

Inhibitors of Mitotic Kinesin Eg5 / Kinesin-5

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Introduction

During cell division, the bipolar organization of mitotic spindles is essential for proper segregation of chromosomes. Inhibition of mitotic-spindle formation is an interesting target in cancer chemotherapy. However, so far used anti-mitotic agents target microtubule stability (e.g. tubulin) during cancer treatment (e.g. taxanes) and cause serious side effects, such as neurotoxicity. Furthermore, the development of resistance against these anti-mitotic agents restrict their use.

Kinesins

A new alternative approach to attack mitotic-spindle formation and causing mitotic arrest is to inhibit the mitotic motors, the **kinesins**, that interact with microtubules. These proteins are exclusively involved in the formation and function of the mitotic spindle and are key regulators of mitotic entry, progression and cytokinesis. Their inhibition leads to cell-cycle arrest and apoptosis, without interfering with other microtubule dependent processes. For reviews see [1, 2].

Eg5

The mitotic kinesin **Eg5** (also called kinesin-5 or kinesin spindle protein [KSP]) plays an important role in the early stages of mitosis [3–11]. It mediates centrosome separation and formation of the bipolar mitotic spindle. Inhibition of Eg5 leads to cell cycle arrest during mitosis and cells with monopolar spindle (monoasters). The recent discovery of small molecules that inhibit human Eg5 by binding to its catalytic motor domain leading to mitotic arrest has attracted more interest in Eg5 as a potential anticancer drug target.

Eg5 Inhibitors

Monastrol (Prod. No. ALX-430-094) [12], a small cell permeable molecule, was the first identified Eg5 inhibitor. Selected other inhibitors which have been reported are:

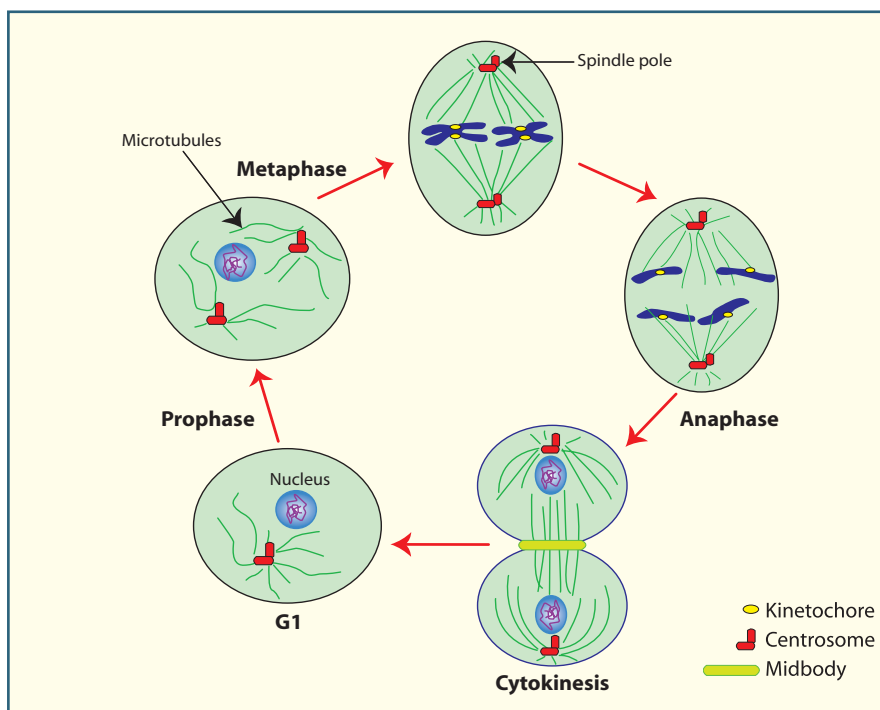


FIGURE 1. Subcellular components involved in the phases of cell division.

Product Highlight

NEW

Dimethylenastron

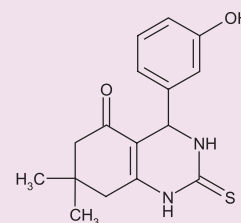
[7,7-Dimethyl-4-(3-hydroxyphenyl)-5-oxo-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-thione]

ALX-270-438-M001

1 mg

Potent, cell permeable non-tubulin-interacting mitosis inhibitor. Blocks mitosis ($IC_{50}=200nM$) by binding to the mitotic kinesin Eg5.

