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Letter

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SAR Exploration Guided by LE and Fsp^3: Discovery of a Selective and Orally Efficacious RORγ Inhibitor

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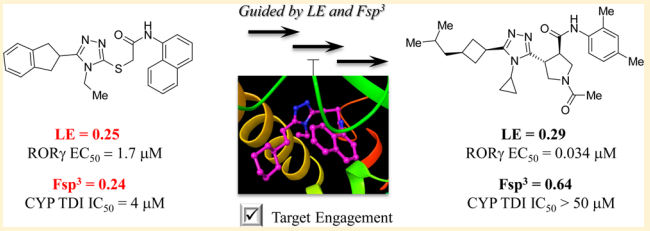
Supporting Information

ABSTRACT: A novel series of RORγ inhibitors was identified starting with the HTS hit **1**. After SAR investigation based on a prospective consideration of two drug-likeness metrics, ligand efficiency (LE) and fraction of sp^3 carbon atoms (Fsp^3), significant improvement of metabolic stability as well as reduction of CYP inhibition was observed, which finally led to discovery of a selective and orally efficacious RORγ inhibitor **3z**.



KEYWORDS: *Th17, immunological diseases, nuclear receptor, RORγ, ligand efficiency (LE), fraction of sp^3 carbon atoms (Fsp^3)*

Two decades after the discovery of Th1 and Th2 cells, a third subset of T helper cells called Th17 cells was identified and has drawn considerable attention since it was suggested to play a central role in the pathogenesis of various autoimmune diseases such as psoriasis and rheumatoid arthritis.[1,2] Among several regulatory pathways in which Th17 development and function are involved, the one regulated by the nuclear receptor RORγ appears to be crucial for controlling the differentiation and function.[3] Given its validity as an emerging drug target for treatment of immunological diseases, many research groups have made significant efforts in the discovery of RORγ modulators in recent years.[4−19]

Since starting our RORγ inhibitor program in 2003, we discovered several structurally diverse hits after a HTS campaign.[20] From these hits we selected compound **1** as the first hit-to-lead series for optimization. In addition to being reasonably potent against RORγ (hLUC EC$_{50}$ = 1.7 μM, FRET EC$_{50}$ = 0.85 μM), compound **1** also demonstrated >20-fold selectivity over five nuclear receptors (hRORα, hFXR, hRXRα, hPR, and hPPARγ) and was structurally unique in comparison to other nuclear receptor modulators.[16−18]

However, this compound has several drawbacks. For example, the microsomal stability in liver microsomes is poor with only 18% remaining at 10 min in human liver microsomes. It also has a modest time-dependent human CYP3A4 inhibition (IC$_{50}$ = 4 μM) probably due to some reactive metabolites formed by the oxidation of **1**. The ligand efficiency is only 0.25, far below the literature consensus value (0.30) for a drug-like molecule.[21] The concept of ligand efficiency (LE) was first introduced by Kuntz[22] and is widely accepted as a reliable index of drug-like qualities.[23] Improvement of LE inevitably results in lower molecular weight and higher potency. We reasoned that a strategy of increasing LE and lowering the lipophilicity should therefore significantly improve the drug-like properties of compound **1**. In addition, compound **1** is a rather flat molecule with a fraction of saturated carbons (Fsp^3) of 0.24. Fsp^3 is a newer index representing drug-likeness.[24] Lovering et al. pointed out that a decrease of Fsp^3 value would result in an increased incidence of CYP inhibition.[25] The desired Fsp^3 value is over 0.47 according to the literature.[24] Thus, we considered that improvement of the poor Fsp^3 value of compound **1** would be a rational way to overcome the CYP inhibition liability. As a result

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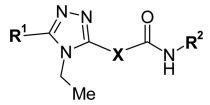
Table 1. Initial SAR Exploration



