Letter

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Discovery of N-(indazol-3-yl)-piperidine-4-carboxylic acids as RORγt Allosteric Inhibitors for Autoimmune Diseases

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ABSTRACT The clinical success of anti-IL-17 monoclonal antibodies (i.e. Cosentyx® and Taltz®) has validated Th17 pathway modulation for the treatment of autoimmune diseases. The nuclear hormone receptor RORγt is a master regulator of Th17 cells and affects the production of a host of cytokines, including IL-17A, IL-17F, IL-22, IL-26 and GM-CSF. Substantial interest has been spurred across both academia and industry to seek small molecules suitable for RORγt inhibition. A variety of RORγt inhibitors have been reported in the past few years, the majority of which are orthosteric binders. Here we disclose the discovery and optimization of a class of inhibitors, which bind differently to an allosteric binding pocket. Starting from a weakly active hit **1**, a tool compound **14** was quickly identified which demonstrated superior potency, selectivity and off-target profile. Further optimization focused on improving metabolic stability. Replacing the benzoic acid moiety with piperidinyl carboxylate, modifying the 4-aza-indazole core in **14** to 4-F-indazole and incorporating a key hydroxyl group led to the discovery of **25**, which possesses exquisite potency and selectivity, as well as an improved pharmacokinetic profile suitable for oral dosing.

T helper 17 (Th17) cells are a subset of effector T cells, which play a key role in regulating immune response.[1,2] Upon stimulation, a unique pattern of cytokines are expressed and secreted from Th17 cells, including IL-17A, IL-17F, IL-22, IL-26, and GM-CSF. The Th17 pathway has been implicated in the pathogenesis of many autoimmune diseases, including psoriasis and psoriatic arthritis, rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and multiple sclerosis (MS).[3] Recent clinical success and FDA approval of several *anti*-IL-17 monoclonal antibodies such as secukinumab (Cosentyx™) and ixekizumab (Taltz™) have validated the approach of modulating the Th17 pathway for the treatment of autoimmune diseases.[4,5]

The nuclear hormone receptor RORγt is a master regulator for the differentiation and development of Th17 cells and affects the production of IL-17 and several other Th17 related cytokines.[6,7] Accordingly, RORγt inhibition by small molecule inhibitors might provide an alternative therapeutic approach to IL-17 antibodies for the treatment of autoimmune diseases.[7,8] Better and/or broader therapeutic outcomes could be attained by simultaneously blocking multiple Th17-secreted cytokines.[8,9]

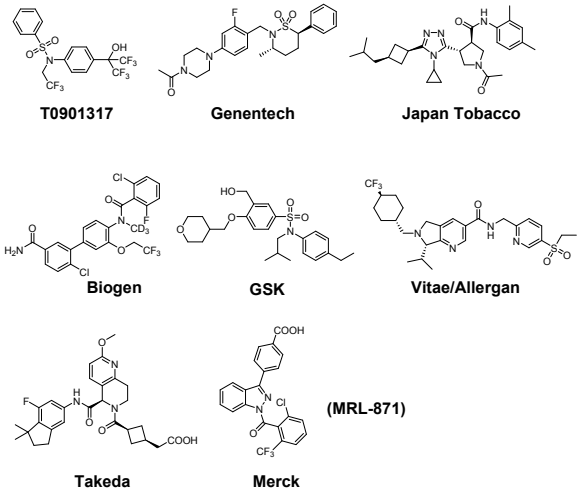
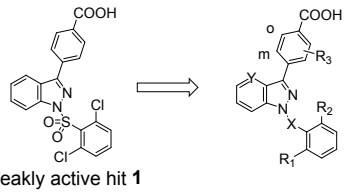


Figure 1. Selected small molecule RORγt inhibitors

Intense interest has been garnered from both academia and industry around identification of small molecule RORγt inhibitors suitable for clinical development.[10-13]

Since the discovery of the non-selective RORγt inhibitor T0901317,[14] a variety of more selective, potent, and structurally differentiating RORγt inhibitors have been reported as exemplified in Figure 1.[10-13,15-16] Several inhibitors have also been advanced to clinical trials, through either oral or topical administration for the treatment of various types of autoimmune diseases.[12,13] While the majority of these inhibitors bind to the canonical orthosteric pocket,[10-13] we recently disclosed the X-ray co-crystal structures of several indazolyl carboxylic acids as represented by MRL-871, which adopted a distinct binding mode[17,18] Two related classes of inhibitors were also reported after our initial disclosure[19,20] This kind of RORγt inhibitors bind to a different allosteric pocket present in RORγt ligand binding domain (LBD), which is different and distal to the canonical ortherosteric pocket of many nuclear hormone receptors including RORγt.[17] Herein we describe in detail the discovery and optimization of this class of inhibitors from a weakly active hit to a highly potent and selective RORγt inhibitor with much more favorable metabolic stability and off-target profile.

