ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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RORc Modulators for the Treatment of Autoimmune Diseases

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Patent Application Title:	Aryl Sultam Derivatives as RORc Modulators		
Patent Application Number:	WO 2015/104356 A1	**Publication date:**	16 July 2015
Priority Application:	US 61/925,845	**Priority date:**	10 January 2014
	US 62/091,063		12 December 2014
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Assignee Company:	F. Hoffmann-La Roche AG [CH/CH]; Grenzacherstrasse 124, CH-4070 Basel (CH) (for all designated States except US) Genentech, Inc.; 1 DNA Way, South San Francisco, California 94080, USA (for US only)		
Disease Area:	Autoimmune diseases such as rheumatoid arthritis, irritable bowel disease, psoriasis, psoriatic arthritis, and spondyloarthridities	**Biological Target:**	The retinoid-receptor related orphan receptor C (RORc)

Summary:

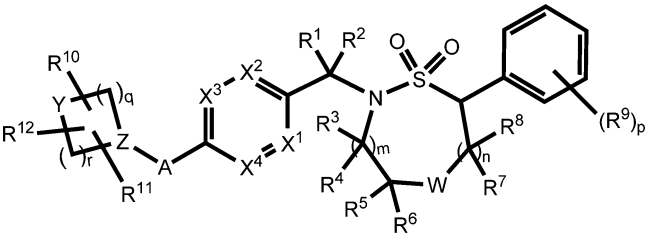
The invention in this patent application relates to aryl sultam derivatives represented generally by formula (I). These compounds possess activities as modulators of the retinoid-receptor related orphan receptor C (RORc or RORγ) and may potentially provide a treatment for several autoimmune diseases.

There are three known forms of the retinoic acid-related orphan receptors (RORs) named RORa (RORα), RORb (RORβ), and RORc (RORγ). They are members of the nuclear hormone receptor subfamily of intracellular transcription factors that are encoded by the genes RORA, RORB, and RORC, respectively.

Interleukin 17 (IL-17) secretes CD4+ T cells including the T helper 17 cells (Th17). The Th17 cells are believed to be involved in pathogenesis of autoimmune diseases such as rheumatoid arthritis, irritable bowel disease, psoriasis, psoriatic arthritis, and spondyloarthridities. The retinoic acid-related orphan receptor C (RORc) plays a major role in the immune response and is recognized as a transcription factor necessary for Th17 cell differentiation. RORc controls gene transcription by binding to DNA as a monomer, which is different from other nuclear receptors that bind as dimers. Studies have shown that selective modulation of RORc may be a viable therapeutic target to develop a treatment of Th17 cell-associated autoimmune diseases.

While there are several known RORc modulators, there is still a need for new compounds such as those described in this patent application that can modulate RORc to inhibit the activity of Th17 cells and can potentially lead to the development of new treatment for autoimmune diseases such as rheumatoid arthritis, irritable bowel disease, psoriasis, psoriatic arthritis, and spondyloarthridities.

Important Compound Classes:

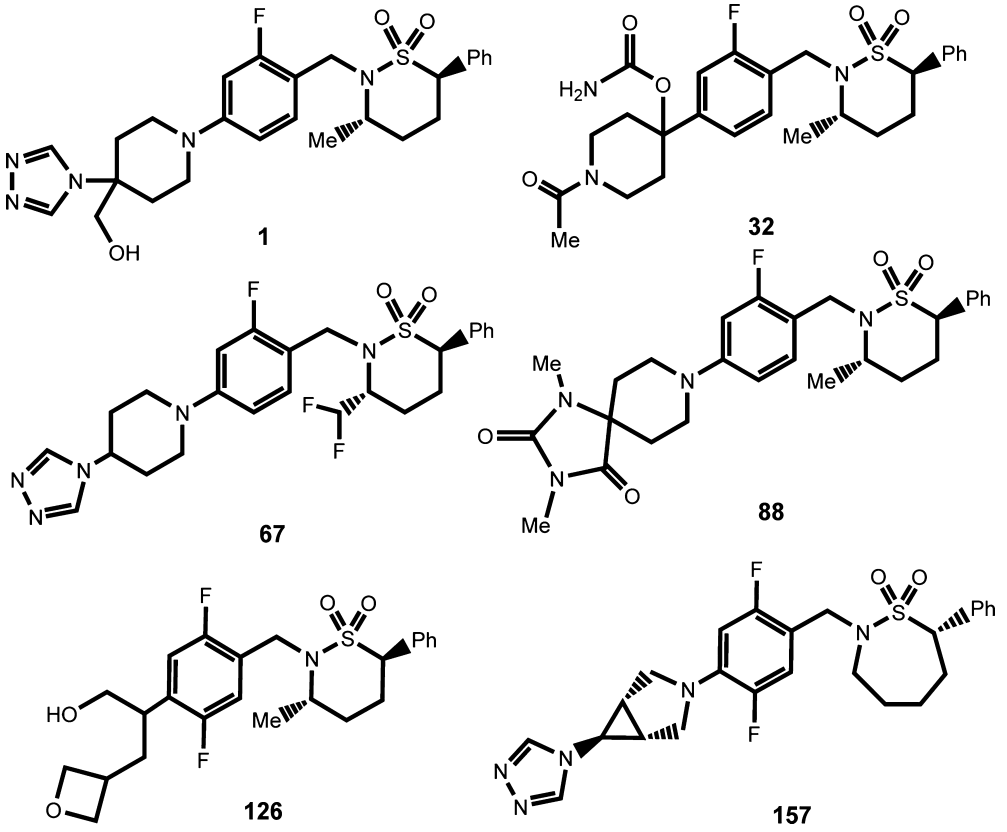


Formula (I)

Received: August 3, 2015
Published: August 14, 2015

Key Structures:

The inventors described the synthesis and structures of 162 compounds as examples of formula (I) including the following representative examples:



Biological Assay:

The following biological tests were described in the patent application to evaluate the activities of the disclosed compounds. No specific data were reported except for the RORc IC_{50} data.

- In Vitro RORc Ligand Binding Assay
- RORc Coactivator Peptide Binding Assay
- Arthritis Mouse Model
- Muscular Sclerosis Mouse Model I
- Muscular Sclerosis Mouse Model II
- Psoriasis Mouse Model I
- Psoriasis Mouse Model II
- Irritable Bowel Disease Mouse Model I
- Chronic Obstructive Pulmonary Disease Mouse Model
- Asthma Mouse Model

Biological Data:

RORc IC_{50} data from the first assay were reported for the compounds of the invention. The following table lists the values obtained from testing the above representative examples:

Compound	IC_{50} (μM)
1	0.100
32	0.410
67	0.026
88	0.0069
126	0.004
157	0.005

Recent Review Articles:

1. Paulissen, S. M. J.; van Hamburg, J. P.; Dankers, W.; Lubberts, E. *Cytokine* **2015**, *74* (1), 43−53.
2. Fauber, B. P.; Magnuson, S. *J. Med. Chem.* **2014**, *57* (14), 5871−5892.
3. Kamenecka, T. M.; Lyda, B.; Chang, M. R.; Griffin, P. R. *Med. Chem. Commun.* **2013**, *4* (5), 764−776.

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Notes

The authors declare no competing financial interest.