(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 October 2008 (16.10.2008)

PCT

(10) International Publication Number
WO 2008/122798 A2

(51) International Patent Classification:
A61K 31/519 (2006.01) *A61K 31/337* (2006.01)
A61K 45/06 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/GB2008/001233

(22) International Filing Date: 9 April 2008 (09.04.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/910,980 10 April 2007 (10.04.2007) US

(71) Applicant *(for all designated States except MG, US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(71) Applicant *(for MG only)*: **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London Greater, London W1K 1LN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BROWN, Jeffery, Lester** [US/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US). **HUSZAR, Dennis** [CA/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US). **MCCOON, Patricia, Elizabeth** [US/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US).

(74) Agent: **ASTRAZENECA INTELLECTUAL PROPERTY**; AstraZeneca AB, S-SE-151 85 Södertälje (SE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

(54) Title: THERAPEUTIC METHODS 711

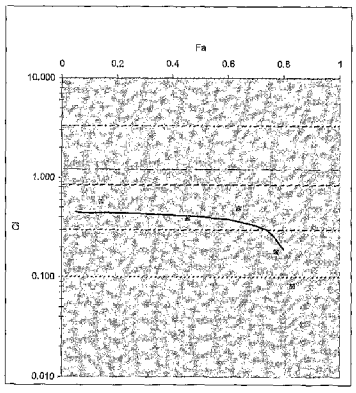


Fig. 3

(57) Abstract: The invention is directed, in part, to a pharmaceutical combination for sequential use in therapy comprising an Eg5 inhibitor, and a microtubule interfering agent.

WO 2008/122798 A2

THERAPEUTIC METHODS 711

FIELD OF THE INVENTION

The present invention relates to combinations of pharmaceutically active substances for use in the treatment of cancer.

BACKGROUND OF THE INVENTION

One sub-class of anti-cancer drugs (taxanes, vinca-alkaloids) now used extensively in the clinic is directed at microtubules and block the cell division cycle by interfering with normal assembly or disassembly of the mitotic spindle (see Chabner, B. A., Ryan, D. P., Paz-Ares, l., Garcia-Carbonero, R., and Calabresi, P: Antineoplastic agents. In Hardman, J. G., Limbird, L.E., and Gilman, A. G., eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th edition, 2001, The MacGraw-Hill Companies, Inc). Taxol® (paclitaxel), one of the most effective drugs of this class, is a microtubule stabilizer. It interferes with the normal growth and shrinkage of microtubules thus blocking the progression of cells through mitosis and resulting in cell death (Blagosklonny, M.V. and Fojo, T.: Molecular effects of paclitaxel: myths and reality (a critical review). *Int J Cancer* 1999, 83:151-156.).

Some of the side effects of treatment with paclitaxel are neutropenia and peripheral neuropathy. Paclitaxel is known to cause abnormal bundling of microtubules in interphase cells. In addition, some tumor types are refractory to treatment with paclitaxel, and other tumors become insensitive during treatment. Paclitaxel is also a substrate for the multi-drug resistance pump, P-glycoprotein (see Chabner *et al.*, 2001).

Thus, there is a need for effective anti-mitotic agents that have fewer side effects than anti-microtubule drugs, and also for agents that are effective against taxane-resistant tumors.

Kinesins are a large family of molecular motor proteins, which use the energy of adenosine 5'-triphosphate (ATP) hydrolysis to move in a stepwise manner along microtubules. For a review, see Sablin, E.P.: Kinesins and microtubules: their structures and motor mechanisms. *Curr Opin Cell Biol* 2000, 12:35-41 and Schief, W. R. and Howard, J.: Conformational changes during kinesin motility. *Curr Opin Cell Biol* 2001, 13:19-28.

Some members of this family transport molecular cargo along microtubules to the sites in the cell where they are needed. For example, some kinesins bind to vesicles and transport them

along microtubules in axons. Several family members are mitotic kinesins, as they play roles in the reorganization of microtubules that establishes a bipolar mitotic spindle.. The mitotic spindle lines up the chromosomes at metaphase of mitosis and coordinates their movement apart and into individual daughter cells at anaphase and telophase (cytokinesis). See Alberts, B., Bray, D., Lewis, J., Raff, M., Roberts, K., and Watson, J. D., Molecular Biology of the Cell, 3rd edition, Chapter 18, The Mechanics of Cell Division, 1994, Garland Publishing, Inc. New York.

