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PATENT HIGHLIGHT

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Treatment of Immunological or Inflammatory Disorders with ITK Kinase Inhibitors

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Title:	Pyrazole Carboxamide Compounds, Compositions and Methods of Use		
Patent Application Number:	WO 2014/023258 Al	**Publication date:**	13 February 2014
Priority Application:	US 61/682,063	**Priority date:**	10 August 2012
	US 61/764,434		13 February 2013
	US 61/764,930		14 February 2013
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Disease Area:	Asthma and immunological or inflammatory disorders mediated by ITK kinase	**Biological Target:**	Inhibition of ITK kinase

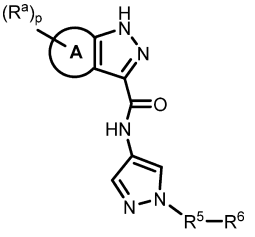
Summary:

The invention in this patent application relates to pyrazole carboxamide derivatives represented generally by formula (I) which are inhibitors of ITK kinase. The compounds may potentially treat immunological or inflammatory disorders and other diseases responsive to the inhibition of ITK kinase.

Interleukin-2-inducible T-cell kinase (ITK) belongs to the Tec family kinases, and it is expressed in T cells, NKT cells, NK cells, and mast cells. Activated ITK kinase mediates T cell receptor (TCR) signals through the phosphorylation and activation of phospholipase C-g (PLCg). Studies show that ITK knockout mice exhibit reduced lung inflammation, mucus production, and airway hyperreactivity in allergic asthma models. The studies also indicated that the kinase activity of ITK is necessary for asthma pathology. Additionally, ITK is found to be expressed at high levels in peripheral blood T cells of human patients with immunological and inflammatory disorders such as atopic dermatitis.

Thus, inhibition of ITK kinase presents a viable therapeutic target to potentially treat the immunological or inflammatory disorders mediated by the activity of this kinase.

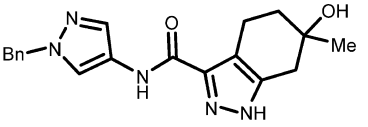
Important Compound Classes:



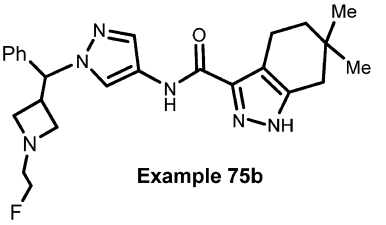
Formula (I)

Received: February 24, 2014
Published: March 06, 2014

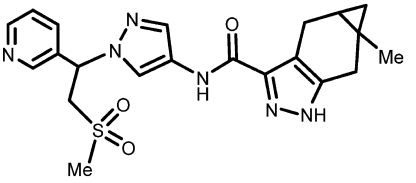
Key Structures: The inventors reported the structures of 154 examples of formula (I) in addition to many of their stereoisomers and structural isomers, including the following four representative compounds. The following compounds represent single enantiomers; however, the absolute stereochemistry was not specified:



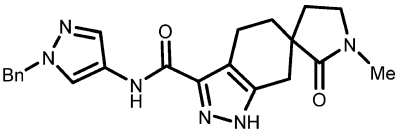
Example 51b



Example 75b



Example 93a



Example 123b

Biological Data: The inventors reported the equilibrium dissociation constant (K_i) values for ITK inhibition by all described examples of formula (I). The K_i values ranged from <0.1 to 4000 nM, as illustrated by the selected examples **51b**, **75b**, **93a**, and **123b** (structures above) listed in the following table:

Compound	ITK Enzyme Ki (nM)
Example 51b	860
Example 75b	0.3
Example 93a	<0.1
Example 123b	4000

Recent Review Articles:

(1.) Ghose, R. *J. Mol. Biol.* **2013**, *425* (4), 679−682.
(2.) Boucheron, N.; Ellmeier, W. *Int. Rev. Immunol.* **2012**, *31* (2), 133−154.
(3.) Lo, H. Y. *Expert Opin. Ther. Pat.* **2010**, *20* (4), 459−469.

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Notes

The authors declare no competing financial interest.