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Patent Highlight

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Spleen Tyrosine Kinase Inhibitors (SYK) as Potential Treatment for Autoimmune and Inflammatory Disorders

Patent Highlight

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Title:	Thiazolopyrimidine Compounds		
Patent Application Number:	WO 2012/130780 A1	**Publication Date:**	4 October 2012
Priority Application:	PCT/CN2011/072211	**Priority Date:**	28 March 2011
Inventors:	Hermann, J. C.; Lowrie, L. E., Jr.; Lucas, M. C.; Luk, K.-C. T.; Padilla, F.; Wanner, J.; Xie, W.; Zhang, X.		
Assignee Company:	F. Hoffmann-La Roche AG; Grenzacherstrasse 124, CH-4070 Basel (CH)		
Disease Area:	autoimmune and inflammatory diseases	**Biological Target:**	SYK (spleen tyrosine kinase)

Summary:

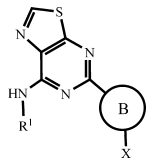
The invention in this patent application relates to the use of novel thiazolopyrimidine derivatives represented by formula **I** that act as spleen tyrosine kinase (SYK) inhibitors. Such inhibitors may potentially be useful for the treatment of autoimmune and inflammatory diseases.

Spleen tyrosine kinase (SYK) is a nonreceptor tyrosine kinase that is essential in the transmission of activating signals from the B-cell receptor (BCR). Abnormal SYK activity has been implicated in the development of several cancer, autoimmune, and inflammatory diseases. Therefore, inhibition of this tyrosine kinase might provide a treatment for patients with these diseases.

SYK is also important in mediating FcεRI mast cell degranulation and eosinophil activation. Mast cells and eosinophils play a key role in controlling several mechanisms associated with allergy and asthma. SYK-deficient mast cells demonstrate defective degranulation, arachidonic acid, and cytokine secretion while SYK-deficient eosinophils show impaired activation in response to FcεR stimulation. SYK has also been implicated in allergic disorders, and its inhibition may provide a useful treatment for asthma and other allergy-induced inflammatory diseases.

Molecules, such as those described in this patent application, that can inhibit or modulate SYK activity may potentially provide a significant therapy for treatment of autoimmune and inflammatory diseases. The patent application describes (and claims) a list of possible immune disorders that may potentially be treated, including "lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes, complications from organ transplants, xeno transplantation, diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, and Leukemia."

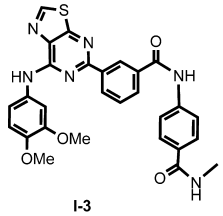
Important Compound Classes:



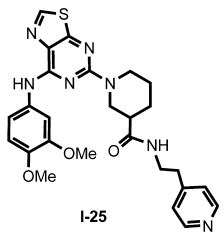
Formula (I)

Definitions B = phenyl, pyridinyl, pyrrolidinyl, or piperidinyl

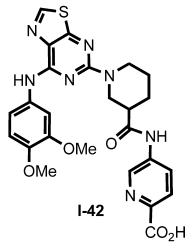
Key Structures: The patent application describes a list of 68 specific examples of formula **I**; the following are six of these compounds:



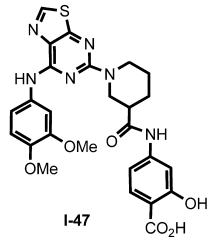
I-3



I-25



I-42



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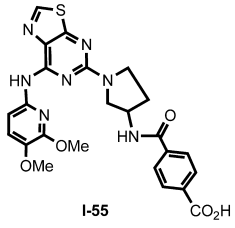
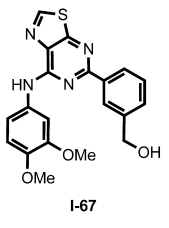


I-55



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Biological Assay: IC_{50} of spleen tyrosine kinase (SYK) inhibition

Biological Data: The IC_{50} values were reported for 68 compounds; the following table contains the data for the above representative examples:

Compound	**IC_{50} h-syk-gst-sf9-c (inactive-dephosphorylated)/μM**
I-3	0.071
I-25	19.90
I-42	0.065
I-47	0.071
I-55	6.152
I-67	0.079

Recent Review Articles:

1. Robak, T.; Robak, E. *Expert Opin. Invest. Drugs* **2012**, *21* (7), 921−947
2. Ratcliffe, A. J. *RSC Drug Discovery Ser.* **2012**, *19* (Kinase Drug Discovery), 218−243.
3. Moretto, A. F.; Dehnhardt, C.; Kaila, N.; Papaioannou, N.; Thorarensen, A. *Recent Pat. Inflammation Allergy Drug Discovery* **2012**, *6* (2), 97−120.

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Notes

The authors declare no competing financial interest.