HsEg5 (homo sapiens Eg5) (Accession X85137; see Blangy, A., Lane H.A., d'Heron, P., Harper, M., Kress, M. and Nigg, E.A.: Phosphorylation by p34cdc2 regulates spindle association of human Eg5, a kinesin-related motor essential for bipolar spindle formation in vivo. *Cell* 1995, 83(7): 1159-1169) or, KSP (kinesin spindle protein), is a mitotic kinesin whose homologs in many organisms have been shown to be required for centrosome separation in the prophase of mitosis, and for the assembly of a bipolar mitotic spindle. For a review see Kashina, A.S., Rogers, G.C., and Scholey, J.M.: The bimC family of kinesins: essential bipolar mitotic motors driving centrosome separation. *Biochem Biophys Acta* 1997, 1357: 257-271. Eg5 forms a tetrameric motor, and it is thought to cross-link microtubules and slide them in an anti-parallel orientation, generating the force required to separate the spindle poles during mitosis (Walczak, C. E., Vernos, I., Mitchison, T. J., Karsenti, E., and Heald, R.: A model for the proposed roles of different microtubule-based motor proteins in establishing spindle bipolarity. *Curr Biol* 1998, 8:903-913). Several reports have indicated that inhibition of Eg5 function leads to metaphase block and the appearance of monopolar, or monoastral, mitotic spindles. Recently an Eg5 inhibitor called monastrol was isolated in a cell-based screen for mitotic blockers (Mayer, T.U., Kapoor, T. M., Haggarty, S.J., King, R.W., Schreiber, S.L., and Mitchison, T.J.: Small molecule inhibitor of mitotic spindle bipolarity identified in a phenotype-based screen. *Science* 1999, 286: 971-974).

Monastrol treatment was shown to be specific for Eg5 over kinesin heavy chain, another closely related motor with different functions (Mayer *et al.*, 1999). Monastrol blocks the release of ADP (adenosine 5'-diphosphate) from the Eg5 motor (Maliga, Z., Kapoor, T. M., and Mitchison, T.J.: Evidence that monastrol is an allosteric inhibitor of the mitotic kinesin Eg5. *Chem & Biol* 2002, 9: 989-996 and DeBonis, S., Simorre, J.-P., Crevel, I., Lebeau, L, Skoufias, D. A., Blangy, A., Ebel, C., Gans, P., Cross, R., Hackney, D. D., Wade, R. H., and Kozielski, F.: Interaction of the mitotic inhibitor monastrol with human kinesin Eg5. *Biochemistry* 2003, 42:

338-349) an important step in the catalytic cycle of kinesin motor proteins (for review, see Sablin, 2000; Schief and Howard, 2001). Treatment with monastrol was shown to be reversible and to activate the mitotic spindle checkpoint which stops the progress of the cell division cycle until the chromosomes are fully attached to a bipolar mitotic spindle (Kapoor, T.M., Mayer, T. U., Coughlin, M. L., and Mitchison, T.J.: Probing spindle assembly mechanisms with monastrol, a small molecule inhibitor of the mitotic kinesin, Eg5. *J Cell Biol* 2000, 150(5): 975-988). Recent reports also indicate that inhibitors of Eg5 lead to apoptosis of treated cells and are effective against several tumor cell lines and tumor models (Mayer *et al.*, 1999).

Although Eg5 is thought to be necessary for mitosis in all cells, one report indicates that it is over-expressed in tumor cells (International Patent Application WO 01/31335), suggesting that they may be particularly sensitive to its inhibition. Eg5 is not present on the microtubules of interphase cells, and monastrol has no detectable effect on microtubule arrays in interphase cells (Mayer et al., 1999), thus Eg5 inhibition may not produce the peripheral neuropathy associated with treatment with paclitaxel and other anti-microtubule drugs. Eg5 is targeted to microtubules by phosphorylation at an early point in mitosis (Blangy *et al.*, 1995). See also: Sawin, K. E. and Mitchison, T.J.: Mutations in the kinesin-like protein Eg5 disrupting localization to the mitotic spindle. *Proc Natl Acad Sci USA* 1995, 92(10): 4289-4293. Certain pyrimidones have recently been described as being inhibitors of KSP (WO 03/094839, WO 03/099211, WO 03/050122, WO 03/050064, WO 03/049679, WO 03/049527, WO 04/078758, WO 04/106492 and WO 04/111058).