Table 1. SAR exploration from arylsulfonamide hit 1



Weakly active hit **1**

	X	Y	R_1	R_2	R_3	Fret IC_{50} (nM)[a]	Gal4 IC_{50} (nM)[a]
1	SO_2	CH	Cl	Cl	H	958	NA[b]
2	CH_2	CH	Cl	Cl	H	158	3116
3	CO	CH	Cl	Cl	H	5	400
4	CO	CH	Cl	O^{i}Pr	H	48	393
5	CO	CH	Cl	CF_3	H	2	127
6	CO	C-F	Cl	CF_3	H	3	72
7	CO	C-F	Cl	CF_3	o-F	13	131
8	CO	C-F	Cl	CF_3	o-Cl	84	610
9	CO	C-F	Cl	CF_3	o-NH_2	93	687
10	CO	C-F	Cl	CF_3	o-OH	3	17
11	CO	C-F	Cl	CF_3	o-OMe	586	NA
12	CO	C-F	Cl	CF_3	m-F	3	34
13	CO	C-F	Cl	CF_3	m-Cl	10	190

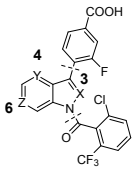
[a]IC_{50} values are the mean of at least two runs. Potency values represent for N=2 data differed by less than 3 fold, and otherwise additional replicae were collected.[b]NA stands for not tested.

Emerging from a high-throughput screening (HTS) campaign, several indazole derivatives represented by arylsulfonamide **1** were identified as weakly active RORγt inhibitors in a time-resolved fluorescence energy transfer (TR-FRET) cofactor recruitment biochemical assay (IC_{50} = 958 nM).[17] Our initial optimization effort began by exploring different indazole nitrogen capping groups (Table 1). Switching the sulfonamide moiety in **1** to a methylene group (**2**) boosted binding affinity six folds. Conversion of sulfonamide to carboxamide **3** further improved binding affinity and afforded the first analog with single digit nanomolar activity (IC_{50} = 5 nM). Benzamide **3** also exhibited good activity in a cellular chimeric RORgt-Gal4 report assay (Gal4) in HEK-293 cells (IC_{50} = 400 nM).[17]

This encouraging result prompted us to explore a variety of other amides. In general, analogs having bis-ortho substituents (**4**, **5**) attached to the benzoyl moiety were preferred over their counterparts with mono-ortho or non-ortho substitution because of their superior potency and chemical stability to amide hydrolysis. Eventually 2-Cl-6-CF_3 substituted analog **5** emerged not only by virtue of its potency, but also due to its high stability under both basic and acidic conditions. At this point, gratifyingly we also were able to obtain the co-crystal structure of **5** (**MRL-871**),[17] which not only revealed its unique allosteric binding mode, but also provided useful structural insight to guide our subsequent SAR exploration and optimization.

We next began to investigate the effect of substitution around the benzoic acid ring moiety. Since 4-F substitution on the indazole core was slightly more favorable for cellular activity (e.g. **6** *vs* **5**), subsequent SAR exploration was carried out in the same context (**7**-**13**). Ortho-substituents next to the carboxylate moiety (F, Cl, or NH_2) were generally detrimental for potency (**7**-**9**). In contrast, the presence of ortho-OH further improved both biochemical and cellular potency. Conversion of **10** into its MeO-analog **11** led to a significant drop in potency. Substitution at *meta*-position was also briefly explored (**12**, **13**), with *meta*-fluoro substitution showing marginal benefit.

Table 2. Indazole core modification



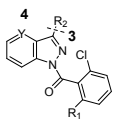
		Fret IC_{50} (nM)[a]	Gal4 IC_{50} (nM)[a]	clogP
14		6	90	5.4
15		6	99	5.3
16		18	177	4.2
17		9	187	4.9

[a]IC_{50} values are the mean of at least two runs.

With potent analogs such as **10** and **12** (**MRL-299**)[17] in hand, one of our goals early on was to identify a tool compound with

sufficient potency, metabolic stability, and favorable off-target profile suitable for preliminary *in vitro* and *in vivo* proof-of-biology studies. For this purpose, the compounds in Table 2 were prepared. Incorporation of a nitrogen atom into either the 4 or 6 position of the core was tolerated with minimal loss of activity (**14-16**). However, nitrogen substitution at the 6 position of the indazole core (**15)** led to notable CYP inhibition (CYP3A4 IC_{50} = 4.8 μM). Aza-indole analog **17** was also tolerated with a slight decrease in potency relative to **14**. Aza-indazole analog **14** (**MRL-248**)[21] was profiled in a Eurofins panel of counter screening at a concentration of 10 uM against a panel of 108 additional kinases, receptors, transporters, and nuclear receptors and showed only weak activity again one target in the panel (PPARγ, IC_{50} = 2 uM). In contrast, compound **12** showed 9 hits with >50% inhibition under the same conditions. Compound **14** also showed no appreciable activity against a panel of related nuclear hormone receptors.[21] In addition, sufficient oral exposure could be achieved with **14** in a high dose mouse pharmacokinetic study. Based on its PK and selectivity profile, compound **14** was chosen as a tool compound and utilized extensively in various *in vitro* and *in vivo* studies.[21, 22]

