ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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Inhibitors of PI3Kβ as Potential Treatment for Cancer

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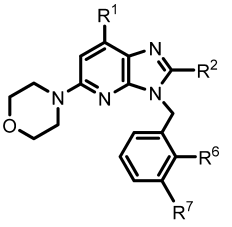
Patent Application Title:	Imidazopyridine Derivatives as PI3 Kinase Inhibitors		
Patent Application Number:	WO 2013/095761 A1	**Publication date:**	27 June 2013
Priority Application:	US 61/577,912	**Priority date:**	20 December 2011
Inventors:	Rivero, R. A.; Tedesco, R.		
Assignee Company:	Glaxosmithkline LLC, One Franklin Plaza, 200 North 16th Street, Philadelphia, Pennsylvania 19102, United States		
Disease Area:	Cancer and other diseases related to PTEN loss	**Biological Target:**	Phosphoinositide 3-kinase (PI3K)

Summary: The invention in this patent application relates to imidizopyridine derivatives represented generally by formula (I) that inhibit the PI3 kinases, particularly PI3Kβ, and may potentially be used in treatment of cancer and other diseases.

The phosphoinositide 3-kinase (PI3K) family consists of 15 proteins that have distinct substrate specificities and modes of regulation. There are a number of different classes of PI3Ks. Class 1 PI3Ks have a catalytic subunit known as p110 with four types (isoforms): p110α, p110β, p110γ, and p110δ.

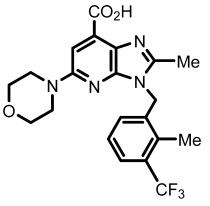
The PI3K signaling pathway is activated in many human cancers, and its importance in carcinogenesis is well established. A study has confirmed a link between PI3K pathway and cancer. In addition, overexpression studies have implicated PI3Kβ isoform to be necessary for transformations induced by the loss or inactivation of the PTEN both in vitro and in vivo. PTEN is a tumor suppressor gene identified to be frequently mutated or deleted in various human cancers. Besides carcinogenesis, PTEN deficiency and the corresponding PI3K-Akt gene overexpression may be related to other disorders such as fibrogenesis, arthritis, nephropahty, and liver cirrhosis. These findings indicate that inhibition of PI3K p110β is a promising target for treatment of cancer and other diseases related to PTEN loss or deficiency.

Important Compound Classes:

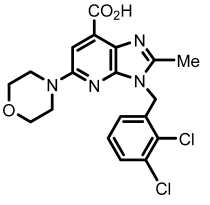


Formula (I)

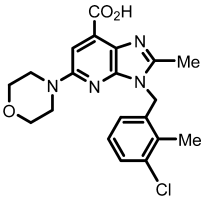
Key Structures: The inventors described the synthesis of 8 examples of the compounds of formula (I) including the following three compounds:



Example **3**



Example **4**



Example **5**

Biological Assay:

- HTRF in Vitro Profiling Assays for PI3K Inhibition
- Cellular Assays: inhibition of phosphorylation of AKT in PTEN deficient tumor cell line MDA-MB-468
- Cellular Assays: cell growth inhibition in PTEN-deficient cell line MDA-MB-468

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Biological Data: The biological data from the above assays are listed in the table for the three representative examples shown above:

Compound	PI3K b pIC_{50}	IC_{50} pAKT (nM) MDA-MB-468	Prolif EC_{50} (nM) MDA-MB-468
Example 3	8.3	435.86	41
Example 4	8.3	41.4	152.8
Example 5	8.8	15.88	18.1

Claims: Claims 1−3: composition of matter, variations of formula (I)

Claim 4: 8 specific compounds of formula (I) listed by chemical names

Claims 5−8: methods of treatments of diseases with detailed lists of possible diseases

Claims 9−11: use of compounds as medicaments with detailed lists of possible diseases

Recent Review Articles:

1. Kurtz, J.-E.; Ray-Coquard, I. *Anticancer Res.* **2012**, *32* (7), 2463−2470.

2. Shepherd, P. R.; Denny, W. A. *Cancer Discovery* **2012**, *2* (5), 393−394.

3. Shuttleworth, S. J.; Silva, F. A.; Cecil, A. R. L.; Tomassi, C. D.; Hill, T. J.; Raynaud, F. I.; Clarke, P. A.; Workman, P. *Curr. Med. Chem.* **2011**, *18* (18), 2686−2714.

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Notes

The authors declare no competing financial interest.