ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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Pim Kinase Inhibitors for the Treatment of Cancer and Possibly More

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Title:	Cyclic Ether Pyrazol-4-yl-heterocyclyl-carboxamide Compounds and Methods of Use		
Patent/ Patent Application Number:	WO 2014/048939 Al	**Publication date:**	3 April 2014
Priority Application:	US 61/705,791	**Priority date:**	26 September 2012
	US 61/864,882		12 August 2013
Inventors:	Blackaby, W.; Burch, J.; Hodges, A. J.; Sharpe, A.; Sun, M.; Wang, X.		
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, CA 94080, USA (for US only)		
Disease Area:	Cancer and hyperproliferative disorders	**Biological Target:**	Inhibition of the proviral integration site for Moloney murine leukemia virus protein 1 kinase (Pim-1)

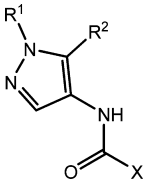
Summary:

The invention in this patent application relates to cyclic ether pyrazol-4-yl-heterocyclyl-carboxamide compounds represented generally by formula (I) with activities as Pim kinase inhibitors. These compounds may potentially be useful as cancer therapeutics to treat various forms of cancer and hyperproliferative disorders.

The proviral integration site for Moloney murine leukemia virus proteins 1, 2, and 3 (Pim-1, Pim-2, and Pim-3) are a family of oncogenic serine/threonine kinases. They are regulated primarily at the transcriptional level and do not require post-translational modification for activity. These kinases play an important role in cell survival and proliferation, and they are overexpressed in several human cancers and inflammatory states. Pim kinases function in a similar manner to the PI3k/Akt/mTOR signaling axis in cellular proliferation and survival pathways; they also phosphorylate several of the same targets including the cell growth and apoptosis regulators Bad (Bcl-2-associated death promoter) and eiF4E-BP1. Phosphorylation of Bad increases Bcl-2 activity and thus promotes cell survival, while phosphorylation of eiF4E-BP1 causes depression of eiF4E, promoting mRNA translation and cellular growth. Overexpression and dysregulation of Pim kinases have been observed frequently in many hematopoietic cancers such as leukemia and lymphoma. Pim-1 has been recognized to promote cell cycle progression through phosphorylation of CDC25A, p21, and Cdc25C; its overexpression has been linked to multiple human cancers, including prostate cancer, acute myeloid leukemia, and other hematopoietic malignancy. Pim-3 has also been implicated in pancreatic cancer and hepatocellular carcinoma.

Thus inhibition of the Pim kinases is a promising clinical target that may provide therapeutic benefit in treatment of different forms of cancer. Furthermore, Pim kinases were found to play an important role in normal immune system function. Thus, in addition to the potential use of Pim inhibitors as oncology therapeutics, their use could potentially be extended to provide therapy for inflammation, autoimmune conditions, allergy, and immune suppression for organ transplantation.

Important Compound Classes:



Formula (I)

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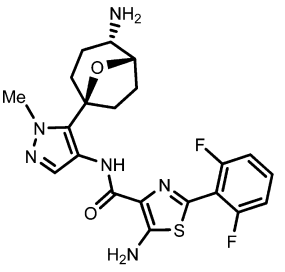
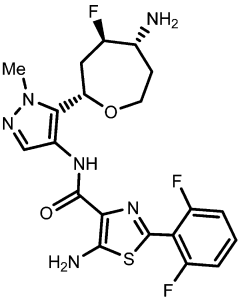
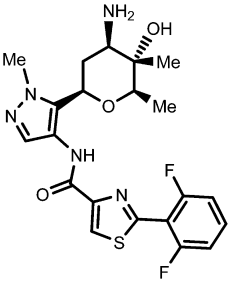
Key Structures: The inventors reported the structures of 310 compounds as examples of formula (I) including the four representative compounds illustrated here:



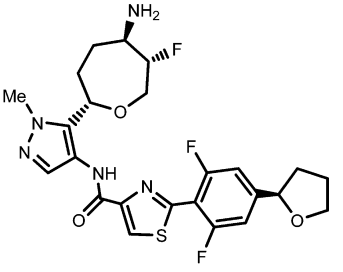
115



135



341



380

Biological Assay:

- Pim kinase binding activity
- In vitro cell proliferation potency assays
- hERG assays

Biological Data: The inventors reported the biological data resulting from the above assays for many of the examples. The data for the representative examples **115**, **135**, **341**, and **380** (structures above) are listed in the following table:

Compound	Prolif BaF3 IL3 (IC_{50}) μM	Prolif BaF3 PIM1 (IC_{50}) μM	Prolif MM1S ATP (EC_{50}) μM	PIM-1 LC3K (K_i) μM
115	3.4	0.0192	0.0718	0.0000060
135	12.7	2.5	4.3	0.0000100
341	>25	0.0968	6.9	0.0000030
380	12.2	0.0372	1.7	0.0000710

Recent Review Articles:

(1) Blanco-Aparicio, C.; Carnero, A. *Biochem. Pharm.* **2013**, *85* (5), 629−643.
(2) Alvarado, Y.; Giles, F. J.; Swords, R. T. *Expert Rev. Hematol.* **2012**, *5* (1), 81−96.
(3) Swords, R.; Kelly, K.; Carew, J.; Nawrocki, S.; Mahalingam, D.; Sarantopoulos, J.; Bearss, D.; Giles, F. *Curr. Drug Targets* **2011**, *12* (14), 2059−2066.

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Notes

The authors declare no competing financial interest.