Discovery of Potent and Orally Bioavailable Inverse Agonists of the Retinoic Acid Receptor-Related Orphan Receptor C2

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Supporting Information

ABSTRACT: The further optimization of a recently disclosed series of inverse agonists of the nuclear receptor RORC2 is described. Investigations into the left-hand side of compound **1**, guided by X-ray crystal structures, led to the substitution of the 4-arylthiophenyl residue with the hexafluoro-2-phenylpropan-2-ol moiety. This change resulted in to compound **28**, which combined improved drug-like properties with good cell potency and a significantly lower dose, using an early dose to man prediction. Target engagement *in vivo* was demonstrated in the thymus of mice by a reduction in the number of double positive T cells after oral dosing.

KEYWORDS: Retinoic acid-related orphan receptor C, autoimmune diseases, nuclear receptor, IL-17, dose to man prediction

Inverse agonists for the retinoic acid-related orphan receptor gamma C2 (RORC2) have been intensely pursued as potential drugs for the treatment of autoimmune disorders.^{1–7} RORC2 is expressed exclusively in the thymus and in cells of the immune system, where it acts as the key transcription factor for the differentiation and development of T_H17 and other IL-17 producing cells.⁸ Blocking T_H17 maturation and cytokine expression with an inverse agonist of RORC2 presents an attractive alternative to antibody treatment.⁹ Several antibodies targeting diverse parts of the IL-17 pathway have achieved clinical proof-of-concept in autoimmune diseases such as psoriasis, psoriatic arthritis, and ankylosing spondylitis.^{10–12}

Previously we have described a class of inverse agonists of RORC2, exemplified by **1** (Table 1).¹³ Compound **1** and analogues bind inside the ligand-binding domain (LBD) of RORC2 and modulate receptor function through the ether substituent of the 4-arylthienyl group, which interferes with the cofactor recruitment site on helix 12 (AF2 domain).^{13,14} Large,

lipophilic ether groups were necessary to achieve inverse agonism in compounds devoid of the acetamide function shown in **1**. Its introduction allowed us to reduce the size of the left-hand side to a methoxy-substituted aryl and to improve physicochemical properties.

Although **1** combined good inhibition of IL-17A production in the cell assay with oral bioavailability in rodents, prediction of the clinically efficacious dose, used within AstraZeneca to evaluate compound quality, revealed that gram amounts of **1** would be required for once-daily treatment.¹⁵

The calculation is based on a conservative approach, where we assumed that 75% of the dose of **1** would be absorbed from the gut and that the minimum concentration required for effective depletion of IL-17 over 24 h would be equal to three times the unbound potency in the IL-17 cell assay. Clearance

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Table 1. Profile of Compound 1^a

IL-17 cell pIC ₅₀ total/free ^b	7.2/7.9
hPPB (% free) ^c	1.3
Cl _{int} RH/HH (μL/min/10 ⁶ cells) ^d	5/5.5
Rat PK ^e : Cl (mL/min/kg), t _{1/2} (h), Vss (L/kg), F (%)	2.5, 2.7, 0.34, 19
eDtM (mg, QD) ^f	2400

^aSee Supporting Information for assay details. ^bInhibition of IL-17 production from human primary T_H17 cells; free potency calculated based on protein content in the assay medium. ^cBinding to human plasma protein determined by equilibrium dialysis. ^dRat and human hepatocyte intrinsic clearance. ^ePharmacokinetic profile in rat. ^fEarly dose to man prediction.

was predicted from human hepatocytes and the volume of distribution using the Oie–Tozer equation.¹⁵

Parallel with the SAR leading to **1**, we had investigated the possibility to simplify the 4-arylthienyl motif of the non-acetamide series, exemplified by **3** (Table 2), to improve its physicochemical properties.

Changing the left-hand side of **3** to a para-substituted biphenyl as in **5** was superior with respect to potency to **3** or the meta-substituted analogue **4**, but did not improve physicochemical properties.¹⁶ The X-ray crystal structure of compound **2**, a cell active (pIC₅₀ = 5.81) inverse agonist, identified from a high-throughput screening campaign, helped us in addressing this issue.¹⁷ Soaking **2** in the agonist form of the RORC2 LBD returned the (R)-enantiomer as the bound species (Figure 1). An overlay with **1** showed that both compounds established the same hydrogen bond interactions with their amide moieties to Glu379 and Phe377, respectively. The isopropyl group on the phenyl substituent of **2** partially filled the volume occupied by the methoxy residue of the 4-aryl group on the thiophene, indicating that the 4-chlorophenyl group in **5** could be replaced with a simpler residue.

