ACS Medicinal Chemistry Letters

Patent Highlight

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Combination Therapy: JAK PI3K/mTOR. A Novel Approach for Cancer Treatment

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Title:	JAK PI3K/mTOR Combination Therapy		
Patent Application Number:	WO 2013/023119 A1	**Publication Date:**	14 February 2013
Priority Application:	US 61/522,001	**Priority Date:**	10 August 2011
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Disease Area:	Myeloproliferative neoplasms (MPNs) and solid tumors	**Biological Target:**	JAK kinase and PI3K/mTOR

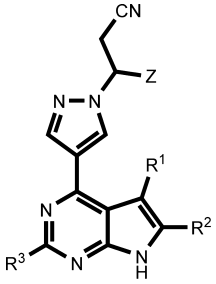
Summary:

The invention in this patent application describes a combination therapy comprising JAK inhibitors represented by formula (I) and dual PI3K/mTOR inhibitor represented by formula II. The combination therapy can potentially treat some forms of cancer such as myeloproliferative neoplasms (MPNs) and solid tumors [myeloproliferative neoplasms (MPNs) are conditions that cause blood cells, platelets, white blood cells, and red blood cells to grow abnormally in the bone marrow].

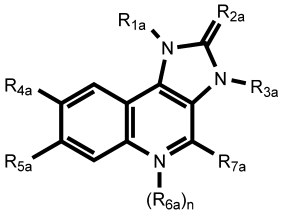
Separately, each one of these has been targeted for treatment of cancer. Janus-associated kinase (JAK) inhibitors are potential candidates for treatment of myeloproliferative disorders and cancer. Mammalian target of rapamycin (mTOR) inhibitors shrink tumors by inhibiting the effect of mTOR, which is a downstream mediator of the PI3K/Akt pathway.

The patent application states that administering the combination of a JAK kinase inhibitor (e.g., a compound of formula I) and a dual PI3K/mTOR inhibitor (e.g., a compound of formula II) surprisingly delivers synergistic effects in treatment of several forms of cancer, such as MPNs and solid tumors. The use of this combination therapy via the coadministration of the two types of agents is a novel approach that can benefit cancer patients who do not respond to or are resistant to currently available therapies. Additionally, this new therapeutic strategy could be useful in optimizing the efficacy to allow the use of lower doses of each drug, hence reducing the side effects of currently available cancer therapies.

Important Compound Classes:



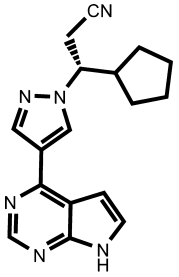
(I)



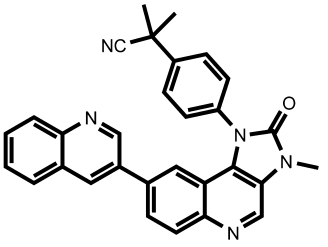
(II)

Key Structures:

The two compounds **B** and **A** were named specifically and claimed as compounds of formula **I** and formula **II**, respectively. The two compounds were used separately or in combination for biological testing as dual P13K/mTOR inhibitor (compound **A**) and JAK inhibitor (compound **B**) (note: compound **B** structure was generated from the chemical name).



Compound B
JAK inhibitor



Compound A
dual PI3K/mTOR inhibitor

Biological Data:

The in vitro data indicated that the combination of PI3K/mTOR inhibitors with JAK1/2 inhibitors produced synergism. Thus, concurrent targeting of PI3K/mTOR and JAK/STAT pathway might represent a new therapeutic strategy to optimize efficacy and reduce toxicity in patients with MPN.

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In vivo data: a SCID BaF3 JAK2^{V617F}-luciferase mouse model was used to determine the effects of drugs targeting PI3K/Akt/mTOR pathway alone and in combination with JAK2 inhibitor. The following table shows some data for the mean life span treatment groups using compounds **A** and **B** shown above:

Treatment	Mean Lifespan (Days)	Lifespan Increase (%) vs Vehicle
Vehicle	16	--
60 mpk Compound **B**	19	19%
45 mpk Compound **A**	24	42%
60 mpk Compound **B** plus 45 mpk Compound **A**	29.5	54%

Recent Review Articles:

Karlsson, A.; Garcia-Echeverria, C. *RSC Drug Discovery Ser.* **2012**, *21* (Designing Multi-Target Drugs), 206−220.
Emerling, B. M.; Akcakanat, A. *Cancer Res.* **2011**, *71* (24), 7351−7359.

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Notes

The authors declare no competing financial interest.