SUMMARY OF THE INVENTION

The present invention is directed, in part, to a pharmaceutical combination of an Eg5 inhibitor and a microtubule interfering agent for sequential use in therapy, and uses of the combination in methods of treatment of the human or animal body.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph depicting the results obtained from the simultaneous exposure of (+) N-(3-amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-methyl-benzamide and paclitaxel. (Fa = fraction affected and Ci = combination index).

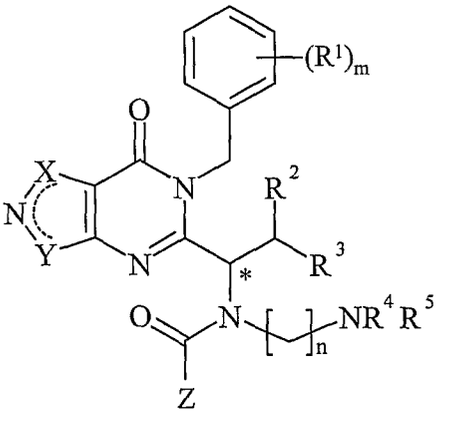
Figure 2 is a graph depicting the results obtained from the sequential exposure of paclitaxel followed by (+) N-(3-amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-methyl-benzamide. (Fa = fraction affected and Ci = combination index).

Figure 3 is a graph depicting the results obtained from the sequential exposure of : (+) N-(3-amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-methyl-benzamide followed by paclitaxel. (Fa = fraction affected and Ci = combination index).

DETAILED DESCRRIPTION

The present invention is based on the finding that the sequential administration of an Eg5 inhibitor and a microtubule interfering agent such as taxane, in any order, is useful for inhibiting cell proliferation and is therefore useful in methods of treatment of the human or animal body.

In one aspect, the Eg5 inhibitor is selected from an enantiomer of a compound of Formula (I):



I

including a pharmaceutically acceptable salt thereof,

wherein:

X is selected from -C(CH_3)- or -S- provided that when X is -S- then Y is -C(CH_3)-;

Y is selected from -C(CH_3)- or -O- or -S- provided that when Y is -C(CH_3)- then X is not -C(CH_3)-;

m is 0 or 1;

R^1 is F when m is 1;

R^2 and R^3 are independently selected from H or C_{1-3}alkyl; wherein if both R^2 and R^3 are selected from C_{1-3}alkyl they are identical;

n is 2 or 3;

R^4 and R^5 are independently selected from H or C_{1-3}alkyl;

Z is optionally substituted phenyl, or optionally substituted benzothiophene wherein the number of optional substituents is 1 or 2 and each is independently selected from F, Cl, Br, CH_3 or CH_2CH_3; and

"*" represents a chiral center;

wherein said enantiomer is substantially free of the other enantiomer; and wherein the optical rotation of the enantiomer, when said enantiomer is dissolved at a concentration of 1mg/ml in methanol, at 20.0 °C measured at 589 nM is (+).

Examples of a compound of Formula (I) include:

(+) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-4-methyl-benzamide;

(+) N-(3-Amino-propyl)-N-{1-[5-(4-fluoro-benzyl)-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl]-propyl}-4-methyl-benzamide;

(+) N-(3-Amino-propyl)-N-{1-[5-(3-fluoro-benzyl)-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl]-propyl}-4-methyl-benzamide;

(+) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-4-bromo-benzamide;

(+) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-4-chloro-benzamide;

(+) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-3-fluoro-4-methyl-benzamide;

(+) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-2,3-dichloro-benzamide;

(+) Benzo[b]thiophene-2-carboxylic acid (3-amino-propyl)-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]amide;

