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PATENT HIGHLIGHT

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Inhibitors of Bruton's Tyrosine Kinase (Btk) May Treat Inflammation, Immunological Disorders, and Cancer

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Title:	8-Fluorophthalazin-1(2*H*)-one Compounds as Inhibitors of Btk Activity		
Patent Application Number:	WO 2013/067264 Al	**Publication date:**	10 May 2013
Priority Application:	US 61/555,398	**Priority date:**	3 November 2011
Inventors:	Crawford, J. J.; Ortwine, D. F.; Wei, B.; Young, W. B.;		
Assignee Company:	Genentech, Inc.; 1 DNA Way, South San Francisco, California 94080, United States		
Disease Area:	Disorders mediated by Btk such as inflammation, immunological disorders, and cancer	**Biological Target:**	Bruton's Tyrosine Kinase (Btk)

Summary:

The invention in this application introduces 8-fluorophthalazin-1(2*H*)-one derivatives represented generally by Formulas (I) and (II). These derivatives are inhibitors of the Bruton's tyrosine kinase (Btk) and may potentially treat disorders mediated by Btk including inflammation, immunological disorders, and cancer.

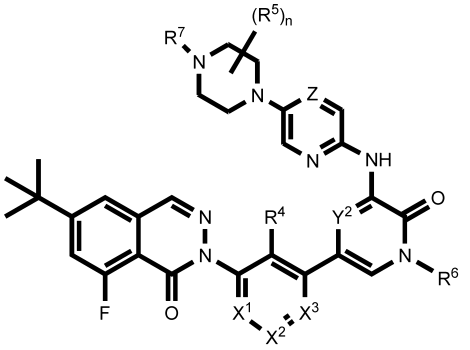
Btk plays an essential role in the maturation of the B-cells; it regulates early B-cell development as well as mature B-cell activation, signaling, and survival. B-cell signaling through the B-cell receptor (BCR) can lead to a wide range of biological outputs, depending on the developmental stage of the B-cell.

Studies on Btk deficiency have provided evidence that implicate Btk in allergic disorders, autoimmune disease, and/or inflammatory disease. In addition, studies have provided strong evidence to support the role of B-cells and the humoral immune system in the pathogenesis of autoimmune and/or inflammatory diseases. Mutation of Btk in humans causes X-linked agammaglobulinaemia (XLA), a rare genetic disorder that is associated with impaired maturation of B-cells and affects the body's ability to fight infection. Btk deficiency in mice improved conditions such as SLE (systemic lupus erythematosus) and arthritis. Thus, inhibition of Btk can be a useful clinical target that leads to inhibition of B-cell mediated pathogenic activities.

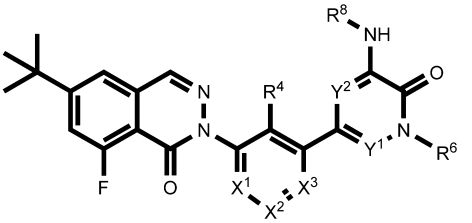
Btk is important for the function of osteoclasts, mast cells, and monocytes. Btk deficiency in humans is associated with reduction in TNF-alpha production by activated monocytes. Thus, inhibition of Btk activity can provide a useful treatment for allergic disorders, autoimmune, and/or inflammatory diseases such as SLE, rheumatoid arthritis, idiopathic thrombocytopenic purpura (ITP), asthma, and other related disorders. Since Btk plays a role in the function of osteoclasts, its inhibition may also be a useful treatment for bone disorders such as osteoporosis.

In addition, Btk plays a role in apoptosis; therefore, its inhibition may potentially provide a treatment for cancer, B-cell lymphoma, leukemia, and other hematological malignancies.

Important Compound Classes:



Formula (**I**)



Formula (**II**)

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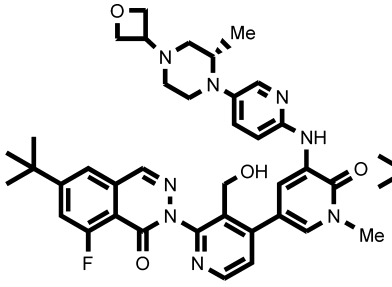
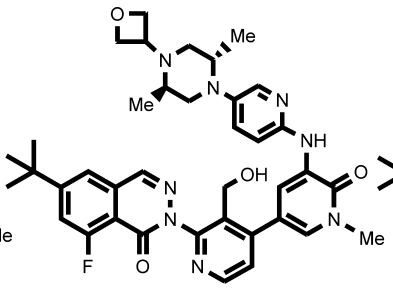
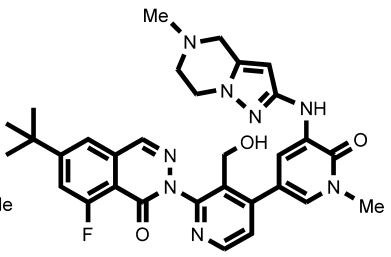
Key Structures: Compounds **105**, **110**, and **128** are examples of the compounds of formula I/II:



Compound **105**



Compound **110**



Compound **128**

Biological Assay: The following assays are described in the application (examples 901−908):

(i) Biochemical Btk Assay (ii) Ramos Cell Btk Assay (iii) B-Cell Proliferation Assay
(iv) T Cell Proliferation Assay (v) CD86 Inhibition Assay (vi) B-ALL Cell Survival Assay
(vii) CD69 Whole Blood Assay (viii) In Vitro Cell Proliferation Assay

Biological Data: The IC_{70} values from CD69 Hu Blood FACS assay are reported for several examples; the values for compounds **105**, **110**, and **128** (above) are representatives (concentration units were not specified):

Compound	CD69 Hu Blood FACS- IC_{70}
105	0.0060
110	0.0059
128	0.0272

Recent Review Articles:

1. Davids, M. S.; Brown, J. R. *Leuk. Lymphoma* **2012**, *53* (12), 2362−2370.
2. Uckun, F. M.; Qazi, S. *Expert Opin. Ther. Patents* **2010**, *20* (11), 1457−1470.
3. Mohamed, A. J.; Yu, L.; Backesjo, C.-M.; Vargas, L.; Faryal, R.; Aints, A.; Christensson, B.; Berglof, A.; Vihinen, M.; Nore, B. F.; et al. *Immunol. Rev.* **2009**, *228* (1), 58−73.

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Notes

The authors declare no competing financial interest.