

Treatment of Immunological or Inflammatory Disorders with ITK Kinase Inhibitors

Ahmed F. Abdel-Magid*

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

Title: Pyrazole Carboxamide Compounds, Compositions and Methods of Use

Patent Application Number: WO 2014/023258 A1

Priority Application: US 61/682,063
US 61/764,434
US 61/764,930

Inventors: Brookfield, F.; Burch, J.; Goldsmith, R. A.; Hu, B.; Lau, K. H. L.; Mackinnon, C. H.; Ortwine, D. F.; Pei, Z.; Wu, G.; Yuen, P.-W.; Zhang, Y.

Assignee Company: F. Hoffmann-La Roche AG, Grenzacherstrasse, 124, CH-4070 Basel (CH) (for all designated States except US)
Genentech, Inc., 1 DNA Way, South San Francisco, California 94080, USA (for US only)

Disease Area: Asthma and immunological or inflammatory disorders mediated by ITK kinase

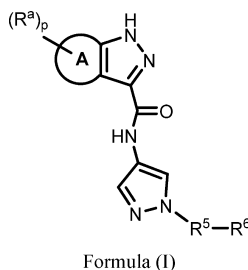
Biological Target: Inhibition of ITK kinase

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:

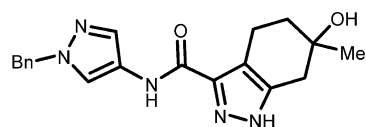
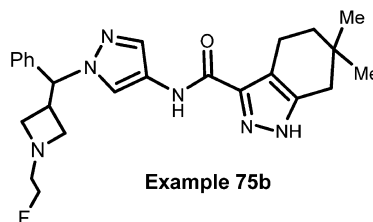
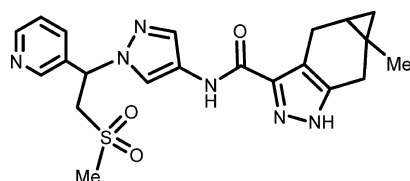
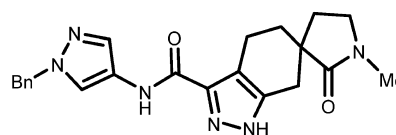


Received: February 24, 2014

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 K_i (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.

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.