Table 3. SAR of benzoic acid replacement



	Y	R_1	R_2	Fret IC_{50} (nM)[a]	Gal4 IC_{50} (nM)[a]
18	N	CF_3		461	3766
19	N	CF_3	 racemic	76	1302
20	C-F	CF_3		7	300
21	C-F	CF_3	 racemic	4	107
22	C-F	CF_3	 racemic	39	1188
23	C-F	CF_3	 (3R, 4S)	51	2035
24	C-F	CF_3	 (3S, 4R)	2	53
25	C-F		 (3S, 4R)	1	49

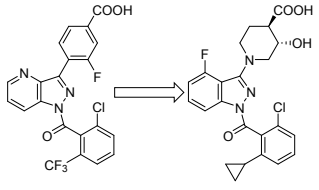
[a]IC_{50} values are the mean of at least two runs.

Our next goal focused on improving the metabolic stability of **14** while maintaining its favorable potency, selectivity and off-target profile. Met ID studies of incubating **14** in hepatocytes revealed acyl-glucuronidation as one of its major clearance mechanisms. Unfortunately, several attempts to overcome this metabolism pathway by converting the carboxylate into other typical acid bio-isosteres, such as tetrazole or acyl-sulfonamide groups led to significant loss of potency.[23] Another tactic to mitigate glucuronidation is to introduce steric hindrance next to the carboxylate moiety,[24] but none of the *o*-substituents (i.e. **8-9, 11**) except OH (**10**) was not tolerated in our case as noted previously. Unfortunately, compound **10** also showed poor metabolic stability.

At this stage, we envisioned a strategy of saturating the benzoic acid ring moiety, and prepared the compounds in Table 3. Piperidyl carboxylate **18** showed much weak activity, while its cyclohexenyl counterpart **19** displayed modest activity**.** Hydrogenation of alkene in **19** gave both *cis*- and *trans*- isomer, but neither of them led to any improvement. Gratifyingly, switching to 4-F-indazole core (**20**) exhibited significant gain in potency compared to the corresponding analog with the azaindazole core (**18**). Cyclohexenyl analogs (**21**) also benefited greatly from the same core change.

Next, our efforts then focused on incorporation of additional polar substituents to reduce the lipophilicity and improve other ancillary properties of these analogs.[25] Introduction of β-OH substitution next to the carboxylate was quite encouraging (**22-24**). Although racemic cis-isomer **22** was less potent, one enantiomer of its corresponding trans-isomer (**24** *vs* **23**) displayed better biochemical and cellular activity than **20**. Later, we also found that 2-Cl-6-(cyclopropyl)-benzoyl moiety (**25**) imparted additional gain in potency compared with 2-Cl-6-CF_3 benzoyl (**24**) as the indazole capping group.

Compound **25** was selected for broad profiling and demonstrated a much more favorable overall profile compared with our tool compound **14** (Figure 2). Besides excellent binding and cellular activity, **25** also exhibited very good potency in a Th17 differentiation/IL17A production assays in primary human peripheral blood mononuclear cells (PBMCs).[17] Furthermore, **25** was metabolically more stable than **14,** and demonstrated improved *in vivo* pharmacokinetic profile in both rat and dog PK studies. In addition, **25** showed a clean off-target profile in Eurofins Panlabs panel (Supporting information). Consistent with its lower clogP and higher Fsp^3, **25** also shows improvement in physiochemical properties (e.g. solubility @ pH=2).[26]



	14	25
Potency		
Fret IC_{50} (nM)	6	1
Gal4 IC_{50} (nM)	90	49
PBMC IC_{50} (nM)	33	13
***In vivo* PK**		
Rat: Cl (ml/min/Kg), T1/2 (h), Vd (L/kg), F%	76, 0.4, 0.8, 16%	13, 3.7, 0.6, 35%
Dog: Cl (ml/min/Kg), T1/2 (h), Vd (L/kg), F%	4.5, 1.4, 0.4, 45%	1.4, 3.1, 0.3, 65%
Other properties		
PPB(rat, dog)	98.7%, 98.7%	98.7%, 99.7%
clogP	4.6	2.7
Fsp^3	0.05	0.35
Solubility (μM) @ pH=2 and 7	<2, 147	28, 153

Figure 2. Overall profile of **25** *vs* **14**

Gratifyingly, we also obtained an X-ray co-crystal structure of **25** bound to RORγt ligand binding domain (LBD) (Figure 3). The carboxylate group forms several H-bond interactions with RORγt backbone or residues, including Phe498, Ala497 and Gln329. The 2-Cl-6-(cyclopropyl)-phenyl group is positioned nearly perpendicular to the plane of the indazole core. The *β*-hydroxy group of the piperidine ring forms an intramolecular H-bond with the carboxylate moiety, as well as Phe498.