LIT: Development and biological evaluation of potent and specific inhibitors of mitotic Kinesin Eg5: M. Gartner, et al.; *Chembiochem* **6**, 1173 (2005) ■ Synthesis and biological evaluation of new tetrahydro-beta-carbolines as inhibitors of the mitotic kinesin Eg5: N. Sunder-Plassmann, et al.; *Bioorg. Med. Chem.* **13**, 6094 (2005) ■ Inhibitors of kinesin Eg5: antiproliferative activity of monastrol analogues against human glioblastoma cells: C. Muller, et al.; *Cancer Chemother. Pharmacol.*, (2006) (in print)



CONTINUED ON BACKCOVER

Dihydropyrazoles [13], Terpendole E [14], S-Trityl-L-cysteine (Prod. No. ALX-105-011) [15], *trans*-HR22C16 (Prod. No. ALX-270-373) [16], CK0106023 [17], Dimethylenastron (Prod. No. ALX-270-438) [18, 19], *Trans*-24 (Prod. No. ALX-270-439) [19], 4-Phenyl-tetrahydroisoquinolines [20], Phenothiazine and carbazole derivatives [21].

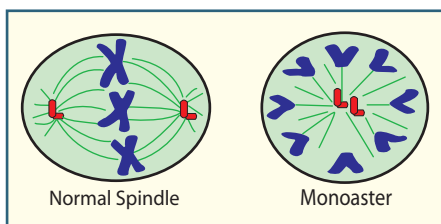


FIGURE 2. Model of a normal bipolar spindle and a monoaster.

LIT: [1] Kinesin superfamily proteins and their various functions and dynamics: N. Hirokawa and R. Takemura; *Exp. Cell Res.* **301**, 50 (2004) • [2] Kinesin: walking, crawling or sliding along?: A. Yildiz & P.R. Selvin; *Trends Cell Biol.* **15**, 112 (2005) • [3] A „slow“ homotetrameric kinesin-related motor protein purified from *Drosophila* embryos: D.G. Cole, et al.; *J. Biol. Chem.* **269**, 22913 (1994) • [4] Phosphorylation by p34cdc2 regulates spindle association of human Eg5, a kinesin-related motor essential for bipolar spindle formation in vivo: A. Blangy, et al.; *Cell* **83**, 1159 (1995) • [5] A bipolar kinesin: A.S. Kashina, et al.; *Nature* **379**, 270 (1996) • [6] Phosphorylation by p34cdc2 protein kinase regulates binding of the kinesin-related motor HsEg5 to the dyactin subunit p150: A. Blangy, et al.; *J. Biol. Chem.* **272**, 19418 (1997) • [7] The bipolar kinesin, KLP61F, cross-links microtubules within inter-polar microtubule bundles of *Drosophila* embryonic mitotic spindles: D.J. Sharp, et al.; *J. Cell Biol.* **144**, 125 (1999) • [8] Microtubule motors in mitosis: D.J. Sharp, et al.; *Nature* **407**, 41 (2000) • [9] The bipolar mitotic kinesin Eg5 moves on both microtubules that it crosslinks: L.C. Kaptein, et al.; *Nature* **435**, 114 (2005) • [10] Mitotic kinesin inhibitors induce mitotic arrest and cell death in Taxol-resistant and -sensitive cancer cells: A.I. Marcus, et al.; *J. Biol. Chem.* **280**, 11569 (2005) • [11] Functional analysis of human microtubule-based motor proteins, the kinesins and dyneins, in mitosis/cytokinesis using RNA interference: C. Zhu, et al.; *Mol. Biol. Cell* **16**, 3187 (2005) • [12] Small molecule inhibitor of mitotic spindle bipolarity identified in a phenotype-based screen: T.U. Mayer, et al.; *Science* **286**, 971 (1999) • [13] Kinesin spindle protein (KSP) inhibitors. Part 1: The discovery of 3,5-diaryl-4,5-dihydropyrazoles as potent and selective inhibitors of the mitotic kinesin KSP: C.D. Cox, et al.; *Bioorg. Med. Chem. Lett.* **15**, 2041 (2005) • [14] A novel action of terpendole E on the motor activity of mitotic Kinesin Eg5: J. Nakazawa, et al.; *Chem. Biol.* **10**, 131 (2003) • [15] In vitro screening for inhibitors of the human mitotic kinesin Eg5 with antimitotic and antitumor activities: S. DeBonis, et al.; *Mol. Cancer Ther.* **3**, 1079 (2004) • [16] HR22C16: a potent small-molecule probe for the dynamics of cell division: S. Hotha, et al.; *Angew. Chem. Int. Ed. Engl.* **42**, 2379 (2003) • [17] Antitumor activity of a kinesin inhibitor: R. Sakowicz, et al.; *Cancer Res.* **64**, 3276 (2004) • [18] Development and biological evaluation of potent and specific inhibitors of mitotic Kinesin Eg5: M. Gartner, et al.; *ChemBiochem* **6**, 1173 (2005) • [19] Synthesis and biological evaluation of new tetrahydro-beta-carbolines as inhibitors of the mitotic kinesin Eg5: N. Sunder-Plassmann, et al.; *Bioorg. Med. Chem.* **13**, 6094 (2005) • [20] Inhibitors of human mitotic kinesin Eg5: Characterization of the 4-phenyl-tetrahydroisoquinoline lead series: C.M. Tarby, et al.; *Bioorg. Med. Chem. Lett.* **16**, 2095 (2006) • [21] Phenothiazine and carbazole-related compounds inhibit mitotic kinesin Eg5 and trigger apoptosis in transformed culture cells: H. Okumura, et al.; *Toxicol. Lett.* **166**, 44 (2006)

