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Discovery of *oxa*-sultams as RORc inverse agonists showing reduced lipophilicity, improved selectivity and favorable ADME properties

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ABSTRACT

Modification of the δ-sultam ring of RORc inverse agonist **2** led to the discovery of more polar *oxa*-sultam **65**. The less lipophilic inverse agonist (**65**) displayed high potency in a biochemical assay, which translated into inhibition of IL-17 production in human peripheral blood mononuclear cells. The successful reduction of lipophilicity of this new analog gave rise to additional improvements in ROR selectivity and aqueous kinetic solubility, as well as reduction in plasma protein binding, while maintaining high cellular permeability.

The retinoic acid receptor-related orphan receptor c (RORc or RORγ)[1] is a nuclear receptor (NR) and the master transcription factor for interleukin (IL)-17.[2] It is required for the differentiation of naïve CD4+ T cells into T helper-17 (T_H-17)[2] cells, as well for the development of type 3 innate lymphoid cells (ILC3).[3,4] These cells are characterized by the production of diverse pro-inflammatory cytokines, mainly IL-17,[2] but also IL-22[5] and granulocyte macrophage colony stimulating factor (GM-CSF)[7] and play a key role in host defense against *Candida* infection.[6]

IL-17 is a critical driver of inflammation,[8–11] and antibodies directly targeting the IL-17 family of cytokines have demonstrated positive effects for the treatment of psoriasis,[12,13] rheumatoid arthritis,[14] ankylosing spondylitis[15] and uveitis[16] in clinical trials. The recent approval of anti-IL-17 antibody secukinumab (Cosentyx) for the treatment of moderate-to-severe plaque psoriasis has further validated this approach.[17] On this basis, it has been proposed that the modulation of IL-17 expression through small molecule inhibitors of RORc is of significant importance for the treatment of inflammatory diseases.[18–21]

Our group recently reported the discovery of the RORc inverse agonist tertiary sulfonamide **1** (Fig. 1).[22] Through the incorporation of a polar *N*-acetylpiperazine unit, co-crystallization of **1** with the human RORc-ligand binding domain (LBD) [PDB: 4WQP][23] revealed a key single hydrogen bond from the oxygen of the acetyl group to an ordered water molecule in an arginine-rich region of the ligand-binding pocket. However, the rest of the contacts made with sulfonamide **1** remained as van der Waals interactions with the predominantly hydrophobic residues in the ligand-binding pocket. This series of tertiary sulfonamide ligands (exemplified by **1**) suffered from poor metabolic stability due to rapid N-dealkylation product formation upon incubation with human or rat liver microsomes.[22,24] A successful cyclization strategy gave rise to sultam (cyclic sulfonamide) **2**, which mitigated N-dealkylation and possessed suitable DMPK properties for oral dosing.[24] Sultam **2** remained a lipophilic ligand with a *c*Log*P* of 3.8 and a ligand-lipophilicity efficiency (LLE)[25,26] of 4.2, based on its biochemical potency (12 nM). Highly lipophilic compounds are often associated with non-specific toxicity due to undesired secondary pharmacology,[27] as well as low aqueous solubility,[28] cellular permeability[29] and increased plasma-protein binding.[30] Therefore, we sought to minimize those risks by designing new sultam-based RORc ligands

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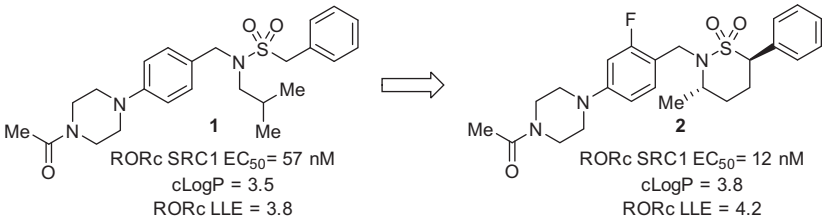


Figure 1. Initial tertiary sulfonamide and sultam RORc inverse agonist ligands reported by Genentech.

