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PATENT HIGHLIGHT

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Rho Kinase Inhibitors: Potentially Versatile Therapy for the Treatment of Cardiovascular Diseases and More

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Title:	Tricyclic Pyrido-Carboxamide Derivatives as Rock Inhibitors		
Patent Application Number:	WO 2015/002915 A1	**Publication date:**	8 January 2015
Priority Application:	US 61/842,098	**Priority date:**	2 July 2013
Inventors:	Quan, M. L.; Hu, Z.; Wang, C.; Patil, S.		
Assignee Company:	Bristol-Myers Squibb Company; Route 206 and Province Line Road, Princeton, New Jersey 08543, United States		
Disease Area:	Cardiovascular, renal, neurological, and fibrotic diseases as well as cancer, bronchial asthma, erectile dysfunction, and glaucoma	**Biological Target:**	Rho-Kinase (ROCK)

Summary:

The invention in this patent application relates to tricyclic carboxamide derivatives represented generally by formula (I). These compounds are Rho kinase inhibitors and may be useful for the treatment or prophylaxis of disorders associated with aberrant Rho kinase activity such as cardiovascular, renal, neurological, and fibrotic diseases as well as cancer, bronchial asthma, erectile dysfunction, and glaucoma.

Rho kinase (ROCK) is a member of the serine-threonine protein kinase family; it exists in two isoforms, ROCK1 and ROCK2. It is an effector molecule of the small GTP-binding protein RhoA, which plays a key role in multiple cellular signaling pathways. The RhoA/ROCK signaling pathway is involved in several cellular functions such as actin organization, cell adhesion, cell migration, and cytokinesis. It is also involved directly in regulating smooth muscle contraction. Contraction of the smooth muscle in the vasculature increases blood pressure and leads to hypertension. The RhoA/ROCK signaling pathway plays an important role in signal transduction initiated by several vasoactive factors including angiotensin II and platelet-derived growth factor (PDGF), which are implicated in the pathogenesis of cardiovascular diseases.

Recent animal and clinical studies in addition to research on known ROCK inhibitors such as fasudil and Y-27632 have implicated Rho kinase in cardiovascular diseases such as hypertension, atherosclerosis, restenosis, stroke, heart failure, coronary vasospasm, cerebral vasospasm, ischemia/reperfusion injury, pulmonary hypertension, and angina, as well as renal disease and erectile dysfunction. Research has identified ROCK as a promising therapeutic target to design ROCK inhibitors as new treatments of a wide range of diseases and disorders. Thus, ROCK inhibitors may potentially provide useful treatments for the above-mentioned diseases in addition to various others, including airway inflammation and hyper-responsiveness, cancer, and fibrotic diseases, as well as neurological disorders, such as spinal-cord injury, Alzheimer disease, multiple sclerosis, and neuropathic pain. Studies have shown that the ROCK inhibitor fasudil progressively reduced coronary stenosis and promotes a regression of coronary constrictive remodeling in a porcine model of IL-1 beta-induced coronary stenosis. It also reduced both the infarct size and neurologic deficit in a rat stroke model. The ROCK inhibitor Y-27632 improved ventricular hypertrophy, fibrosis, and function in a model of congestive heart failure in Dahl salt-sensitive rats. Because of the demonstrated effects of ROCK on smooth muscle, ROCK inhibitors may also be useful in the treatment of smooth muscle hyper-reactivity diseases such as asthma and glaucoma.

Other studies have demonstrated that inhibition of the RhoA/ROCK signaling pathway allows the formation of multiple competing lamellipodia that disrupt the productive migration of monocytes. ROCK inhibitors may also be beneficial for the treatment of diseases such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease as a consequence of the dependence of immune cell migration upon the RhoA/ROCK signaling pathway.

According to a 2012 report from the American Heart Association, cardiovascular diseases account for 32.8% of all deaths in the US, with coronary heart disease alone accounting for 1 in 6 overall deaths. These alarming statistics point to a shortage in effective treatments for cardiovascular diseases despite the large number of currently available medications. Thus, there remains an unmet medical need for new effective cardiovascular disease treatments.

ROCK inhibitors such as the compounds described in this patent application may potentially provide alternative treatments and satisfy the unmet need for additional therapeutics to treat cardiovascular diseases. They may potentially treat additional diseases such as cancer, neurological diseases, renal diseases, fibrotic diseases, bronchial asthma, erectile dysfunction, and glaucoma.

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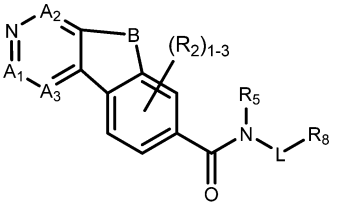
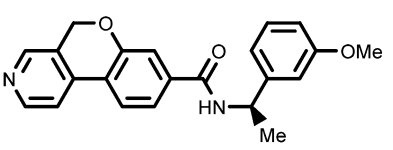
Important Compound Classes:

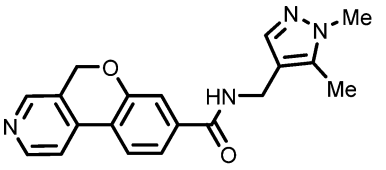


Formula (I)

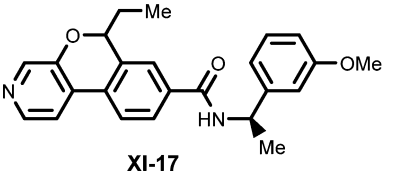
Key Structures: The inventors listed the structures of 420 compounds of formula (I) divided into 16 subgroups (I to XVI). The following four compounds are representative examples:



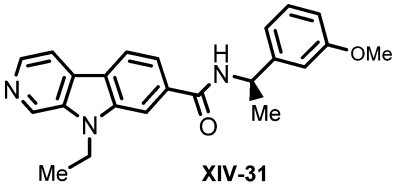
I-1



I-144



XI-17



XIV-31

Biological Assay: *In Vitro* Assays: Determination of the effectiveness of compounds of the invention as ROCK inhibitors

Biological Data: The inventors reported the ROCK inhibitory activities of the compounds of formula (I). IC_{50} values ranging from 0.18 to 9920 nM were reported for the ROCK2 inhibitory activities of the invention compounds including the four representative examples listed in the following table:

Compound	ROCK2 IC_{50} (nM)
I-1	0.51
I-144	9920
XI-17	0.18
XIV-31	1.16

Recent Review Articles:

1. Kolluru, G. K.; Majumder, S.; Chatterjee, S. *Nitric Oxide* **2014**, *43*, 45−54.
2. Feng, Y.; Lo Grasso, P. V. *Expert Opin. Ther. Pat.* **2014**, *24* (3), 295−307.
3. Shi, J.; Wei, L. *J. Cardiovasc. Pharmacol.* **2013**, *62* (4), 341−354.

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Notes

The authors declare no competing financial interest.