(+) N-(2-Amino-ethyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-4-methyl-benzamide;

(+) N-[1-(5-Benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-N-(3-dimethylamino-propyl)-4-methyl-benzamide;

(+) N-[1-(5-Benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-N-(3-isopropylamino-propyl)-4-methyl-benzamide;

(+) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isoxazolo[5,4-d]pyrimidin-6-yl)-propyl]-4-methyl-benzamide;

(+) N-(3-Amino-propyl)-N-{1-[5-(4-fluoro-benzyl)-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl]-2-methyl-propyl}-4-methyl-benzamide;

(+) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-methyl-benzamide;

(+) N-(3-Amino-propyl)-N-{1-[5-(3-fluoro-benzyl)-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl]-2-methyl-propyl}-4-methyl-benzamide;

(+) N-(2-Amino-ethyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-bromo-benzamide;

(+) N-(2-Amino-ethyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-methyl-benzamide;

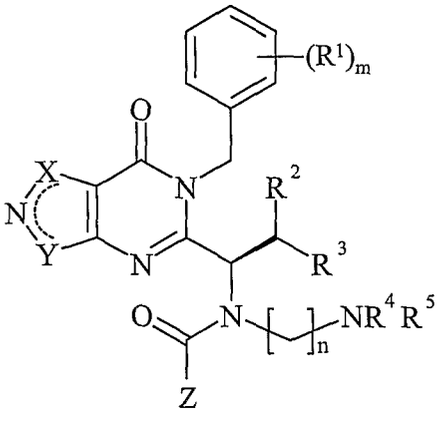
(+) N-(2-Amino-ethyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-3-fluoro-4-methyl-benzamide;

(+) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-3-fluoro-4-methyl-benzamide;

(+) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-bromo-benzamide;

(+) N-[1-(5-Benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-N-(3-dimethylamino-propyl)-4-methyl-benzamide;
(+) N-[1-(5-Benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-N-(3-dimethylamino-propyl)-4-bromo-benzamide;
(+) N-[1-(5-Benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-N-(3-dimethylamino-propyl)-3-fluoro-4-methyl-benzamide;
(+) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isoxazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-methyl-benzamide;
(+) N-(3-Amino-propyl)-N-{1-[5-(4-fluoro-benzyl)-3-methyl-4-oxo-4,5-dihydro-isoxazolo[5,4-d]pyrimidin-6-yl]-2-methyl-propyl}-4-methyl-benzamide;
(+) N-(3-Amino-propyl)-N-{1-[5-(3-fluoro-benzyl)-3-methyl-4-oxo-4,5-dihydro-isoxazolo[5,4-d]pyrimidin-6-yl]-2-methyl-propyl}-4-methyl-benzamide;
(+) N-(3-Amino-propyl)-N-[1-(6-benzyl-3-methyl-7-oxo-6,7-dihydro-isothiazolo[4,5-d]pyrimidin-5-yl)-propyl]-4-methyl-benzamide;
or a pharmaceutically acceptable salt thereof;
wherein the (+) optical rotation of the enantiomer is measured at a concentration of 1mg/ml in methanol, at 20.0 °C at 589 nM.

In another aspect, the Eg5 inhibitor can be selected from an enantiomer of a compound of Formula (Ia):



Ia

including a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof,

wherein:

X is selected from -C(CH_3)- or -S- provided that when X is -S- then Y is -C(CH_3)-;

Y is selected from -C(CH_3)- or -O- or -S- provided that when Y is -C(CH_3)- then X is not -C(CH_3)-;

m is 0 or 1;

R^1 is F when m is 1;

R^2 and R^3 are independently selected from H or C_{1-3}alkyl; wherein if both R^2 and R^3 are selected from C_{1-3}alkyl they are identical;

n is 2 or 3;

R^4 and R^5 are independently selected from H or C_{1-3}alkyl;

Z is optionally substituted phenyl, or optionally substituted benzothiophene wherein the number of optional substituents is 1 or 2 and each is independently selected from F, Cl, Br, CH_3 or CH_2CH_3;

wherein said enantiomer is substantially free of the (S) enantiomer.