Replacement of the 4-chlorophenyl group in **5** with isopropyl resulted in inactive compound **6**. Speculating that either a polar group, mimicking the methoxy group in **1**, or enhanced steric bulk could lead to active compounds led us to the preparation of analogues containing a diverse set of para-substituents. While introduction of an isopropyl cyano (**7**) or methoxy (**8**) substituent improved activity in the FRET and cell assay and also physicochemical properties, the bis-trifluoromethyl-isopropanol moiety in **9** proved to be the optimal choice, leading to efficacious inhibition of IL-17A production. The introduction of the two trifluoromethyl groups led to a relatively high logD, but overall solubility with respect to **3** was improved, due to the slight acidic nature of the hydroxy group (measured pK_a = 8.85). Methoxy and nitrile analogues **10** and **11** exhibited marginally improved potency in the cell assay but were 8-fold less soluble. Elimination of the hydroxy group from **9** reduced activity by about 10-fold (**12**), whereas elimination of one trifluoromethyl group resulted in inactive compound **13**.

The hexafluoro-2-phenyl-propan-2-ol moiety is part of T0901317, a known agonist of the liver X receptor, from which diverse groups developed structurally diverse inverse agonists of RORC2.^{18–20} Compound **9** did not display any

Table 2. Modification of the LHS^a

Cmpd	R	pIC ₅₀ (% eff.)		logD ^d	Sol. (μM) ^e
		FRET ^b	IL-17 ^c		
3		6.8 (-96)	ND	>4.1	0.4
4		6.8 (-98)	5.8 (-46)	>4	1.5
5		7.2 (-85)	6.5 (-44)	>4	0.6
6		<5	N.D.	3.5	11
7		6.5 (-52)	5.7 (-63)	2.5	42
8		6.9 (-63)	6.0 (-36)	2.5	181
9		7.6 (-92)	7.0 (-89)	3.6	53
10		7.5 (-46)	7.1 (-66)	4	7
11		7.0 (-62)	7.3 (-84)	4.3	7
12		6.9 (-56)	6.2 (-61)	3.9	67
13		<5	N.D.	2.1	206

^apIC₅₀ data are the mean of at least two independent measurements unless otherwise stated; see Table S1. ^bRecruitment of SRC1-derived coactivator peptide; pIC₅₀ SEM is <0.37. ^cInhibition of IL-17A production from human primary T_H17 cells; % efficacy (% eff.) relative to DMSO control; pIC₅₀ SEM is <0.31. ^dDistribution coefficient between 1-octanol and aqueous phosphate buffer at pH 7.4. ^eDetermined from DMSO stock solutions in aqueous buffer at pH 7.4. ND, not determined.

agonistic activity against LXRα and β up to a concentration of 10 μM in a reporter gene assay. It was also found to be inactive against other ROR isoforms and related retinoic acid receptors α, β, and γ.

Combining the hexafluoro-2-phenyl-propan-2-ol moiety with the phenylglycine residue found in **1** resulted in **14**, which combined enhanced cell potency and full efficacy in suppressing IL-17 production with superior metabolic stability

Figure 1. Overlay of **1** (1.84 Å, PDB: 6ESN, carbons in cyan) and HTS hit **2** (2.1 Å, PDB: 6R7A carbons in orange) in the RORC2 LBD.

and solubility compared to **1** (Table 3). The unsubstituted amine **15** is about 6-fold less potent in the cell assay. This potency difference is not reflected in the FRET assay, which is also observed for other compounds in Table 3. The result is due to the assay conditions, placing a limit on the highest pIC_{50} that can be determined at around 7.5. Compounds **14** and **15** displayed agonistic activity on RORA in the lower

micromolar range, as determined by a cofactor recruitment assay, but were inactive as inverse agonists, as all compounds in Table 3. Compound **14** was also inactive against RORB or other nuclear receptors such as retinoic acid receptors α , β , and γ .

We briefly investigated the SAR around the acetamide residue to see if we could further improve cell potency, without compromising on the physicochemical properties. Carbamate **16** was comparable in potency to amide **14**, whereas urea **17** and sulphonamide **18** were inferior. Increasing the size of the amide substituent to isobutyl, as in **19**, improved cell potency by about 3-fold, but at the expense of metabolic stability and solubility. Introduction of a hydroxy group into the isobutyl residue as in **20** improved overall properties, but not cell potency.

