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Patent Highlight

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PAK1: A Therapeutic Target for Cancer Treatment

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Title:	Serine/Threonine PAKl Inhibitors		
Patent Application Number:	WO 2013/026914 A1	**Publication date:**	28 February 2013
Priority Application:	US 61/527,453	**Priority date:**	25 August 2011
Inventors:	Aliagasmartin, I.; Crawford, J.; Lee, W.; Mathieu, S.; Rudolph, J.		
Assignee Company:	F. Hoffmann-La Roche AG; Grenzacherstrasse 124, CH-4070 Basel (CH), Switzerland		
Disease Area:	cancer	**Biological Target:**	serine/threonine protein kinase PAK1

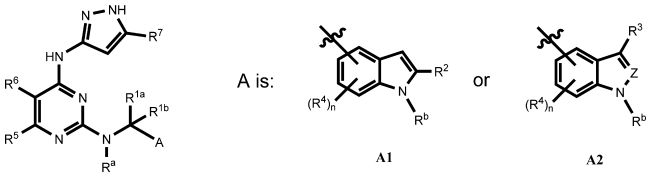
Summary:

The invention in this patent application relates to compounds represented by formula **I** that inhibit serine/threonine protein kinase PAK1 and can potentially be useful in treating hyperproliferative and neoplastic diseases.

Protein kinases catalyze phosphorylation of the hydroxyl groups of specific tyrosine, serine, or threonine residues in proteins. This process can be essential in regulating a wide variety of cell processes, such as metabolism, cell proliferation, cell differentiation, and cell survival. Disorder of any of these cell processes potentially results in diseases such as cancer and diabetes. Protein kinases exist as two main kinds: protein tyrosine kinases (PTKs) and serine-threonine kinases (STKs). Both can be receptor protein kinases or nonreceptor protein kinases. The p21-activated protein kinase (PAK) is a family of nonreceptor serine/threonine protein kinases (STKs) that play important roles in cytoskeletal organization, cellular morphogenesis, cellular processes, and cell survival. There are six members in the PAK family subdivided into two groups: group I (contains PAK 1−3) and group II (contains PAK 4−6). PAKs serve as important mediators of Rac and Cdc42 GTPase function as well as pathways required for Ras-driven tumorigenesis.

The PAK family members are important signaling molecules that frequently overexpressed in many cancerous tissues. Many human malignancies are associated with aberrant levels and overactivities of PAK, in general, and PAK1, in particular. Discovering new compounds that inhibit or modulate the activity and the signal transduction pathways of the overactive and/or overexpressed serine/threonine kinases, particularly PAK1, may be useful in treating hyperproliferative and neoplastic diseases.

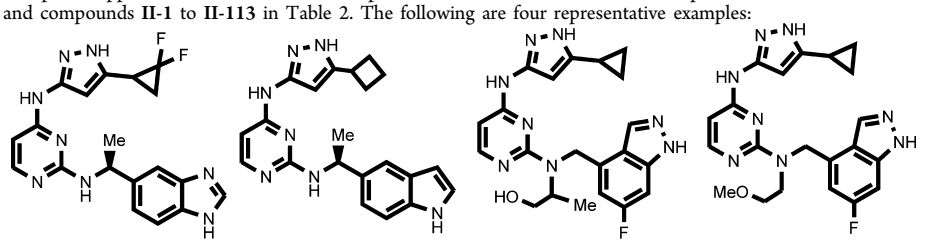
Important Compound Classes:



Formula (I)

Key Structures:

The patent application listed two sets of compounds of formula **I** in two tables. Compounds **I-1** to **I-122** in Table 1 and compounds **II-1** to **II-113** in Table 2. The following are four representative examples:



I-62 **I-114** **II-56** **II-94**

Biological Assay:

GST-PAKl-KD Inhibition Assay

MEK1(S298)2 Phosphorylation Assay

Biological Data:

The biological data are shown for the above four representative examples:

Compound	PAK1 inhibition K_i (μM)	MEKl (S298) phosphorylation IC_{50} (μM)
I-62	0.00513	0.244
I-114	0.00675	0.133
II-56	0.0042	0.0708
II-94	0.0368	0.0641

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Recent Review Articles:

Yi, C.; Maksimoska, J.; Marmorstein, R.; Kissil, J. L. *Biochem. Pharmacol.* 2010, *80* (5), 683−689.

Kichina, J. V.; Goc, A.; Al-Husein, B.; Somanath, P. R.; Kandel, E. S. *Expert Opin. Ther. Targets* 2010, *14* (7), 703−725.

Ong, C. C.; Jubb, A. M.; Zhou, W.; Haverty, P. M.; Harris, A. L.; Belvin, M.; Friedman, L. S.; Koeppen, H.; Hoeflich, K. P. *Oncotarget* 2011, *2* (6), 491−6.

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Notes

The authors declare no competing financial interest.