Particular compounds of Formula (Ia) include:

(R) *N*-(3-Amino-propyl)-*N*-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-*d*]pyrimidin-6-yl)-propyl]-4-methyl-benzamide;

(R) N-(3-Amino-propyl)-N-{1-[5-(4-fluoro-benzyl)-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl]-propyl}-4-methyl-benzamide;

(R) N-(3-Amino-propyl)-N-{1-[5-(3-fluoro-benzyl)-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl]-propyl}-4-methyl-benzamide;

(R) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-4-bromo-benzamide;

(R) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-4-chloro-benzamide;

(R) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-3-fluoro-4-methyl-benzamide;

(R) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-2,3-dichloro-benzamide;

(R) Benzo[b]thiophene-2-carboxylic acid (3-amino-propyl)-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]amide;

(R) N-(2-Amino-ethyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-4-methyl-benzamide;

(R) N-[1-(5-Benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-N-(3-dimethylamino-propyl)-4-methyl-benzamide;

(R) N-[1-(5-Benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-N-(3-isopropylamino-propyl)-4-methyl-benzamide;

(R) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isoxazolo[5,4-d]pyrimidin-6-yl)-propyl]-4-methyl-benzamide;

(R) N-(3-Amino-propyl)-N-{1-[5-(4-fluoro-benzyl)-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl]-2-methyl-propyl}-4-methyl-benzamide;

(R) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-methyl-benzamide;

(R) N-(3-Amino-propyl)-N-{1-[5-(3-fluoro-benzyl)-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl]-2-methyl-propyl}-4-methyl-benzamide;

(R) N-(2-Amino-ethyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-bromo-benzamide;

(R) N-(2-Amino-ethyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-methyl-benzamide;

(R) N-(2-Amino-ethyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-3-fluoro-4-methyl-benzamide;

(R) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-3-fluoro-4-methyl-benzamide;

(R) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-bromo-benzamide;

(R) N-[1-(5-Benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-N-(3-dimethylamino-propyl)-4-methyl-benzamide;

(R) N-[1-(5-Benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-N-(3-dimethylamino-propyl)-4-bromo-benzamide;

(R) N-[1-(5-Benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-N-(3-dimethylamino-propyl)-3-fluoro-4-methyl-benzamide;
(R) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isoxazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-methyl-benzamide;
(R) N-(3-Amino-propyl)-N-{1-[5-(4-fluoro-benzyl)-3-methyl-4-oxo-4,5-dihydro-isoxazolo[5,4-d]pyrimidin-6-yl]-2-methyl-propyl}-4-methyl-benzamide;
(R) N-(3-Amino-propyl)-N-{1-[5-(3-fluoro-benzyl)-3-methyl-4-oxo-4,5-dihydro-isoxazolo[5,4-d]pyrimidin-6-yl]-2-methyl-propyl}-4-methyl-benzamide; or
(R) N-(3-Amino-propyl)-N-[1-(6-benzyl-3-methyl-7-oxo-6,7-dihydro-isothiazolo[4,5-d]pyrimidin-5-yl)-propyl]-4-methyl-benzamide;
or a pharmaceutically acceptable salt thereof.

Said compounds of formula (Ia) may be used, where appropriate, with any of the definitions, claims or embodiments defined hereinbefore or hereinafter, particularly where compounds of formula (I) are referred to.

In one embodiment, stereoisomers of Formula (I) are substantially free of all other stereoisomers.

The term "substantially free" refers to less than 10% of the other isomer, more particularly less than 5%, in particular less than 2%, more particularly less than 1%, particularly less then 0.5%, in particular less than 0.2%.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds, for example, compounds of Formula (I) or Formula (Ia), wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, phosphoric, and the like; and the salts prepared from organic acids such as lactic, maleic, citric, benzoic, methanesulfonic, and the like. The pharmaceutically acceptable salts of the invention also include salts prepared with one of the

following acids benzene sulfonic acid, fumaric acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid or L-tartaric acid.

Thus in one aspect of the invention there is provided a compound of the invention, particularly one of the Eg5 inhibitors described herein, as a pharmaceutically acceptable salt, particularly a benzene sulfonic acid, fumaric acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid or L-tartaric acid salt.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred.

