

P21-Activated Kinase 4 (PAK4) Inhibitors as Potential Cancer Therapy

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Title:	Serine/Threonine Kinase Inhibitors		
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Priority Application:	US 61/813,925	Priority date:	19 April 2013
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Disease Area:	Cancer or hyperproliferative diseases	Biological Target:	Group II p21-activated protein kinases (PAKs): PAK4, PAK5, and PAK6, particularly PAK4

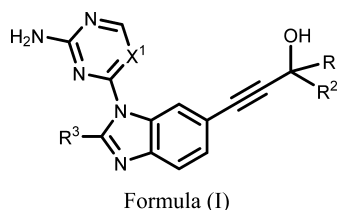
Summary: The invention in this patent application relates to benzo[d]imidazol derivatives represented generally by formula (I), which are selective inhibitors of group II p21-activated protein kinases (PAKs) particularly PAK4. The compounds may be useful for the treatment of hyperproliferative and neoplastic diseases by inhibiting signal transduction pathways, which commonly are overactive or overexpressed in cancerous tissues.

The P21-activated kinases (PAKs) are members of the STE20 family of serine/threonine kinases. They regulate many cellular processes that are commonly perturbed in cancer, including migration, polarization, and proliferation. PAKs are positioned downstream of the RAS family of small GTPases that transduce mitogenic signals from cell surface receptor tyrosine kinases to intracellular serine/threonine kinases. The PAK family contains six members divided into two groups based on sequence and structural similarities. Group I PAKs contains PAK1, PAK2, and PAK3; these members are well characterized and have been studied in greater details. Group II PAKs contains PAK4, PAK5, and PAK6. The function and regulation of the members of this group are considerably less characterized compared to group I members. The two groups share a number of conserved structural characteristics, such as a p21-binding domain, multiple proline-rich regions, and a carboxy-terminal kinase domain. Yet, the kinase domains of the two groups share only about 50% identity suggesting that they may recognize different substrates and control unique cellular processes.

The group II family member PAK4 acts as a key effector of the Rho family GTPases. Studies have shown PAK4 to be overexpressed and/or genetically amplified in lung, colon, prostate, pancreas, and breast cancer cell lines and tumor tissues. It has been implicated in cellular transformation and cell proliferation and survival. Additional studies have indicated that PAK4 is required for efficient migration and/or invasion of prostate, ovarian, pancreatic, and glioma cancer cell lines.

These studies have identified a key role for PAK4 kinase in cancer development, which made its inhibition an attractive therapeutic target for the treatment of cancer. However, the efforts of identifying effective PAK4 inhibitors are not so far successful in producing selective small molecule inhibitors with high potency and selectivity for group II PAKs in general and PAK4 in particular. For example, one of the reported PAK4 inhibitors is the Pfizer's ATP competitive inhibitor PF-3758309. This compound is not selective and shows activity against both groups I and II PAKs. It also inhibits a number of other kinases that were tested in vitro. Therefore, the identification of new selective inhibitors of Group II PAKs is still needed. The inventors present the compounds described in this patent application as selective inhibitors of PAK4 activity to meet this need.

Important Compound Classes:



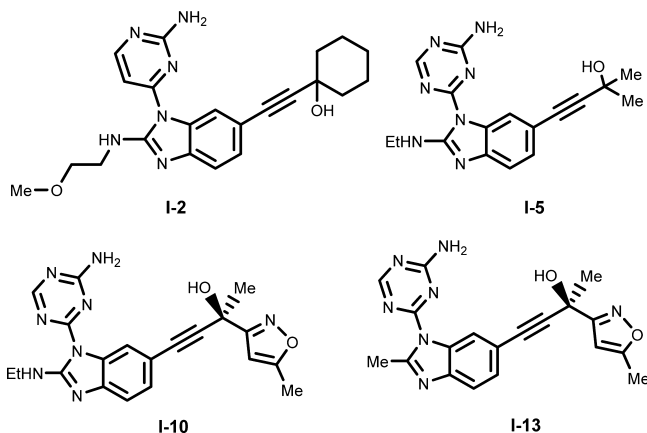
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Key Structures:

The inventors listed the names and/or structures of 23 examples of formula (I) including the following four compounds:



Biological Assay:

1. PAK4-FL (full length) IC₅₀ Caliper Assay Protocol
2. PAK4-KD (kinase domain) IC₅₀ Zylite Assay Protocol
3. PAK1-KD (kinase domain) IC₅₀ Caliper Assay Protocol
4. PAK1-KD (kinase domain) IC₅₀ Zylite Assay Protocol
5. Migration assay
6. Invasion assays
7. Viability assays

Biological Data:

Data from assays 2 and 4 (above) are listed in the table for the representative compounds to show the selective inhibition of PAK4.

Compound	PAK4-KD (kinase domain) IC ₅₀ Zylite Assay Protocol IC ₅₀ (μM)	PAK1-KD (kinase domain) IC ₅₀ Zylite assay Protocol IC ₅₀ (μM)
I-2	0.00477	2
I-5	0.0655	9.6
I-10	0.0053	>4.5
I-13	0.0355	>4.5

Recent Review Articles:

- Radu, M.; Semenova, G.; Kosoff, R.; Chernoff, J. *Nat. Rev. Cancer* **2014**, *14* (1), 13–25.
 King, H.; Nicholas, N. S.; Wells, C. M. *Int. Rev. Cell Mol. Biol.* **2014**, *309*, 347–38.
 Crawford, J. J.; Hoeflich, K. P.; Rudolph, J. *Expert Opin. Ther. Pat.* **2012**, *22* (3), 293–310.

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Notes

The authors declare no competing financial interest.