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Discovery of Biaryl Amides as Potent, Orally Bioavailable and CNS Penetrant RORγt Inhibitors

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KEYWORD: RORγt inhibitor, Th17 cell differentiation, biaryl amides, EAE, multiple sclerosis

ABSTRACT: A novel series of biaryl amides was identified as RORγt inhibitors through core replacement of a starting hit **1**. SAR exploration on the biaryl moiety led to discovery of potent RORγt inhibitors with good oral bioavailability and CNS penetration. Compounds **9a** and **9g** demonstrated excellent *in vivo* efficacy in EAE mice dose dependently with once daily oral administration.

T helper (Th) 17 cells, a lineage of $CD4^+$ effector T cells characterized by the production of IL-17A and IL-17F, are pathogenic in human autoimmune inflammatory diseases including multiple sclerosis (MS).[1-4] The presence of IL-17 was detected in MS lesions, and Th17 cells were observed in the infiltrations of mouse experimental autoimmune encephalomyelitis (EAE) central nerve system (CNS).[5,6] Differentiation and function of Th17 cells are controlled by the transcription factor retinoic acid receptor-related orphan receptor-gamma-t (RORγt).[7-9,11] It has been shown that the genetic deficiency of RORγt in mice severely impaired Th17 cell differentiation and conferred resistance to EAE.[10] RORγt inhibitors has potential utility in reducing the activity of Th17 cells and therefore can be developed as therapeutic agents for the treatment of Th17 cell mediated autoimmune diseases.[12-18]

A few small molecule RORγt inhibitors have been reported in literature.[19] Digoxin,[20] SR1001[21] and Ursolic acid[22] were first reported to inhibit RORγt and ameliorate EAE in mice via intraperitoneal administration. Other small molecular RORγt inhibitors[23-31] were later disclosed. Recently, we reported discovery of thiazole ketone amides (e.g., **2**) and thiophene ketone amides (e.g., **3**) as novel RORγt inhibitors based on a high throughput screening (HTS) hit **1** (Figure 1).[32] These ketones, especially the thiophene ketones, showed good RORγt activities but were poorly orally bioavailable and lack of CNS penetration that is believed to be important for developing an effective oral MS drug. In this paper, we report the discovery of novel biaryl amides as first potent, orally bioavailable and CNS penetrant RORγt inhibitors which demonstrated EAE *in vivo* efficacy dose dependently via oral administration.

The lack of CNS penetration of thiazole/thiophene ketones was attributed to their ketone moiety as the non-ketone thiazole amide **1** is CNS penetrant with a brain-to-blood ratio (Br/Bl) of 1.5 in a mouse CNS study (i.p., 2mg/kg).[33] Encouraged by the CNS data of **1**, we conducted thiazole core replacement with a number of different aromatic rings (**4a-4i**), aiming to identify a suitable scaffold for multi-property optimization (Table 1). Among the five-membered ring analogs, 2,4-substituted thiophene **4c** showed the best RORγt potency in the FRET assay.[32,34] The heteroatom such as oxygen and nitrogen on the ring decreased (**4a**) and even abolished (**4d**, **4f**, **4h**) RORγt activities. For the six-membered ring analogs, para-substituted aryl amide (**4i**) showed better RORγt potency than the meta-substituted one (**4g**). Because of its reasonable RORγt potency, good CNS penetration (Br/Bl = 2.0), and improved ligand efficiency (LE) and lipophilic ligand efficiency (LLE) (0.33 and 2.3 for **4i** compared to 0.29 and 1.9 for **1**, respectively)[35] and easy modification/diversification, the aryl amide **4i** was used as the new chemistry starting point for optimization.

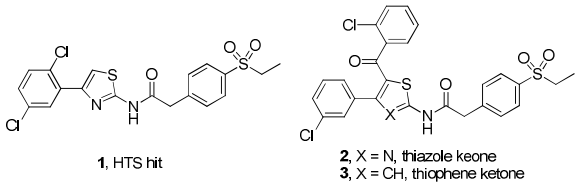


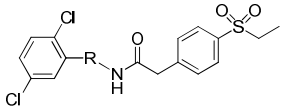
Figure 1. Structures of RORγt inhibitors (**1**-**3**)

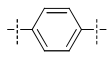
In order to explore SAR of the biaryl moiety of the amide, a versatile synthesis of the general structures of biaryl amides was developed (Scheme 1).[36] Biaryl amines **7** were prepared from either bromoanilines **5** through Suzuki coupling with aryl boronic acids, or from reaction of aryl bromides with aniline boronic esters **6**, obtained from **5**. Coupling **7** with acids **A**, or acid chlorides **B**, or perfluorophenyl esters **C** afforded the desired biaryl amides **8** or **9**. The biaryl amides could also be prepared by first coupling of **5** with **A** to form amides **10**, which were converted to the target compounds directly via Suzuki coupling, or via its boronic ester intermediate **11**.