Any microtubule interfering agent can be used in the combination of the present invention. Microtubule interfering agents include both microtubule stabilizing agents and microtubule destabilizing agents.

In one example, a microtubule stabilizing agent can be a taxane or an epothilone. Taxanes are known in the art and include (2aR,3aR,4aR,6R,9S,11S,12S,12aR,12bS)-6,12b-diacetoxy-9-[3(S)-(tert-butoxycarbonylamino)-2(R)-hydroxy-3-phenylpropionyloxy]-12-benzoyloxy-11-hydroxy-8,13,13-trimethyl-2a,3,3a,4,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]-cyclopropa[4,5]benz[1,2-b]oxet-5-one dihydrate; Paclitaxel (Taxol), BMS 184476 (7-methylthiomethylpaclitaxel); BMS 188797; BMS 275183; CYC-3204 (a penetratin-paclitaxel conjugate); docosahexaenoic acid-paclitaxel conjugate (Taxoprexin^{Tm}); DJ-927; Docetaxel (Taxotere); XRP9881 (RPR-109881A); XRP6258 (RPR112658); Milataxel; MST 997; MBT-206; NBT-287; ortataxel; Protax-3; PG-TXL; PNU-166945; 106258; BMS-188797; 109881; BAY 598862 (IDN 5109; semisynthetic taxane); paclitaxel protein-bound (Abraxane^{Tm}), Protaxel and MAC-321 (Taxalog). Example of epothilones include epothilone A, B and D.

In yet another example, the microtubule interfering agent is a destabilizing agent such as a vinca-alkaloid. Vinca-alkaloids include vinblastine, vincristine, vindesine and vinorelbine.

The pharmaceutical combination of the invention is for sequential administration and the combination includes a preparation of each active ingredient. The preparation of an Eg5 inhibitor disclosed above are known in the art, for example, as described in WO2006/018628, the contents of which are incorporated herein by reference. Preparation of microtubule interfering agents such as taxanes are also well known in the art.

By sequential administration is meant that the Eg5 inhibitor and the microtubule interfering agent are administered separately, in any order, to achieve the desired therapeutic effect. In one example, the Eg5 inhibitor is administered before the taxane. In another example, the taxane is administered before the Eg5 inhibitor.

To achieve the desired therapeutic effect, the sequential administration of each agent may be at least 6 hours apart but no more than 80 hours apart. In one example, the Eg5 inhibitor and taxane are administered at least 6 hours apart, 12 hours apart, 18 hours apart, 24 hours apart, 28 hours apart, 36 hours apart, 48 hours apart, 52 hours apart, 60 hours apart, 68 hours apart or 72 hours apart.

By therapeutic effect is meant a measurable objective clinical response. For example, the sequential administration of an Eg5 inhibitor and a microtubule interfering agent results in an objective stabilization of the tumour or objective shrinkage of the tumour. Objective stabilization can include tumour growth of no more than 25%, for example, measured from the longest diameter of a single tumour mass. Objective shrinkage can include a reduction of tumour length or diameter, for example, of greater than 15%, 20% or more than 25%.

The present invention provides a method for the treatment of anti-cell proliferation such as cancer. Cancers that can be treated include breast cancer, colorectal cancer, ovarian cancer, lung (non small cell) cancer, malignant brain tumors, sarcomas, melanoma and lymphoma.

Thus, according to the invention, the invention includes a method of treating a cancer comprising administering sequentially an Eg5 inhibitor, or a pharmaceutically acceptable salt thereof, and a microtubule interfering agent, to a human or animal patient in need thereof.

According to a further aspect of the invention there is provided a pharmaceutical combination which is administered sequentially that comprises an Eg5 inhibitor, or a pharmaceutically acceptable salt thereof, and a microtubule interfering agent, for use in the treatment of cancer.

Moreover the invention includes:

Use of pharmaceutical combination of an Eg5 inhibitor, or a pharmaceutically acceptable salt thereof, and a microtubule interfering agent, for the manufacture of a medicament for treating cancer, wherein for the treatment the Eg5 inhibitor and the microtubule interfering agent are administered sequentially, in any order.