compd	R^1	X	R^2	RORγ-LUC EC_{50}[a] (μM) human	RORγ-LUC EC_{50}[a] (μM) mouse	LE[b]	Fsp^3[c]
1	2-indanyl	SCH_2	1-naphthyl	1.7	0.70	0.25	0.24
2		OCH_2		>20	>20	<0.21	0.24
3a		$(CH_2)_2$		1.0	0.40	0.26	0.27
3b[d]		$CH(Me)CH_2$		1.7	1.1	0.25	0.30
3c[d]		$CH_2CH(Me)$		1.3	0.67	0.25	0.30
3d[d]		$CH(OH)CH_2$		>20	>20	<0.20	0.27
3e	*c*-Hex	$(CH_2)_2$		>20	4.5	<0.23	0.43
3f	*c*-HexCH_2			14	2.6	0.23	0.46
3g	*c*-Hex$(CH_2)_2$			0.82	0.30	0.28	0.48
3h	*i*-Pr$(CH_2)_2$			13.0	1.4	0.25	0.41
3i	*t*-Bu$(CH_2)_2$			6.7	0.83	0.25	0.43
3j	Ph$(CH_2)_2$			2.5	0.63	0.25	0.24
3k	*c*-Hex$(CH_2)_2$		3-Cl-2-Me-Ph	0.96	0.64	0.29	0.59
3l			2,4-di-Me-Ph	0.90	0.60	0.30	0.61
3m			3,5-di-Me-Ph	2.9	3.1	0.27	0.61

[a]The EC_{50}s are mean values of at least two replicates. [b]LE = −1.37 log EC_{50}(LUC hRORγ)/number of heavy atoms. [c]Fsp^3 = number of sp^3 hybridized carbons/total carbon count. [d]Racemic.

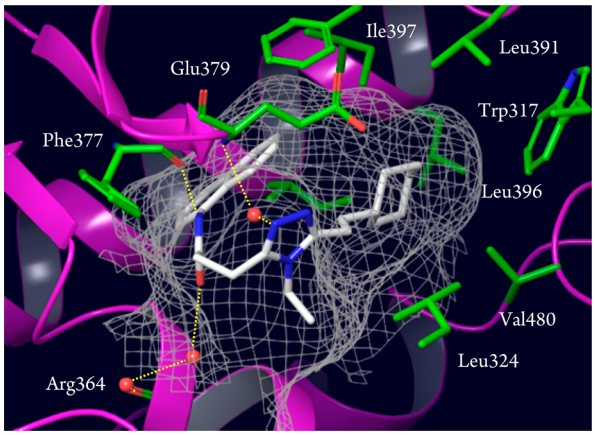
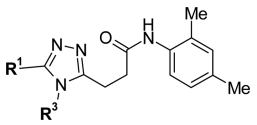


Figure 1. X-ray structure of inhibitor **3g** in human RORγ (PDB code 5AYG). Hydrogen bonds are depicted as dashed lines (yellow) and water molecules are shown as spheres (red).

of the above analysis, we decided to optimize compound **1** by improving two drug-likeness metrics, LE and Fsp^3, aiming to improve metabolic stability and reduce CYP inhibition.

Initially, exploration of the sulfide portion was performed (**2**, **3a**) and a carbon-substituted analogue **3a** showed a slight improvement of ligand efficiency (Table 1). Introduction of a small substituent on the ethylene part of this molecule, however, afforded no further improvement (**3b—3d**). Thus, we chose **3a** as a reference compound for further exploration. By changing the volume and shape of the substituents (**3e—3j**), we systematically examined the role of the R^1 portion of the molecule, and **3g** showed improved LE, while its Fsp^3 value was doubled from that of **1**. It is also noteworthy that the close analogue **3j** showed reduced potency, which suggested that non-planar substituents were preferred in this region of the binding pocket. For R^2 exploration, disubstituted phenyl analogues[26] were synthesized (**3k—3m**), and compound **3l** showed significant improvements of both LE and Fsp^3 (Table 1). We were

Table 2. SAR of R^1 Portion and R^3 Portion



compd	R^1	R^3	RORγ-LUC EC_{50}[a] (μM) human	RORγ-LUC EC_{50}[a] (μM) mouse	LE	Fsp^3	MS in liver S9 (remaining %) 10 min	MS in liver S9 (remaining %) 60 min
3l	*c*-Hex$(CH_2)_2$	Et	0.90	0.60	0.30	0.61	36	0
3n		*c*-Pr	0.98	0.45	0.28	0.63	55	23
3o		*c*-Bu	9.5	1.8	0.23	0.64	49	27
3p		2,2-di-F-*c*-Pr	0.92	0.50	0.27	0.63	75	59
3q[b]	2-Bu$(CH_2)_2$	*c*-Pr	3.9	1.4	0.27	0.59	63	27
3r	*i*-Pr$(CH_2)_3$		1.7	0.61	0.29	0.59	67	27
3s	*t*-Bu$(CH_2)_3$		2.8	1.3	0.27	0.61	71	51

[a]The EC_{50}s are mean values of at least two replicates. [b]Racemic.

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encouraged to see such improvements, particularly because of the potential of **3l** for further modifications.

