RORc Modulators for the Treatment of Autoimmune Diseases

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Patent Application Title: Aryl Sultam Derivatives as RORc Modulators
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Disease Area: Autoimmune diseases such as rheumatoid arthritis, irritable bowel disease, psoriasis, psoriatic arthritis, and spondyloarthritides
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 spondyloarthritides. 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 spondyloarthritides.

Important Compound Classes:

![Formula (I)](image-url)
Key Structures: The inventors described the synthesis and structures of 162 compounds as examples of formula (I) including the following representative examples:

![Structures of representative examples](image)

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 IC₅₀ 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 IC₅₀ 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:

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC₅₀ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.100</td>
</tr>
<tr>
<td>32</td>
<td>0.410</td>
</tr>
<tr>
<td>67</td>
<td>0.026</td>
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<tr>
<td>88</td>
<td>0.0069</td>
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<tr>
<td>126</td>
<td>0.004</td>
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<tr>
<td>157</td>
<td>0.005</td>
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</tbody>
</table>

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Notes
The authors declare no competing financial interest.