ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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Inhibitors of ATR Kinase for Treatment of Cancer

Ahmed F. Abdel-Magid*

Therachem Research Medilab (India) Pvt. Ltd., Jaipur, India

Title:	Pyrazine Compounds Useful as Inhibitors of ATR Kinase		
Patent/Patent Application Number:	WO 2013/071093 A1	**Publication date:**	16 May 2013
Priority Application:	US 61/557,801	**Priority date:**	9 November 2011
	US 61/620,714		5 April 2012
Inventors:	Charrier, J.-D.; O'Donnell, M.; Everitt, S. R.		
Assignee Company:	Vertex Pharmaceuticals Inc.; 130 Waverly Street, Cambridge, MA 02139, USA		
Disease Area:	Cancer	**Biological Target:**	Ataxia Telangiectasia and Rad3-Related Protein (ATR)

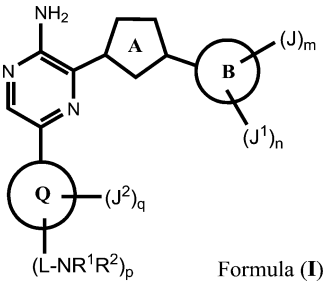
Summary:

The invention in this patent application describes pyrazine derivatives represented generally by Formula (I) that act as inhibitors of ATR protein kinase and may potentially be used for treatment of cancer.

ATR (ataxia telangiectasia and Rad3-related protein) is a serine/threonine protein kinase that is involved in cellular responses to DNA damage. In healthy cells, ATR acts with ataxia telangiectasia mutated (ATM) kinase and other proteins to regulate cells' DNA damage response (DDR), which activates cell cycle checkpoints to stimulate DNA repair and promote cell survival. ATR, ATM, and the other proteins are capable of activating functionally redundant DNA repair processes to compensate for one another; thus, the cells do not rely mostly on one of the proteins for the DNA damage repair.

In contrast, many cancerous cells harbor some defective DNA repair processes such as ATM signaling, which increase their dependence on other DNA repair proteins including ATR. As a result, cancerous cells are more dependent on ATR activity for survival than healthy cells. One important finding is that disruption of ATR activity promotes the death of cancer cell both in the presence and in the absence of DNA damaging agents. Thus, the use of potent and selective ATR inhibitors may provide a promising therapy for treatment of cancer either as single agents or in combination therapies with radiotherapy or chemotherapy.

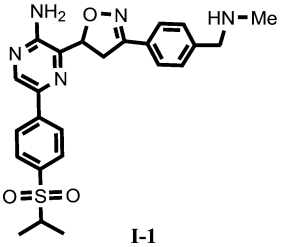
Important Compound Classes:



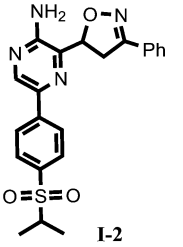
Formula (**I**)

Key Structures:

Detailed synthesis was described for two examples (I-1 and I-2):



I-1



I-2

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Biological Assay: The following assays were described:

- Cellular ATR Inhibition Assay
- ATR Inhibition Assay
- Cisplatin Sensitization Assay
- Single Agent HCT116 Activity

Biological Data: The data for ATR inhibition was given as inhibition constant (K_i) for compounds I-1 and I-2:

Compound	ATR Inhibition Ki (nM)
I-1	16
I-2	90

Recent Review Articles:

1. Toledo, L. I.; Murga, M.; Fernandez-Capetillo, O. *Mol. Oncol.* **2011**, *5* (4), 368−373.
2. Nam, E. A.; Cortez, D. *Biochem. J.* **2011**, *436* (3), 527−536.
3. Smits, V. A. J.; Warmerdam, D. O.; Martin, Y.; Freire, R. *Front. Biosci., Landmark Ed.* **2010**, *15* (3), 840−853.

AUTHOR INFORMATION

Corresponding Author

*Address: 1383 Jasper Drive, Ambler, Pennsylvania 19002, United States. Tel: 215-913-7202. E-mail: afmagid@comcast.net.

Notes

The authors declare no competing financial interest.