To confirm target engagement of the newly discovered RORγ inhibitors, we did an X-ray cocrystal analysis, which revealed that **3g** binds to the ligand binding pocket of human RORγ with a unique U-shaped conformation (Figure 1). According to the structure, **3g** made a direct hydrogen bond to Phe377 (2.97 Å), while the ligand formed water-mediated hydrogen bonds to both Arg364 (2.91 Å) and Glu379 (2.95 Å). The structure also suggested that the van der Waals contacts of the cyclohexylethyl moiety was important, and fine-tuning of this part was attempted later during the final optimization.

Although **3l** showed a favorable LE value, improvements on human CYP3A4 inhibition (IC_{50} = 12 μM) and metabolic stability (36% remaining at 10 min in human liver microsomes) were still unsatisfactory, thus further exploration was needed to obtain a selective RORγ inhibitor suitable for *in vivo* study.

A closer look at this molecule revealed that the compound contains several flexible C−C bonds, which result in entropic energy loss in order to maintain the binding conformation. In addition, these rotatable bonds may be contributing to the decent CYP inhibition profiles seen with these compounds.[27] Therefore, we designed and synthesized some constrained analogues in an effort to stabilize the binding conformation and mask plausible metabolic sites simultaneously.

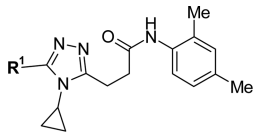
First, the ethyl group at the R^3 portion was transformed into carbocycles, and the effect was examined (Table 2). As the size of the ring increased, we observed a decrease in the LE metric (**3n**—**3p**). However, compound **3n** showed a marked improvement in metabolic stability with the least reduction of LE value. Therefore, this substituent was retained for further optimization. Our optimization of the R^1 portion began with a brief investigation of the terminal position since relatively sharp SAR had been observed at this region during the initial SAR exploration. Compounds **3q**−**3s** were synthesized as **3n** analogues, and **3r** showed a higher LE value with a slight increase of metabolic stability; thus, this terminal structure was chosen, and constrained subunits were inserted between this part and the triazole part.

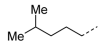
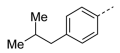
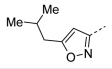
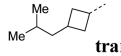
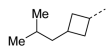
Among the compounds shown in Table 3, **3w** showed best LE value with a slight increase of metabolic stability. Most importantly, this compound's potency reached a low submicromolar EC_{50} in the human LUC assay.

Finally, cyclic scaffolds were incorporated between the triazole ring and the amide bond to generate a U-shaped conformation best mimicking the binding mode required for this series of molecules. Among the **3w** analogues listed in Table 4, **3y** and **3z**[28] showed good EC_{50} in the tens of nanomolar range, and most gratifyingly, **3z** achieved the original goal of good metabolic stability as well as reduction of CYP inhibitory activity.

Given its most promising activity in terms of LUC potency as well as metabolic stability, **3z** was considered the best choice for

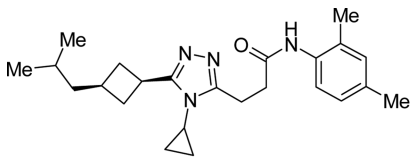
Table 3. Optimization of R^1 Portion[a]



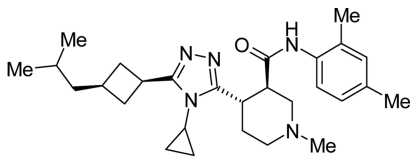
Compd	R^1	RORγ-LUC EC_{50} (μM) human	mouse	LE	Fsp^3	MS in liver S9 (remaining %) 10 min	60 min
3r		**1.7**	**0.61**	**0.29**	**0.59**	**67**	**27**
3t		**1.8**	**0.12**	**0.25**	**0.42**	**84**	**55**
3u		**0.45**	**0.054**	**0.29**	**0.48**	**83**	**31**
3v	 trans	**0.40**	**0.053**	**0.30**	**0.63**	**68**	**31**
3w	 cis	**0.14**	**0.035**	**0.32**	**0.63**	**70**	**39**

[a]The EC_{50}s are mean values of at least two replicates.

