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PATENT HIGHLIGHT

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Benzoxazine Derivatives As CRAC Modulators

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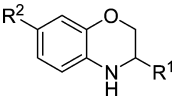
Title:	Benzoxazine Derivatives As CRAC Modulators		
Patent/Patent Application Number:	WO2013/050270A1	**Publication date:**	April 11th, 2013
Priority Application:	US 61/543,436	**Priority date:**	October 5th, 2011
Inventors:	Bhagirath, N.; Brameld, K. A.; Kennedy-Smith, J.		
Assignee Company:	F. Hoffmann-La Roche, AG.		
Disease Area:	Arthritis, respiratory disease	**Biological Target:**	Calcium release-activated calcium channel (CRAC)

Summary: The inflammatory response mediated by interleukin 2 (IL-2) has been linked to a number of important disease states such as rheumatoid arthritis, allergic reactions, and asthma. On-going efforts to identify viable biological targets capable of modulating IL-2 production have included an examination of the calcium channels that regulate calcium influx into T-cell, specifically the calcium release-activated Ca^{2+} channel (CRAC). This channel is a store-operated Ca^{2+} channel present in T-cells, is actived upon antigen binding, and is the primary route of entry for Ca^{2+}. The in-flux of Ca^{2+} stimulates T-cell proliferation and IL-2 production and leads to increases in other pro-inflammatory cytokines such as IL-1, IL-6, and TNFα. Given its important role in the regulation of T-cell Ca^{2+} concentration, it has been suggested that compounds capable of blocking CRAC activity would be useful anti-inflammatory agents. The present patent application describes a series of benzoxazine derivatives capable of blocking the CRAC channel and their method of use for the treatment of the inflammatory diseases arthritis, chronic obstructive pulmonary disorder, and bronchospasm.

Important Compound Classes:



Definitions:

R^1 is phenyl, unsubsituted or mono- or bisubstituted independently with halogen.

R^2 is phenyl unsubsituted or mono- or bisubstituted independently with lower alkyl, halogen, halo-lower alkyl, alkoxy, unsubstituted five-membered heteroaryl ring, or five-membered heteroaryl ring substituted with lower alkyl;

-pyridine, unsubsituted or mono- or bisubstituted independently with lower alkyl, halogen, halo-lower alkyl, alkoxy, $SO_2CH_2CH_3$, unsubstituted five-membered heteroaryl ring, five-membered heteroaryl ring substituted with lower alkyl, unsubstituted six-membered heteroaryl ring, or six-membered heteroaryl ring substituted with an amino moiety;

or

-a five-membered herteroaryl ring, unsubsituted or mono- or bisubstituted independently with lower alkyl, halogen, halo-lower alkyl, alkoxy, unsubstituted five-membered heteroaryl ring, five-membered heteroaryl ring substituted with lower alkyl, unsubstituted six-membered heteroaryl ring, or six-membered heteroaryl ring substituted with lower alkyl.

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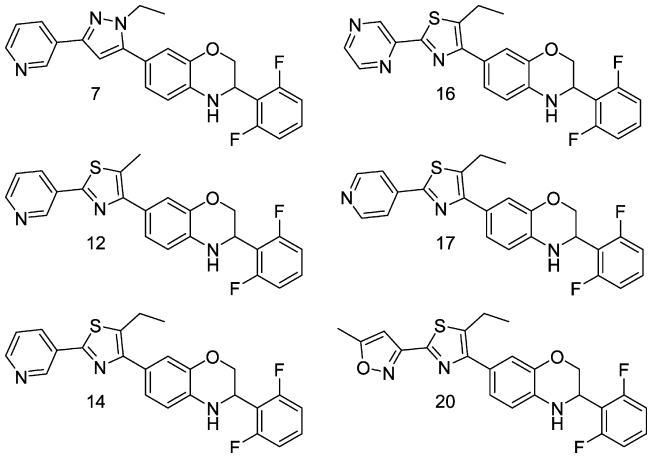
Key Structures:



Recent Review Articles: Derler, I.; Fritsch, R.; Schindl, R.; Romanin, C. CRAC inhibitors: identification and potential. *Expert Opin. Drug Discovery* **2008**, *3* (7), 787−800.

Biological Assay:
Jurkat IL-2 production assay.
Human whole blood (HWB) IL-2 production assay.
^{3}H Thymidine incorporation (MLR) assay.

Biological Data:

Example	Jurkat IL-2 Assay	HWB Assay	MLR Assay
	IC_{50} (μM)		
7	0.07	0.32	0.33
12	0.03	0.43	0.19
14	0.03	0.52	0.1
16	0.02	0.87	0.18
17	0.02	0.32	0.44
20	0.03	0.36	0.43

Claims:
18 Total claims.
11 Composition of matter claims.
7 Method of use claims.

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Notes
The authors declare no competing financial interest.