

Imidazopyrazine Derivatives As Inhibitors of mTOR

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Title: Imidazopyrazine Derivatives As Inhibitors of mTOR

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Inventors: Meng, Z.; Siddiqui, M. A.; Reddy, P. A. P.
Assignee Company: Merck Sharp & Dohme Corp., USA

Disease Area: Cancer Biological Target: Mammalian Target of Rapamycin

(mTOR) Kinase

Summary: This application claims a series of imidazopyrazine analogues that may provide a treatment for cancer.

Important Compound Classes:

Definitions: U is N or CH

Key Structures:

Recent Review Articles:

Malaguti, P.; Vari, S.; Cognetti, F.; Fabi, A. The mammalian target of rapamycin inhibitors in breast cancer: current evidence and future directions. *Anticancer Res.* 2013, 33 (1), 21–28.

Johnson, S. C.; Rabinovitch, P. S.; Kaeberlein, M. mTOR is a key modulator of aging and age-related disease. *Nature* **2013**, 493 (7432), 338–345.

Received: April 11, 2013 Published: April 18, 2013 Biological Assay:

Compound inhibitory activity was evaluated using an HTRF mTOR enzyme assay. Inhibition of mTORC1 and mTORC2 was measured using an immunofluorescent cell-based assay. Inhibition of mTORC1 activity was measured by the reduction of the level of phosphorylated 4E-BP1Thr37/46 (p4E-BP1Thr37/46). Inhibition of mTORC2 activity was measured by the reduction of the level of phosphorylated AKTSer473 (pAKTSer473).

Pharmacological Data:

Compound	pAKTSer473	p4E-BP1Thr37/46
	(IC ₅₀ nM)	(IC ₅₀ nM)
1	1-100	100-1000
2	-	-
3	100-1000	100-1000
4	1000-10000	1000-10000
5	1135	1863
6	1000-10000	>10000
7	>10000	>10000

Synthesis:

Preparation of 7 compounds.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.