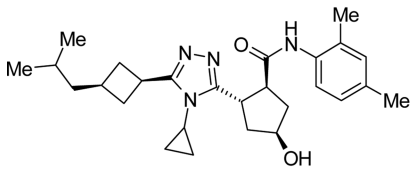
Table 4. SAR of 3w Analogues



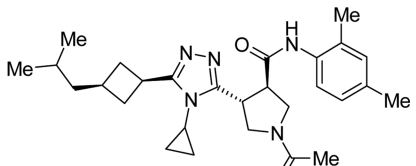
3w



3x



3y



3z

compd	RORγ-LUC EC_{50}[a] (μM) human	mouse	LE	Fsp^3	MS in liver S9 (remaining %) 10 min	60 min	CYP3A4m (preincubation) IC_{50} (μM)
3w	0.14	0.035	0.32	0.63	70	39	5
3x″	0.23	0.29	0.27	0.68	53	21	
3y	0.098	0.038	0.29	0.67	87	76	3
3z	0.034	0.029	0.29	0.64	86	61	>50

[a]The EC_{50}s are mean values of at least two replicates. [b]Racemic.

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further investigations. An HCl salt of this compound was orally administered as a 0.5% methylcellulose suspension into mouse, and good bioavailability as well as a fair amount of plasma exposure (AUC_{0-inf}) were observed at doses of 30 mg/kg and 100 mg/kg (see Supporting Information). Thus, **3z** appeared to be a strong candidate for murine *in vivo* studies. The HCl salt of **3z** was orally administered to mice that were stimulated with a mixture of MOG/PTX and a CD3 antibody. The plasma IL-17 level of each treated mouse was analyzed after 3 or 8 h of the administration (Figure 2). IL-17 release was suppressed in a

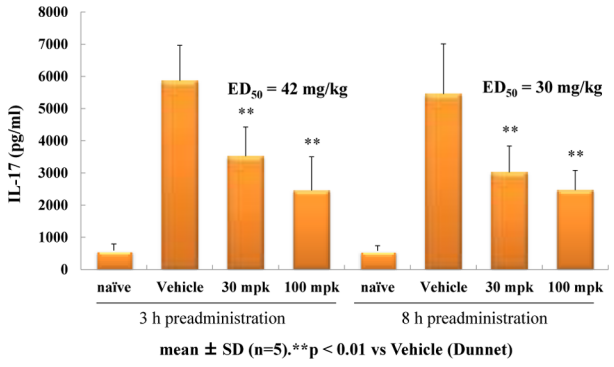

Figure 2. Effect of compound **3z** on the IL-17 level in a CD3-induced mouse PD model.

dose-dependent manner, and both compound-treated groups showed similar results regardless of the difference in the plasma compound concentrations (the predicted free plasma concentration of **3z**; 0.16 μM for 3 h/30 mg and 0.022 μM for 8 h/30 mg). Although the precise mechanism was not fully understood, it may suggest a delayed response of **3z** toward RORγ signaling or the need of sustainable RORγ inhibition for the blockade of IL-17 production.

In summary, we have identified novel RORγ inhibitors. Lead optimization was conducted by optimization of two metrics, ligand efficiency and Fsp^3. This strategy led to the discovery of a selective and orally efficacious RORγ inhibitor **3z**. This compound also showed decent potency against human RORγ in the biochemical assay (FRET EC_{50} = 0.20 μM) with neither inhibitory activity against other nuclear receptors (EC_{50} > 20 μM; hRORα, hRORβ, hSF1, mGR, hRXRα, hVDR, hFXR, mLXRα, hPPARα, hPPARδ, hPPARγ, hPR, hRARα, hRARβ) nor time-dependent CYP inhibition properties (IC_{50} > 50 μM; hCYP3A4m, hCYP2C9, hCYP2D6, hCYP1A2, hCYP2A6, hCYP2C19). We demonstrated that the optimization of these two parameters provided an efficient and rational means to generate drug-like compounds that were metabolically stable with reduced CYP inhibition liabilities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.5b00253.

Synthetic schemes, procedures, experimental data, stereochemical assignment of **3y** and **3z**, assay procedures, and PK profiles of **3z** (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

RORγ, retinoic acid receptor-related orphan receptor gamma; PR, progesterone receptor; PPAR, peroxisome proliferator-activated receptor; SF1, steroidogenic factor 1; GR, glucocorticoid receptor; RXR, retinoid X receptor; VDR, vitamin D receptor; FXR, farnesoid X receptor; LXR, liver X receptor; RAR, retinoic acid receptor; FRET, fluorescence resonance energy transfer; LUC, luciferase; CYP, cytochrome P450; SAR, structure−activity relationship

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(28) Absolute stereochemistry of **3y** and **3z** was assigned based on the alignment of each enantiomer with the binding structure of **3g** (Figure 1).

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