ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

pubs.acs.org/acsmedchemlett

RORγt Modulators Are Potentially Useful for the Treatment of the Immune-Mediated Inflammatory Diseases

Ahmed F. Abdel-Magid*

Therachem Research Medilab (India) Pvt. Ltd., Jaipur, India

Title:	Methylene Linked Quinolinyl Modulators of ROR-Gamma-T		
Patent Application Number:	WO 2014/062658 Al	**Publication Date:**	24 April 2014
Priority Application:	US 61/714,419	**Priority Date:**	16 October 2012
	US 61/725,528		13 November 2012
	US 61/782,257		14 March 2013
Inventors:	Leonard, K. A.; Barbay, K.; Edwards, J. P.; Kreutter, K. D.; Kummer, D. A.; Maharoof, U.; Nishimura, R.; Urbanski, M.; Venkatesan, H.; Wang, A.; Wolin, R. L.; Woods, C. R.; Pierce, J.; Goldberg, S.; Fourie, A.; Xue, X.		
Assignee Company:	Janssen Pharmaceutica NV; Turnhoutseweg 30, B-2340 Beerse (BE)		
Disease Area:	Immune-mediated inflammatory diseases	**Biological Target:**	Retinoic acid-related nuclear receptor gamma t (RORγt)

Summary:

The invention in this patent application relates to quinoline derivatives represented generally by formula (I), which are modulators of the nuclear receptor RORγt and may be useful in preventing and/or treatment of immune-mediated inflammatory diseases.

The T helper type 17 cells (Th17) are a subset of CD4+ T cells. They produce the cytokines IL17A, IL17F, IL-21, and IL-22 that stimulate tissue cells to promote recruitment of granulocytes and produce inflammatory chemokines, cytokines, and metalloproteases. Th17 cells have been implicated in the pathogenesis of several autoimmune diseases such as collagen-induced arthritis (CIA) and experimental autoimmune encephalomyelitis (EAE). Elevated levels of IL17, the main cytokine produced by Th17 cells, are expressed in several allergic and autoimmune diseases.

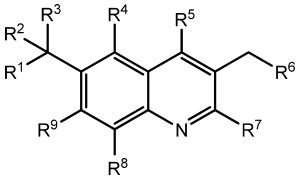
Retinoic acid-related nuclear receptor gamma t (RORγt) is a nuclear receptor that is expressed in the immune system cells and functions as a key transcription factor in Thl7 cells differentiation. Studies have shown that RORγt deficient mice are healthy but display impaired Th17 cell differentiation in vitro, a significantly reduced Th17 cell population in vivo and decreased susceptibility to EAE.

IL-23 is a cytokine that is required for Thl7 cell survival. IL-23 deficient mice do not produce Thl7 cells and are resistant to EAE, CIA, and inflammatory bowel disease (IBD). Genetic studies have revealed a connection between the polymorphisms of the genes for Th17 cell-surface receptors, IL-23R, and CCR6 and susceptibility to IBD, multiple sclerosis (MS), rheumatoid arthritis (RA), and psoriasis.

The anti-p40 monoclonal antibody Ustekinumab (Stelara) that blocks IL-12 and IL-23 has been approved for the treatment of moderate to severe plaque psoriasis in adult patients. Clinical studies on monoclonal antibodies that target IL-23 and inhibit the Th17 subset selectively are currently underway for the treatment of psoriasis. Recent phase II clinical results using both anti-IL-l 7 receptor and anti-IL-17 therapeutic antibodies demonstrated good efficacy in patients with chronic psoriasis, while anti-IL-17 antibodies have produced significantly promising results in early clinical trials in patients with rheumatoid arthritis and uveitis.

The accumulated data point out to the importance of inhibition of the Th17 pathway as a viable clinical target for the treatment of immune-mediated inflammatory diseases. Inhibition of Th17 through the use of compounds with RORγt modulation activities is a promising and potentially beneficial approach that may provide effective treatment for these immune diseases.

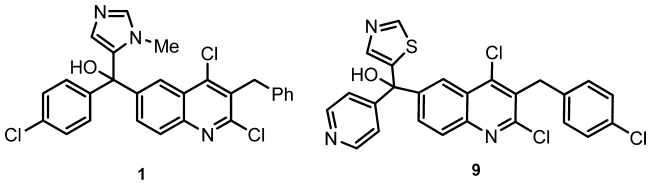
Important Compound Classes:



Formula (I)

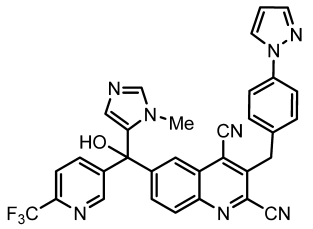
Received: May 26, 2014
Published: June 06, 2014

Key Structures: The inventors reported the structures of 97 compounds of formula (I); several of the compounds were resolved into enantiomers, but the absolute stereochemistry of the enantiomers was not reported. Compounds **1**, **9**, **72B**, and **79C** are representative examples:

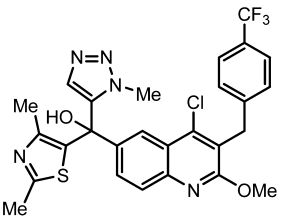


1

9



72B (one enantiomer)



79C (one enantiomer)

Biological Assay: The inventors described the following biological assays to evaluate the compounds of the invention:

In Vitro Biological Data

ThermoFluor Assay

RORγt ThermoFluor Assay Construct

Cell Based Biological Data

RORγt Reporter Assay

Human Th17 Assay

Biological Data: Biological data were reported for all 97 examples of formula (I). Some representative data from the assays are listed for the representative examples in the following table:

Example	ThermoFluor® Assay, Kd μM	RORγt Reporter Assay, IC_{50} μM	RORγt Reporter Assay, % inhibition μM	Human Th17 Assay, IC_{50} μM
1	0.018	0.35	72	0.59
9	0.00083	0.0065	85	0.085
72B	0.00071	0.031	99	0.025
79C	0.000024	0.0025	94	0.0015

Recent Review Articles: Singh, B.; Schwartz, J. A.; Sandrock, C.; Bellemore, S.; Nikoopour, E. *Indian J. Med. Res.* **2013**, *138* (5), 591−594.

Wang, X.; Ma, C.; Wu, J.; Zhu, J. *J. Neurosci. Res.* **2013**, *91* (7), 871−881.

AUTHOR INFORMATION

Corresponding Author

*Address: 1383 Jasper Drive, Ambler, Pennsylvania 19002, United States. Tel: 215-913-7202. E-mail: afmagid@comcast.net.

Notes

The authors declare no competing financial interest.