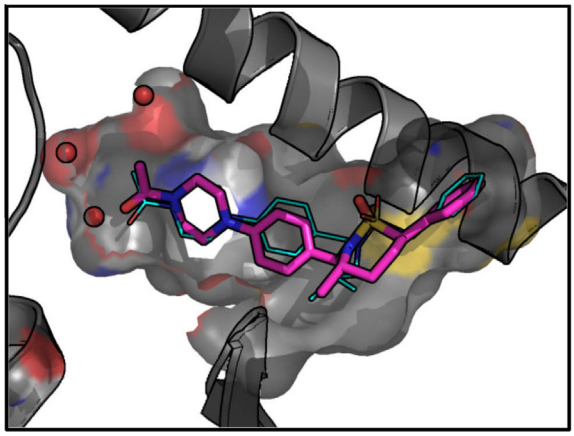


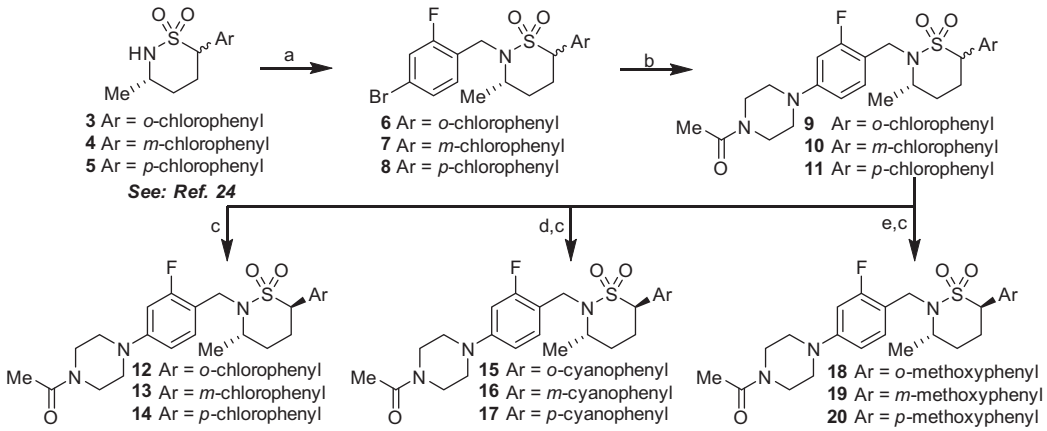
Figure 2. X-ray co-structure of the human RORc-LBD with RORc inverse agonist ligand **1** (cyan lines) (PDB: 4WQP) modeled with sultam **2** (magenta sticks).[31] The surface of the RORc-LBD ligand binding pocket is highlighted adjacent to H-bond acceptor residues in red, H-bond donor residues in blue, sulfur atoms in yellow and lipophilic residues in gray. Water molecules are represented with red spheres. Few opportunities for polar residue interactions are revealed on the right-hand side of the ligand binding pocket (gray and white surface).

that would possess a *c*Log*P* ⩽ 3.0 and LLE ⩾ 5.0. Herein, we report the discovery of RORc inverse agonists possessing a significantly more polar *oxa*-sultam core leading to reduced lipophilicity and improved selectivity, while preserving favorable in vitro ADME properties.

A model of sultam **2**[31] bound to the ligand-binding domain of RORc as found in the X-ray co-structure of the human RORc-LBD with inverse agonist ligand **1** [PDB: 4WPQ] was inspected with the goal of identifying unexplored opportunities for incorporation of polarity within the sultam scaffold (Fig. 2). This analysis quickly revealed that interactions with the polar arginine- and water-rich region of the pocket had already been fulfilled with a polar *N*-acetylpiperazine moiety. Few additional opportunities for polar contacts were identified based on the highly lipophilic nature of the RORc-LBD.[19,32] Consequently, we decided to utilize an empirical approach, synthesizing focused libraries of analogs that would systematically incorporate polar functionality into the aryl-sultam scaffold to determine tolerated changes.

Analogs were evaluated in a fluorescence resonance energy transfer (FRET) assay that monitored the ability of the human RORc-LBD to bind to a coactivator peptide derived from steroid receptor coactivator-1 (SRC1).[33] Compounds disrupting the recruitment of the SCR1 peptide were determined to be inverse agonists. Full inverse agonism (−100% efficacy) corresponded to complete suppression of basal signal. We also used the ligand-lipophilicity efficiency (LLE)[25,26] as a metric to ensure the effective use of non-polar interactions with the goal of achieving LLE values ⩾5.0.

Our initial focused library was aimed at introducing small polar substituents around the arene ring of the (3*S*,6*R*)-3-methyl-6-phenylsultam moiety found in compound **2**. A late-stage functionalization approach, where an advanced chloroarene intermediate was derivatized under transition-metal catalysis, was employed in order to minimize the total number of synthetic steps to access diverse targets (Scheme 1). *Ortho*-, *meta*-, and *para*-chlorophenyl-sultams (**3**–**5**) were synthesized from the corresponding



Scheme 1. Synthesis of substituted aryl sultams. Reagents and conditions: (a) 4-bromo-1-(bromomethyl)-2-fluorobenzene, NaH, DMF, 0 °C; (b) *N*-acetylpiperazine, $Pd(OAc)_2$, RuPhos, NaO*t*-Bu, 1,4-dioxane, 100 °C; (c) chiral column SFC separation, *trans*:*cis* ratio 2:1; (d) $ZnCN_2$, $Pd_2(dba)_3$, SPhos, DMF/H_2O, 150 °C μW; (e) MeOH, $Pd(OAc)_2$, AdBippyPhos, Cs_2CO_3, toluene, 100 °C.