We investigated the binding mode of compound **4i** and its derivatives in RORγt LBD based on the co-crystal structure of a similar aryl amide with RORγt LBD (pdb code: 4NIE).[37] The perpendicular confirmation of the two aryl rings in the left hand side (LHS) of the amides provided preferred inter-molecular interactions with the surrounding hydrophobic residues in the RORγt LBD and was

believed to be important for the RORγt binding affinity (Figure 1). Subsequently, the substitutions on the ortho-positions of the two aryl rings, which force the two aryls to take perpendicular conformation, were studied extensively and the key SAR of the biaryls was summarized in Table 2. Non-substituted biphenyl amide **8a** showed a RORγ FRET pIC_{50} of 6.3. Adding a Cl group on ortho-position of the central phenyl ring (**8b**) enhanced RORγt activity. Keeping the ortho-Cl on the central phenyl ring, adding a hydrophobic group on ortho-position of the terminal phenyl ring provided potent RORγt inhibitors (**8c**-**8f**) with pIC_{50}s ≥ 8.0 in the FRET assay. Biaryl amides **8c**-**8f** also showed good cellular activities in the Th17 cell differentiation assay (pIC_{50} > 6.0).[32-34] Obviously, the cLogP of **8c**-**8f** are relatively high (4.4~5.1, from ChemBioDraw Ultra 12.0). Replacing -O^{i}Pr moiety (**8f**) with -CH_2NMe_2 (**8g**, cLogP 3.7) or changing the phenyl ring to a pyridine ring (**8h**, cLogP 4.0) or other hetero-aromatic rings such as pyrole (**8i**, cLogP 3.5) lowered RORγt potency, which also resulted in essentially no activity in Th17 cell differentiation assay. These findings indicate that the binding pocket where the LHS aryl occupies is hydrophobic and unable to tolerate some polar moieties.

Table 1. SAR of thiazole core replacements

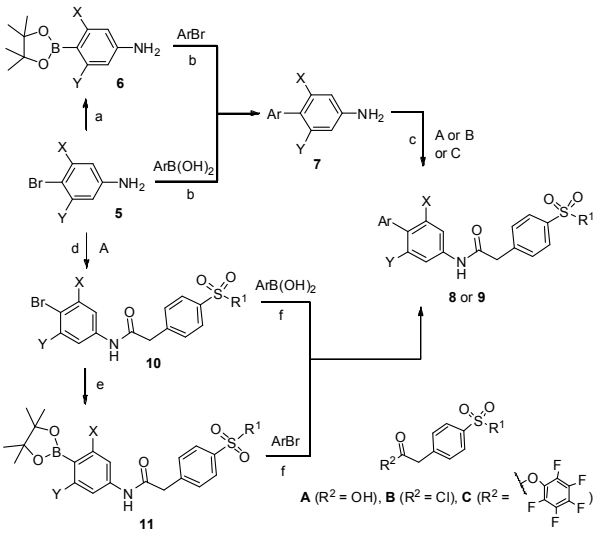


Compd	R	RORγ FRET pIC_{50}[a] (% max inhibition[b])
1		6.0±0.08 (116)
4a		5.1±0.06 (80)
4b		6.4±0.06 (105)
4c		7.1±0.01 (116)
4d		< 4.6
4e		6.3±0.04 (120)
4f		< 4.6
4g		6.2±0.02 (120)
4h		< 4.6
4i		7.0±0.06 (107)

[a]pIC_{50} value is the average of at least two determinations, the error expressed by ±SEM; [b]% max inhibition measured against activation by the surrogate agonist.

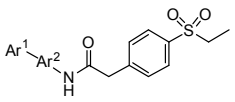
We then fixed the OCF_3 group at ortho-position of the LHS terminal aryl and studied SAR of substitution on the central phenyl ring of the amides (Table 2). Adding a hydrophobic group such as methyl (**8l**) or CF_3 (**8m**) on the central phenyl ring increased Th17 potency while replacing the central phenyl ring with pyridine (**8k**) significantly decreased both RORγt and Th17 potency. Although polar groups like carboxylic acid (**8o**) decreased the RORγt potency dramatically, certain polar groups such as acetyl (**8n**) were found to be tolerated on the central phenyl. Encouraged by this, a number of hetero-aromatic rings were introduced on the central phenyl and the resulting compounds (e.g., **8p**-**8q**) showed good RORγt activity in both FRET and Th17 assays. It is good to see that the cLogP of **8p** and **8q** are relatively lower (3.6 and 3.0, respectively), resulting in higher LLE values (4.7 and 5.4, respectively) although their molecular weights are higher.