Use of an Eg5 inhibitor, or a pharmaceutically acceptable salt thereof, and a microtubule interfering agent, for treating cancer, wherein the Eg5 inhibitor and the microtubule interfering agent are administered sequentially, in any order.

A pharmaceutical combination comprising an Eg5 inhibitor, or a pharmaceutically acceptable salt thereof, and a microtubule interfering agent, for use in treating cancer wherein the Eg5 inhibitor and the microtubule interfering agent are administered sequentially, in any order.

The Eg5 inhibitor and the microtubule interfering agent may be administered orally, sublingually, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints. The Eg5 inhibitor and the microtubule interfering agent combinations may be administered by different routes but typically the compositions will be administered by oral or parenteral administration using conventional systemic dosage forms, such as tablets, capsules, pills, powders, aqueous or oily solutions or suspensions, emulsions and sterile injectable aqueous or oily solutions or suspensions. These dosage forms will usually include one or more pharmaceutically acceptable ingredients which may be selected, for example, from adjuvants, carriers, binders, lubricants, diluents, stabilising agents, buffering agents, emulsifying agents, viscosity-regulating agents, surfactants, preservatives, flavourings and colorants. Preferred routes of administration are orally, intravenously or intramuscularly.

The Eg5 inhibitor, or a pharmaceutically acceptable salt thereof, will normally be administered to a warm-blooded animal at a unit dose of 300 mg or less daily and this would be expected to provide a therapeutically-effective dose. For example, the Eg5 inhibitor will be administered from about 5 mg to 500 mg of active ingredient. In one example the Eg5 inhibitor is a conventional tablet formulation for oral administration containing 5 mg, 10 mg, 20 mg, 40 mg, 100 mg, 250 mg or 300 mg of active ingredient. Conveniently the daily oral dose of an Eg5

inhibitor may be above 5 mg, for example, in the range 5 to 80 mg. For a single dosage form, the active ingredients may be compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 5 mg to about 300 mg of each active ingredient. However the daily dose may be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

The microtubule interfering agent will normally be administered to a warm-blooded animal at a unit dose, for example, from about 1 mg to 500 mg of active ingredient. The dose, usually administered weekly, may be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

The dosage of each of the two drugs and their proportions have to be composed so that the best possible treatment effects, as defined by national and international guidelines (which are periodically reviewed and re-defined), will be met.

According to a further aspect of the present invention there is provided a kit comprising an Eg5 inhibitor, or a pharmaceutically acceptable salt thereof, and a microtubule interfering agent such as taxane; optionally with instructions for use. For example, there is provided a kit comprising:

a) an Eg5 inhibitor, or a pharmaceutically acceptable salt thereof, in a first unit dosage form;

b) a microtubule interfering agent; in a second unit dosage form; and

c) container means for containing said first and second dosage forms; and optionally

d) with instructions for administering the Eg5 inhibitor and the microtubule interfering agent sequentially.

It is contemplated that the invention described herein is not limited to the particular methodology, protocols, and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention in any way.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices and materials are herein described. All publications mentioned herein are incorporated by reference for the purpose of describing and disclosing the materials and methodologies that are reported in the publication which might be used in connection with the invention.

The present invention will now be further understood by reference to the following illustrative examples.

EXAMPLES

The anti-proliferative activity of (+) N-(3-amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-methyl-benzamide was evaluated in combination with paclitaxel (Calbiochem, Ltd) in an MTS tetrazolium colorimetric assay (Promega Corporation). NCI-H460, NCI-H460d/np53 (NCI-H460 cells transfected with a dominant negative p53 construct as described in Shaulian, E. Zauberman, A. Milner, J. Davies, E A. Oren, M. EMBO Journal. 12:2789-97, 1993) and NCI-H226 cells were seeded in 96 well plates on Day 0 and treated with either a single drug, or simultaneously with both drugs, for 24 hours on Day 1. For simultaneous exposure, medium and drug were removed after 24 hours of treatment on Day 2 and replaced with medium alone; cell viability was measured on day 4. For sequential exposure, medium and drug were removed 24 hours after treatment with either (+) N-(3-amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-methyl-benzamide or paclitaxel, and the other drug was added for an additional 24 hours of exposure. Medium and drug were removed on Day 3, replaced with medium alone, and cell viability was measured on Day 4.