Aromatic residues were tolerated, and benzoate **21** or phenylpropionate **23** showed cell potencies similar to **14**. Phenylacetamide **22** was an exception, being 10-fold more active in the cell assay. As observed for **19**, the higher logD resulted in higher turnover in rat hepatocytes and a loss in solubility. Incorporation of nitrogen atoms as in compounds **24–27** caused generally a loss in cell potency with respect to **22**. This was less pronounced for the 2-pyridyl and the 3-pyridazinyl analogues **24** and **26**, but despite their lower logD, turnover in rat hepatocytes and solubility did not improve. Interestingly, the carbamate linkage in **16** and the bulkier amide residues in **19** or **20** as well as introduction of nitrogen atoms into **22** abolished activity on RORA.

The X-ray cocrystal structures of **14** and **22**, obtained by soaking the compounds into the apo crystals of RORC2-LBD in the presence of bound SRC2 peptide, returned their

Table 3. Impact of the Amine Substituent on Activity and Metabolic Stability^a

Cmpd	R	FRET pIC ₅₀ (% eff.) ^b	IL-17 Cell pIC ₅₀ (% eff.) ^c	logD ^d	Sol. (μM) ^e	RH Clint ^f	RORA pIC ₅₀ ^g
1		7.2 (–72)	7.2 (–72)	3.3	205	5	4.5
14	C(O)Me	7.4 (–99)	7.3 (–91)	3.1	621	<1	5.6
15	H	7.4 (–94)	6.6 (–91)	2.8	150	2.5	5.8
16	C(O)OMe	7.3 (–97)	7.2 (–88)	3.6	150	2.5	<4.5
17	C(O)NHMe	7.4 (–98)	6.6 (–89)	3.2	155	5.4	ND
18	SO ₂ Me	7.1 (–97)	6.9 (–91)	2.7	447	<1	ND
19	C(O)CH ₂ -iPr	7.1 (–94)	7.8 (–96)	>4	28	9	<4.5
20	C(O)CH ₂ C(OH)Me ₂	7.1 (–97)	7.3 (–91)	3.3	241	1.3	<4.5
21	C(O)Ph	7.0 (–97)	7.4 (–95)	>4	1.4	3.6	ND
22	C(O)CH ₂ Ph	7.3 (–92)	8.5 (–95)	4	11	23	5.7
23	C(O)(CH ₂) ₂ Ph	7.1 (–100)	7.4 (–97)	>4	0.03	54	ND
24	C(O)CH ₂ –2-pyridyl	7.3 (–97)	7.9 (–97)	3.3	2.7	17	<4.5
25	C(O)CH ₂ –2-pyridazyl	7.2 (–95)	7.0 (–89)	2.5	110	4.3	ND
26	C(O)CH ₂ –3-pyridazyl	7.2 (–95)	7.6 (–89)	2.9	3.4	24	<4.5
27	C(O)CH ₂ –3-pyrimidyl	7.3 (–97)	7.4 (–90)	2.8	177	6	ND
28	C(O)Me (R)	7.5 (–95)	7.5 (–95)	3.0	381	<1	6.3
29	C(O)Me (S)	5.6 (–98)	7.1 (–91)	3.1	326	<1	<4.5

^a pIC_{50} data are the mean of at least two independent measurements unless otherwise stated; see Table S1. ^bRecruitment of SRC1-derived coactivator peptide; pIC_{50} SEM is <0.37. ^cInhibition of IL-17A production from human primary T_H17 cells; % efficacy (% eff.) relative to DMSO control; pIC_{50} SEM is <0.31. ^dDistribution coefficient between 1-octanol and aqueous phosphate buffer at pH 7.4. ^eDetermined from DMSO stock solutions in aqueous buffer at pH 7.4. ND, not determined. ^fRat hepatocyte intrinsic clearance ($\mu L/min/10^6$ cells). ^gTime-resolved (TR)-FRET assay in agonist mode using a peptide derived from PGC1 α 130–154; ND, not determined.

respective *R*-isomers as the bound species (Figure 2). We have shown previously that the ligand interactions in such agonist

Figure 2. Overlay of **1** (1.84 Å, PDB: 6ESN, carbons in cyan), **14** (1.8 Å, PDB: 6R7J, carbons in green), and **22** (1.5 Å, PDB: 6R7K, carbons in pink) with key interactions to the RORC2 LBD.

conformation would render the same binding mode as in the cocrystals without the coactivator peptide.²¹ Their right-hand side moieties overlapped well and established the same hydrogen bonds inside the pocket and outside the LBD, namely, to Arg364, Phe377, and Glu379. The enhanced cell activity of **22** can be explained by the interaction of the phenylacetamide with a hydrophobic stretch outside the LBD.