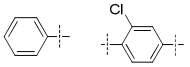
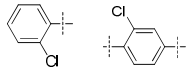
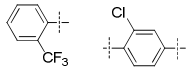
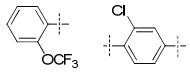
Scheme 1. General synthetic procedures for biaryl amides[a]

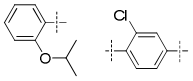
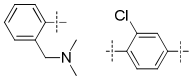
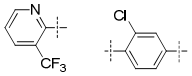
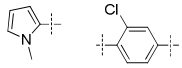
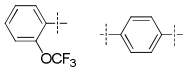
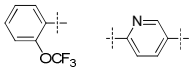
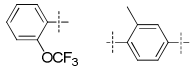
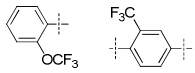
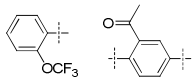
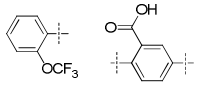
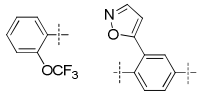
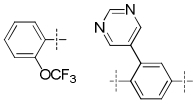
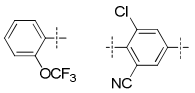
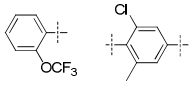
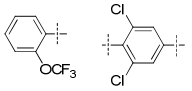


[a]Reagents and conditions: (a) Bis(pinacolato)diborane, $PdCl_2$(dppf), KOAc, DMF, 100 ° C. (b) tri-*tert*-butyl phosphine (tetrafluoroboric acid salt), $Pd_2(dba)_3$, Na_2CO_3, dioxane, 100 ° C, microwave. (c) For acid **A**, EDC, HOBt, DCM; For acid chloride **B**, triethylamine, DCM; For perfluorophenyl ester **C**, DIPEA, DCM, RT. (d) EDC, HOBt, DCM; or HATU, DIPEA, DCM. (e) Bis(pinacolato)diborane, $PdCl_2$(dppf), KOAc, DMF, 100 ° C; or Bis(pinacolato)diborane, $Pd_2(dba)_3$, tricyclohexylphosphine, KOAc, dioxane, 90 ° C. (f) $PdCl_2$(dppf), Cs_2CO_3, CH_3CN, water, 100 ° C, microwave; or $Pd(PPh_3)_4$, Na_2CO_3, dioxane, water, 100 ° C, microwave.

Table 2. Biaryl SAR of the amides



Compd	Ar^1	Ar^2	RORγ FRET pIC_{50}[a] (% max inhibition[b])	Th17 pIC_{50}[a]
8a			6.3±0.30 (90)	<5
8b			7.8±0.04 (109)	5.2
8c			8.3±0.02 (100)	6.0
8d			8.2±0.02 (106)	6.7
8e			8.5±0.10 (98)	7.1

8f		8.0±0.00 (120)	7.1
8g		6.0±0.00 (117)	<5
8h		7.2±0.00 (106)	<5.3
8i		6.8±0.07 (115)	<5.2
8j		8.1±0.00 (113)	6.8
8k		6.4±0.12 (106)	5.1
8l		8.3±0.04 (112)	7.6
8m		8.2±0.02 (113)	6.9
8n		8.0±0.08 (101)	5.6
8o		5.1±0.05 (68)	<5
8p		8.3±0.11 (96)	7.2
8q		8.4±0.01 (112)	>7.5
8r		8.2±0.08 (96)	7.5
8s		8.4±0.12 (93)	>8.5
8t		8.4±0.02 (97)	>8.2

[a]pIC_{50} value is the average of at least two determinations, the error expressed by ±SEM (for FRET assay); [b]% max inhibition measured against activation by the surrogate agonist.

We next added a second substituent to the central phenyl ring to constrain the preferred perpendicular conformation. As expected, additional substituent CN (**8r**), Me (**8s**) or Cl (**8t**) boosted RORγt activities in both FRET and Th17 assays.

