chem.* **2014**, 22, 692–702.

(22) Wang, Y.; Cai, W.; Liu, Q.; Xiang, J. Preparation of N-thiazolyl acetamides as retinoid-related orphan receptor gamma (ROR) modulators. WO2012027965A1, 2012.

(23) Wang, Y.; Yang, T.; Liu, Q.; Ma, Y.; Yang, L.; Zhou, L.; Xiang, Z.; Cheng, Z.; Lu, S.; Orband-Miller, L. A.; Zhang, W.; Wu, Q.; Zhang, K.; Li, Y.; Xiang, J.-N.; Elliott, J. D.; Leung, S.; Ren, F.; Lin, X. Discovery of N-(4-aryl-5-aryloxy-thiazol-2-yl)-amides as potent ROR γ t inverse agonists. *Bioorg. Med. Chem.* **2015**, 23, 5293–5302.

(24) Yang, T.; Liu, Q.; Cheng, Y.; Cai, W.; Ma, Y.; Yang, L.; Wu, Q.; Orband-Miller, L. A.; Zhou, L.; Xiang, Z.; Huxdorf, M.; Zhang, W.;

Zhang, J.; Xiang, J.; Leung, S.; Qiu, Y.; Zhong, Z.; Elliott, J. D.; Lin, X. Discovery of Tertiary Amine and Indole Derivatives as Potent ROR γ t Inverse Agonists. *ACS Med. Chem. Lett.* **2014**, 5, 65–68.

(25) Rene, O.; Fauber, B. P.; de Leon Boenig, G.; Burton, B.; Eidenschenk, C.; Everett, C.; Gobbi, A.; Hymowitz, S. G.; Johnson, A. R.; Kiefer, J. R.; Liimatta, M.; Lockey, P.; Norman, M.; Ouyang, W.; Wallweber, H. A.; Wong, H. Minor Structural Change to Tertiary Sulfonamide RORc Ligands Led to Opposite Mechanisms of Action. *ACS Med. Chem. Lett.* **2015**, 6, 276–281.

(26) Wang, Y.; Cai, W.; Liu, Q.; Lin, X. *Gordon Research Conference; Medicinal Chemistry* (poster); New London, NH, Aug 4–9, 2013.

(27) Hashimoto, Y.; Miyachi, H. Nuclear receptor antagonists designed based on the helix-folding inhibition hypothesis. *Bioorg. Med. Chem.* **2005**, 13, 5080–5093.

(28) Wang, Y.; Cai, W.; Cheng, Y.; Yang, T.; Liu, Q.; Zhang, G.; Meng, Q.; Han, F.; Huang, Y.; Zhou, L.; Xiang, Z.; Zhao, Y.-G.; Xu, Y.; Cheng, Z.; Lu, S.; Wu, Q.; Xiang, J.-N.; Elliott, J. D.; Leung, S.; Ren, F.; Lin, X. Discovery of Biaryl Amides as Potent, Orally Bioavailable, and CNS Penetrant ROR γ t Inhibitors. *ACS Med. Chem. Lett.* **2015**, 6, 787–792.

(29) Wang, Y.; Cai, W.; Liu, Q.; Meng, Q.; Cheng, Y.; Yang, T.; Zhang, G.; Xiang, J.; Wu, C. Preparation of N-substituted 2-[4-(ethylsulfonyl)phenyl]acetamides as retinoid-related orphan receptor gamma modulators. WO2013029338A1, 2013.

(30) Xiao, S.; Yosef, N.; Yang, J.; Wang, Y.; Zhou, L.; Zhu, C.; Wu, C.; Baloglu, E.; Schmidt, D.; Ramesh, R.; Lobera, M.; Sundrud, M. S.; Tsai, P.-Y.; Xiang, Z.; Wang, J.; Xu, Y.; Lin, X.; Kretschmer, K.; Rahl, P. B.; Young, R. A.; Zhong, Z.; Hafler, D. A.; Regev, A.; Ghosh, S.; Marson, A.; Kuchroo, V. K. Small-molecule ROR γ t antagonists inhibit T helper 17 cell transcriptional network by divergent mechanisms. *Immunity* **2014**, 40, 477–489.