On the left-hand side, the bis-trifluoromethyl groups occupied a space in front of the 4-aryl residue of **1**, extending above and below the plane of the phenyl residues, which overlap with the thiophene of **1**. The interaction with Ser404 is lost, and this might be the reason for the activity observed on RORA. The Phe- $C(CF_3)_2OH$ moiety is located in a hydrophobic environment, at about 7–8 Å away from the cofactor recruitment site, but not exactly in the same place as in previously reported inverse agonists (see Figure S3).²⁰ Its local conformation, with the hydroxy group pointing towards helix 12, suggests that it modulates receptor function through indirect interactions with this region (Figure S1). Although a more thorough analysis is needed, an overlay of the LBD's of RORA and RORC suggested that the observed selectivity against RORA with either carbamate, branched, or polar acetamide residues could be due to a narrower and more hydrophobic channel in RORA (Figure S2).

Compound **14** was separated into its enantiomers, and the more active enantiomer **28** was assigned the (*R*)-configuration, based on the X-ray structure. The (*S*)-isomer **29** was about 100-fold less active in the FRET assay but showed higher than expected activity in the cell assay. We believe this to be due to racemization of the compounds in the medium of the cell assay, as we have previously demonstrated for a close derivative of **1**.¹³ Isomer **28** was also more active on RORA. Further profiling of **22**, **28**, and **29** revealed that they showed good crossover to mouse, as evaluated by radioligand binding assays (Table 4). Compound **22** showed moderate stability in human

Table 4. Profile of Selected Compounds

Cmpd	22	28	29
hRORC SPA ^a	7.4	7.3	6.1
mRORC SPA ^a	7.6	6.9	5.4
hPPB (% free) ^b	0.72	12	10
IL-17 cell pIC ₅₀ free ^c	9.4	7.6	7.3
Cl _{int} HH ^d (μL/min/10 ⁶ cells)	4.3	<1	<1
eDTM (mg, QD) ^e	900	250	
Rat PK ^f			
Cl (mL/min/kg), t _{1/2} (h)	53, 4.9	18.2, 3.7	ND
Vss (L/kg), F (%)	10.2, 5	2.2, 20	ND
Mouse PK ^f			
Cl (mL/min/kg), t _{1/2} (h)	ND	14, 3.3	16, 2.9
Vss(L/kg), F (%)	ND	2.4, 27	2.7, 28

^aScintillation proximity competition binding assay (SPA). ^bBinding to human plasma protein determined by equilibrium dialysis. ^cInhibition of IL-17A production from human primary T_H17 cells; % efficacy (% eff.) relative to DMSO control; pIC₅₀ SEM is <0.31. ^dDistribution coefficient between 1-octanol and aqueous phosphate buffer at pH 7.4. ^eDetermined from DMSO stock solutions in aqueous buffer at pH 7.4. ^fPharmacokinetic profile in rat and mouse. For experimental conditions, see Supporting Information. ND, not determined.

hepatocytes, similar to **1**, whereas **28** and **29** were stable. Single dose rat PK of **22** was characterized by high plasma clearance and low bioavailability, in line with clearance data from rat hepatocytes. The rat PK of **28** was comparable to **1**, revealing moderate plasma clearance and reasonable oral bioavailability. Compared to **1**, permeability and efflux of **28**, determined in Caco2-cells, were not significantly improved ($0.3/0.49 \times 10^{-6}$ cm/s and 50/17, respectively). We calculated the early dose to man as described above for compound **1**. A clear improvement for compound **28**, with respect to **1** and **22**, is evident, due mainly to its enhanced metabolic stability, resulting in a significant reduction in predicted human clearance.

We established an *in vivo* model that allowed us to evaluate the effect of RORC2 inhibition in the thymus of mice. Maturation and survival of double positive (CD4⁺CD8⁺) T cells in the thymus depends on RORC2. It has been shown that germline knockout of the receptor in the mouse leads to a reduction of the number of double positive cells.²²

The mouse PK for **28** and **29** displayed almost identical profiles and was similar to the rat PK of **28** (Table 4). Only a small extent of racemization (<5%) was observed in plasma at 24 h.