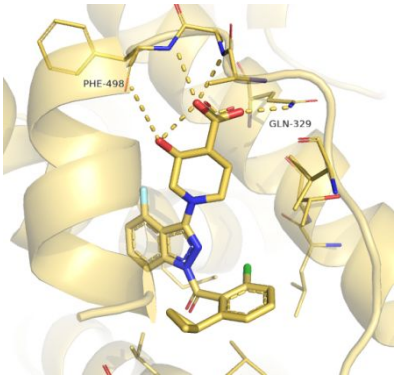


Figure 3. Co-crystal structure of **25** with RORγt LBD domain

Prior to discovery of **25,** compound **14** was chosen for an *in vivo* study in an acute mouse pharmacodynamic (PD) model (Figure 4).[27] Inhibition of RORγt blocks the expression of Bcl-xL in thymocytes. C57BL/6 mice received a single dose of compound **14** and were sacrificed after 2h. Both plasma concentration of **14** and Bcl-xL expression levels in thymocyte were measured. In consistent with pharmacologically induced RORγt inhibition, compound **14** inhibited *in vivo* Bcl-xL expression in a robust dose dependent manner (IC_{50} = 0.71 μM).

Dose (mpk)	Compound 14 plasma concentration (μM)
1	0.18
3	0.73
10	4.1
30	51
100	254

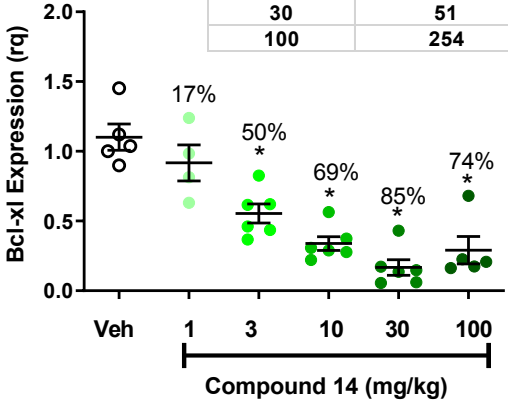


Figure 4. Dose-dependent *in vivo* inhibition of Bcl-xL expression by **14**. The data shown in the figure refer to Mean ± SEM values.

In summary, a class of N-(indazol-3-yl)-piperidine-4-carboxylic acids was discovered as highly potent and selective RORγt allosteric inhibitors. From weakly active hit arylsulfonamide **1**, replacing the sulfonamide with bis-ortho-substituted benzamide and switching the central core from indazole to 4-aza-indazole led to the discovery of early tool compound **14**. Despite its good potency and selectivity, compound **14** exhibited less optimal metabolic stability. Subsequent optimization featured saturation of the benzoic acid moiety in order to slow down metabolic clearance. The initially significant potency loss arising from replacement of the benzoic acid moiety with 4-piperidinyl carboxylic acid could be regained by switching from 4-aza-indazole core to 4-F-indazole core. Incorporation of a *β*-hydroxyl group on the piperidine and swapping of ortho substituent from CF_3 to cyclopropyl culminated in the discovery of **25**. In addition to its superior potency, selectivity, and favorable off-target profile, compound **25** exhibited much improved *in vivo* metabolic stability across species. Furthermore, compound **14** was evaluated in an acute PD model where it demonstrated a robust dose-dependent inhibition of Bcl-xL expression in thymocytes, providing valuable proof of biology for this class of allosteric inhibitors.

ASSOCIATED CONTENT

Supporting Information

Synthetic procedures and analytical data for representative compounds, protocols for biological assays and Bcl-xL PD model, X-ray statistics for **25** RORγt binding to ligand binding domain, and data of panlabs profiling of **25**.
The Supporting Information is available free of charge on the ACS Publications website.

Accession Codes

The PDB code for **25** is 6UCG.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

ROR: retinoid-related orphan receptor; TR-FRET: time-resolved fluorescence energy transfer; PBMC: peripheral blood mononuclear cell; Bcl-xL: B-cell lymphoma-extra large; LBD: ligand binding domain; Met-ID: metabolite identification.

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Discovery of N-(indazol-3-yl)-piperidine-4-carboxylic acids as RORγt Allosteric Inhibitors for Autoimmune Diseases

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