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Patent Highlight

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Inhibition of mTOR Kinase and Cancer Treatment

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Title:	Fused Tricyclic Compounds as mTOR Inhibitors		
Patent Application Number:	WO 2013/016164 A1	**Publication date:**	31 January 2013
Priority Application:	US 61/511,607	**Priority date:**	26 July 2011
Inventors:	Meng, Z.; Patel, M. F.; Siddiqui, M. A.; Reddy, P. A. P.; Nan, Y.		
Assignee Company:	Merck Sharp & Dohme Corp.; 126 East Lincoln Ave., Rahway, New Jersey 07065-0907, United States		
Disease Area:	Cancer	**Biological Target:**	Mammalian target of rapamycin (mTOR) kinase

Summary:

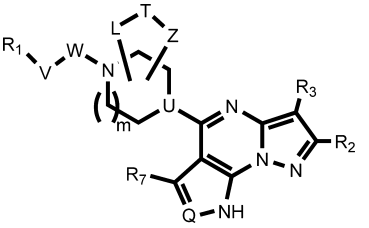
The invention in this patent application relates to pyrazolopyrrolopyrimidine and dipyrazolopyrimidine derivatives represented collectively by formula I. These compounds act as inhibitors of mTOR kinase and may potentially be used in the treatment of cancer and other disorders where mTOR is deregulated.

The mammalian target of rapamycin (mTOR) kinase (a.k.a. FRAP, RAFT, RAPT, or SEP) is a serine/threonine protein kinase that regulates cell growth and cell proliferation, and it plays a gatekeeper role in the control of cell cycle progression. mTor exists in the following two complex forms:

- The mTOR complex 1 (mTORC1) or Raptor-mTOR: partially inhibited by rapamycin, involved in phosphorylation of downstream targets, including eukaryotic translation initiation factor 4E binding protein-1 (4E-BP1) and ribosomal S6 kinase 1 (S6 K1).
- The mTOR complex 2 (mTORC2) or Rictor-mTOR: rapamycin-independent; promotes cellular survival by phosphorylation of AKT. Also involved in metabolism, proliferation, and cytoskeletal organization.

Abnormal mTOR signaling pathway is implicated in many diseases, including cancer and type-2 diabetes. Thus, inhibition of this kinase may potentially lead to a method of cancer treatment. However, to achieve a broad spectrum in antitumor activity and better efficacy in cancer treatment, it is desirable to design mTOR inhibitors that target both complex forms of mTOR kinase, mTORC1 and mTORC2. Small molecule mTOR inhibitors such as the ones presented in this patent application may potentially provide treatment for cancer and other diseases.

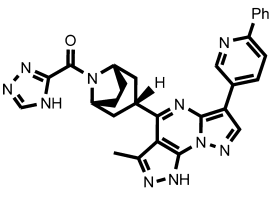
Important Compound Classes:



Formula (I)

Key Structures:

The patent application describes the synthesis details of six examples of formula I, examples 1−6. Three of these examples are represented here:



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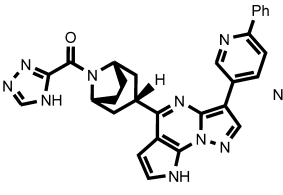

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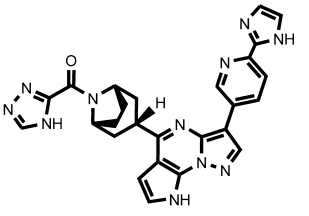

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Biological Assay:

- mTOR kinase assay
- mTOR target engagement assay

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Biological Data: The IC_{50} values from the mTOR target engagement assay are highlighted for compounds 1, 2, and 6 in the table; IC_{50} values are reported in ranges:

Compound	pAKT S473 IC_{50} (nM)	p4E-BP1Thr37/46 IC_{50} (nM)
1	1-100	100-1000
2	1-100	1-100
6	1-100	1-100

Claims: Claims 1−11: Composition of matter, variations of formula (I)

Claim 12: Composition of matter, a list of six compounds by chemical name

Claim 12: Pharmaceutical composition

Claim 14: Compound according to the claims for treatment of cancer

Recent Review Articles:

1. Buitrago-Molina, L. E.; Vogel, A. *Curr. Cancer Drug Targets* 2012, *12* (9), 1045−1061.

2. Riaz, H.; Riaz, T.; Hussain, S. A. *Infectious Agents Cancer* 2012, *7*, 1.

3. Dowling, R. J.; Topisirovic, I.; Fonseca, B. D.; Sonenberg, N. *Biochim. Biophys. Acta (Proteins and Proteomics)* 2010, *1804* (3), 433−439.

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Notes

The authors declare no competing financial interest.