Compound **8t** was used as a tool compound for RORγt biological studies because of its excellent *in vitro* activities as well as good oral exposure and CNS penetration.[38] Encouraged by the profile of **8t**, we incorporated the previous SAR learnings and further optimized the LHS biaryl part as well as right hand side (RHS) sulfone part of the amides, trying to obtain a molecule with more balanced profile (Table 3). Changing the ethyl sulfone in **8t** with a methyl sulfone (**9a**) resulted in a similar RORγt potency and CNS penetration. However, replacing the methyl sulfone with a primary sulfonamide (**9b**) basically eliminate the CNS penetration although the RORγt and Th17 potency remained, possibly due to introduction of two more H-bond donors as well as increase of topological polar surface area (tPSA) in **9b**. Switching OCF_3 (**9a**) to OCF_2 (**9c**) lowered its CNS penetration. The CNS penetration was further decreased when OCF_2 (**9c**) was replaced by a CN group (**9d**). With a Cl group in the para-position of LHS phenyl and only one substituent (F, Me, or Cl) in the ortho position of central phenyl, compounds (**9f-9h**) showed good RORγt potency and CNS penetration. Compared to methyl sulfone **9h**, the ethyl sulfone **9i** demonstrated the best CNS penetration (Br/Bl = 2.0). Clearly, the data of CNS penetration were well correlated to values of tPSA and/or cLogP. As a result, LLE value is relatively low for those biaryl amides with better CNS penetration (Table 3).

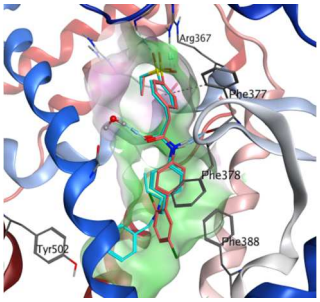


Figure 1 Predicted binding mode of compound **4i** (brown) and structural overlay with a previously published tertiary amine (blue) co-crystal structure with RORγt LBD using Surflex-Dock v2.3 in Sybyl 8.1.[37]

Table 4. Mouse PK[a] of the RORγt inhibitors

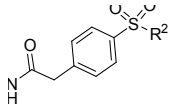
	iv, 1 mg/kg[b]			*po, 2 mg/kg*[c]		
Compd	$T_{1/2}$ (h)	C_{lb} (mL/min/kg)	V_{ss} (L/kg)	C_{max} (ng/mL)	$DNAUC_{0-\infty}$ (ng.h/mL)/(mg/kg)	F (%)
8d	2.2	17.6	3.2	210.7	713	75
8e	4.2	11.6	3.8	202.7	1313	102
9a	9.7	5.5	4.4	213.5	2465	100
9g					4048[d]	

[a]Male C57BL/6 mice; [b]iv formulation: DMSO: 10% hydroxypropyl-β-cyclodextrin = 1:99 (w:v); [c]po formulation: DMSO: 1% methylcellulose (W/V) =1:99; for **9a**, DMSO: 10% hydroxypropyl-β-cyclodextrin; [d]10 mg/kg (po).

Several representative compounds were evaluated for their mouse PK profile (Table 4). Biaryl amides **8d**, **8e** and **9a** demonstrated good PK profile with oral bioavailabilities of 75%, 102% and 100%, respectively. Compound **9g** was only evaluated via po administration and showed excellent oral exposure.

With good Th17 activity and mouse oral exposure, we then evaluated **9a** and **9g** in EAE mice where Th17 cells play a critical role (Figure 2).[33] Compounds **9a** and **9g** were orally administered once daily at 3 doses (1, 3, 10 mg/kg) to EAE mice from the day of immunization. Compared to the control, the treatment with **9a** or **9g** resulted in a delay and significant reduction in clinical severity of EAE in a dose dependent manner. Compared to thiazole