FURTHER READING: Allosteric inhibition of kinesin-5 modulates its processive directional motility: B.H. Kwok, et al.; *Nat. Chem. Biol.* **2**, 480 (2006) • A pathway of structural changes produced by monastrol binding to Eg5: Z. Maliga, et al.; *J. Biol. Chem.* **281**, 7977 (2006)

Selected Latest Review Articles

Inhibitors of Mitotic Kinesins: Next-Generation Antimitotics: V. Sarli & A. Gianni; *ChemMedChem* **1**, 293 (2006) • A standardized kinesin nomenclature: C.J. Lawrence, et al.; *J. Cell Biol.* **167**, 19 (2004)

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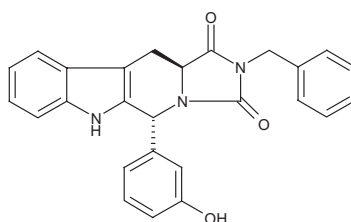
NEW *Trans*-24

[*(5R, 11aS)*]-2-Benzyl-5-(3-hydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione]

ALX-270-439-M001 1 mg

Potent, cell permeable non-tubulin-interacting mitosis inhibitor. Blocks mitosis (IC_{50} =650nM) by binding to the mitotic kinesin Eg5.

LIT: Synthesis and biological evaluation of new tetrahydro-beta-carbolines as inhibitors of the mitotic kinesin Eg5: N. Sunder-Plassmann, et al.; *Bioorg. Med. Chem.* **13**, 6094 (2005)



Monastrol

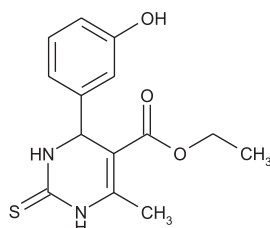
[4-(3-Hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-4*H*-pyrimidin-5-carboxylic acid ethyl ester]

ALX-430-094-M001 1 mg

ALX-430-094-M005 5 mg

Cell permeable non-tubulin-interacting mitosis inhibitor. Blocks mitosis (IC_{50} =14μM) by binding to the mitotic kinesin Eg5.

LIT: Small molecule inhibitor of mitotic spindle bipolarity identified in a phenotype-based screen: T.U. Mayer, et al.; *Science* **286**, 971 (1999) • Monastrol, a selective inhibitor of the mitotic kinesin Eg5, induces a distinctive growth profile of dendrites and axons in primary cortical neuron cultures: S.Y. Yoon, et al.; *Cell Motil. Cytoskeleton* **60**, 181 (2005) • Interaction of the mitotic kinesin Eg5 inhibitor monastrol with P-glycoprotein: T. Peters, et al.; *Naunyn-Schmiedeberg's Arch. Pharmacol.* **372**, 291 (2006)

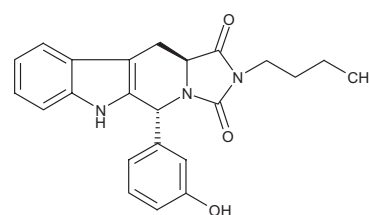


trans-HR22C16

ALX-270-373-M001 1 mg

Cell permeable non-tubulin-interacting mitosis inhibitor. Blocks mitosis (IC_{50} =800nM) by binding to the mitotic kinesin Eg5.

LIT: HR22C16: A Potent Small-Molecule Probe for the Dynamics of Cell Division: S. Hotha, et al.; *Angew. Chem. Int. Ed. Engl.* **42**, 2379 (2003)



NEW S-Trityl-L-cysteine

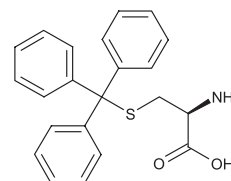
[NSC 83265]

ALX-105-011-M100 100 mg

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Potent, cell permeable cysteine thioether displaying anti-mitotic and anti-tumor properties. Inhibits mitosis by blocking basal and microtubule-activated ATPase activities of the mitotic kinesin Eg5 (IC_{50} =1μM and 140nm). Induces mitotic arrest in HeLa cells (IC_{50} =700nM) and inhibits the growth of NCI tumor cell line panel (GI_{50} =1.31 μM).

LIT: In vitro screening for inhibitors of the human mitotic kinesin Eg5 with antimitotic and antitumor activities: S. DeBonis, et al.; *Mol. Cancer Ther.* **3**, 1079 (2004) • S-trityl-L-cysteine is a reversible, tight-binding inhibitor of the human kinesin eg5 that specifically blocks mitotic progression: D.A. Skoufias, et al.; *J. Biol. Chem.* **281**, 17559, (2006)



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