Compounds were then dosed orally at 50 mg/kg twice a day for 2 days to six-week-old C57BL/6 female mice. Afterwards, a single cell suspension from each thymus was prepared and cells stained for flow cytometric analysis to assess the absolute numbers of double positive (CD4⁺CD8⁺) thymocytes (Figure 3). Compound **28** significantly reduced their number by about 40% ($p = 0.008$), whereas enantiomer **29** had no effect. Exposure levels for compounds **28** and **29** at 48 h were similar, with 240 ± 150 and 145 ± 45 nM, respectively. Free terminal plasma exposure of compound **28** was calculated to be 28 nM, which corresponds to the unbound IC₅₀ value in the cell assay. The lack of effect for **29** is in line with its weak binding activity on mouse RORC.

In summary we have further improved our series of phenylglycine based RORC2 inverse agonist. Investigations into the left-hand side of compound **1**, inspired by the X-ray cocrystal structure of **2**, led to the substitution of the aryl-thiophenyl residue with a hexafluoro-2-phenyl-propan-2-ol

Figure 3. Effect of compounds **28** and **29** on the number of CD4⁺CD8⁺ T cells in the thymus of mice.

moiety, reducing the number of aromatic rings from three to two and led to compound **28**, which showed good cellular potency with full suppression of IL-17 production. It also resulted in an overall improvement in drug-like properties. Using early dose to man prediction as a benchmark, compound **28** requires 6-fold lower dosing compared to **1**. Oral dosing to mice showed engagement of RORC2 *in vivo*, as demonstrated by a reduction in the number of double positive T cells in the thymus.

For the synthesis of phenylglycine derivatives, amine **15** was prepared by amide coupling of **30** to acid **32**¹³ and subsequent deprotection of the Boc group. Reaction with the appropriate acylating reagent furnished the desired products. Acetate **14** was further separated into the enantiomers **28** and **29** (Scheme 1).

Scheme 1. Synthesis of Analogues **14**, **16**, **22**, **28**, and **29**^a

^aReagents and conditions: (a) HATU, *i*-PrNEt₂, CH₂Cl₂ 85%; HCl, 1,4-dioxane, RT or TFA, CH₂Cl₂, quant.; (b) for **14**: MeCN, AcCl, NEt₃, 89%; for **16**: MeCN, MeOCOCl, *i*-PrNEt₂, 64%; for **22**: PhCH₂CO₂H, T₃P, TEA, CH₂Cl₂, RT, 85%; (c) SFC, 30% *i*-PrOH in CO₂, 120 bar: **28** (41%), **29** (41%).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmmedchemlett.9b00158.

Experimental procedures and characterization data for intermediates and all final compounds, conditions for biological assays, and crystal structure information (PDF)

Accession Codes

PDB accession codes 6R7A (**2**), 6R7K (**22**), and 6R7J (**14/28**). The authors will release the atomic coordinates and experimental data upon publication.

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F.N., A.L., J.J., J.M., and T.G.H. conceived and designed the experiments; F.N., S.v.B., R.I.O., T.H., M.L., J.M., M.Lep., R.C., and Y.Xi. designed and/or synthesized compounds; A.A. and Y.X. provided X-ray structure data; A.L., M.C., J.J., N.K., M.R., M.B., and A.L. designed and/or performed and analyzed the *in vivo* studies; J.M. and E.L.H. provided *in vitro* assay data; F.N. wrote the manuscript with contributions from Y.X., A.L., J.M., S.v.B., and M.C.

Notes

All animal experiments were approved by the Pharmaron's Institutional Animal Care and Use Committee (IACUC) in Pharmaron and by the Gothenburg Ethics Committee for Experimental Animals Sweden; both conform to Directive 2010/63/EU. Animal handling conformed to standards established by the Council of Europe ETS123 AppA, NIH guidelines on animal welfare, Chinese legislation and Pharmaron's IACUC policies and procedures, the Helsinki Convention for the Use and Care of Animals, Swedish legislation, and AstraZeneca Global Internal Standards.

The authors declare no competing financial interest.

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■ ABBREVIATIONS

FRET, fluorescence resonance energy transfer; HATU, O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium-hexafluorophosphate; LBD, ligand binding domain; PK, pharmacokinetics; ROR, retinoic acid receptor-related orphan receptor; SAR, structure–activity relationship; SPA, scintillation proximity assay; SRC, steroid receptor coactivator

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