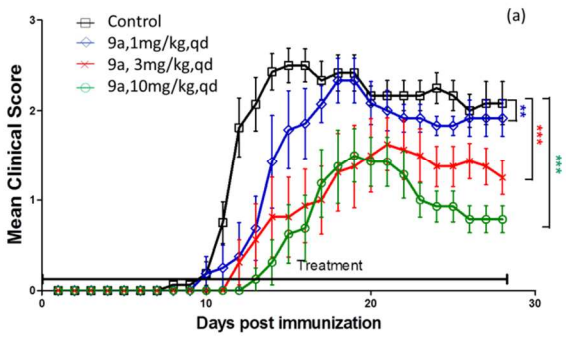
Table 3. SAR of the biaryl amides



Compd	R^1	Z	X	Y	R^2	RORγ FRET pIC_{50}[a] (% max inhibition[b])	Th17 pIC_{50}[a]	Br/Bl[c] (AUC_{brain}/AUC_{blood})	tPSA[d]	cLogP[d]	LLE[e]
8t	H	OCF_3	Cl	Cl	Et	8.4±0.02 (97)	>8.2	0.78 (946/1220)	72.5	5.2	3.2
9a	H	OCF_3	Cl	Cl	Me	8.3±0.15 (96)	7.4	0.79 (658/835)	72.5	4.7	3.6
9b	H	OCF_3	Cl	Cl	NH_2	8.5±0.11 (108)	8.1	0.08 (388/4878)	98.5	4.5	4.0
9c	H	OCF_2	Cl	Cl	Et	8.5±0.26 (107)	8.0	0.39 (462/1182)	72.5	4.6	3.9
9d	H	CN	Cl	Cl	Et	8.2±0.11 (94)	7.1	0.10 (200/1928)	87.0	4.2	4.0
9e	F	CN	Cl	Cl	Et	8.4±0.03 (96)	6.8	0.06 (76/1378)	87.0	4.3	4.1
9f	Cl	OCF_3	F	H	Me	8.0±0.28 (101)	7.3	1.17 (2354/2017)	72.5	4.7	3.3
9g	Cl	OCF_3	Me	H	Me	8.2±0.08 (92)	7.2	1.47 (3517/2397)	72.5	4.5	3.7
9h	Cl	OCF_3	Cl	H	Me	8.1±0.09 (98)	7.6	0.98 (1696/1729)	72.5	5.0	3.1
9i	Cl	OCF_3	Cl	H	Et	8.2±0.01 (99)	8.1	2.0 (1764/881)	72.5	5.5	2.7

[a]pIC_{50} value is the average of at least two determinations, the error expressed by ±SEM (for FRET assay) ; [b]% max inhibition measured against activation by the surrogate agonist; [c]brain to blood ratio[33]; [d]obtained from ChemBioDraw Ultra 12.0; [e]LLE = pIC_{50}-cLogP.[35]

ketone amide **2** which only showed EAE efficacy up to day 20 at 100mg/kg twice daily dosing,[32] the biaryl amides **9a** and **9g** are much more efficacious. This could be attributed to their good *in vitro* activities as well as much improved oral exposure and CNS penetration. However, it should be noted that although **9g** had more brain exposure than **9a**, it exhibited less efficacy than **9a** in EAE experiments, indicating that there might be additional factors such as "free" brain concentration affecting *in vivo* efficacy.



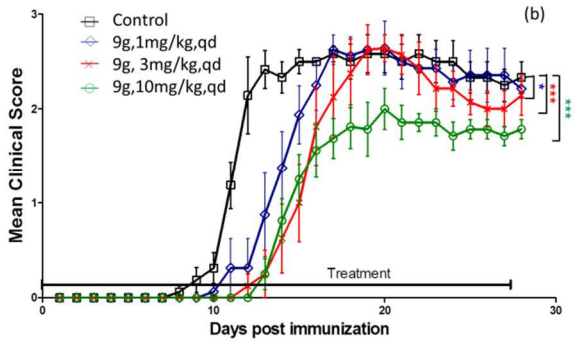


Figure 3. (a) Treatment efficacy of compound **9a** in mouse EAE in different doses (1, 3, 10mg/kg, p.o., q.d.). (c) Treatment efficacy of compound **9g** in mouse EAE in different doses (1, 3, 10mg/kg, p.o., q.d.). Repeated ANOVA, followed by Dunnett's Multiple Comparison Test was applied,*p<0.05,**p<0.01,***p<0.001. *Notes*:

In summary, we have discovered a novel series of biaryl amides as RORγt inhibitors. Detailed SAR study on the LHS biaryl moiety of the amides led to discovery of potent RORγt inhibitors with

excellent oral bioavailability and CNS penetration. The key compounds **9a** and **9g** demonstrated a dose dependent EAE efficacy in mice when administrated orally once a day. Further optimization on sulfone moiety of the biaryl amides to balance potency and some developability properties such as solubility is on-going.

ASSOCIATED CONTENT

Supporting Information

Synthetic procedures and compound characterization; molecular modeling studies; mouse CNS measurement description. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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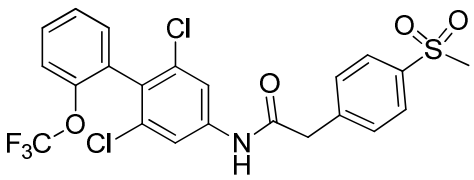

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