(+) N-(3-amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-methyl-benzamide and paclitaxel were combined at constant ratio of IC50[paclitaxel]:IC50[(+) N-(3-amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-methyl-benzamide] (see Table 1 for examples of drug concentrations used in each cell line) and a dose response curve was

generated for each drug alone and in combination. A Combination Index (CI; Chou and Talalay, Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors. Adv Enzyme Regul. 1984;22:27-55) was calculated from the dose response curve, and a Combination Index curve generated which indicates whether the drug combinations are antagonistic (CI values >1), additive (CI values ~1), or synergistic (CI values <1).

Table 1 **IC_{50} Values Used to Determine paclitaxel: (+) N-(3-amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-methyl-benzamide Ratio and Top Concentration Used in Combination (uM)**

Drug	H460		H460dnp53		H226	
	IC50	Top Conc.	IC50	Top Conc.	IC50	Top Conc.
Paclitaxel	0.009	1.0	0.0037	1.0	0.018	10.0
Eg5 Inhibit	0.010	1.11	0.004	1.11	0.023	12.83

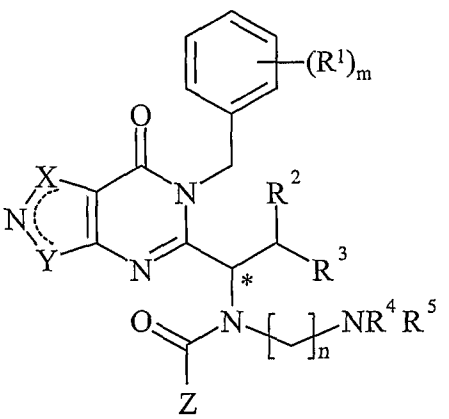
Shown in Figures 1-3 are representative combination index curves for treatment of NCI-H460 cells with (+) N-(3-amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-methyl-benzamide and paclitaxel. Simultaneous treatment (Fig 1) resulted in synergy at lower inhibitory concentrations (ICs), but additivity and antagonism were observed at higher IC's. In contrast, sequential exposure of cells to (+) N-(3-amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-methyl-benzamide and paclitaxel, in either order, resulted in a synergistic enhancement of growth inhibition at all drug concentrations tested (Figs 2 and 3).

In NCI-H226 cells (CI curves not shown) simultaneous treatment resulted in antagonism and additivity at lower ICs, and synergy at higher drug concentrations. Simultaneous treatment of NCI-H460d/np53 cells (CI curves not shown) resulted primarily in antagonism. However, comparable to the observations in NCI-H460 cells, sequenced treatment of both NCI-H226 and NCI-H460d/np53 cell lines was primarily synergistic in either sequence tested.

What is claimed is:

1. A pharmaceutical combination for sequential use in therapy comprising:

an Eg5 inhibitor selected from an enantiomer of a compound of Formula (I):



I

including a pharmaceutically acceptable salt thereof,

wherein:

X is selected from $-C(CH_3)-$ or -S- provided that when X is -S- then Y is $-C(CH_3)-$;

Y is selected from $-C(CH_3)-$ or -O- or -S- provided that when Y is $-C(CH_3)-$ then X is not $-C(CH_3)-$;

m is 0 or 1;

R^1 is F when m is 1;

R^2 and R^3 are independently selected from H or C_{1-3}alkyl; wherein if both R^2 and R^3 are selected from C_{1-3}alkyl they are identical;

n is 2 or 3;

R^4 and R^5 are independently selected from H or C_{1-3}alkyl;

Z is optionally substituted phenyl, or optionally substituted benzothiophene wherein the number of optional substituents is 1 or 2 and each is independently selected from F, Cl, Br, CH_3 or CH_2CH_3; and

"*" represents a chiral center;

wherein said enantiomer is substantially free of the other enantiomer; and wherein the optical rotation of the enantiomer, when said enantiomer is dissolved at a concentration of 1mg/ml in methanol, at 20.0 °C measured at 589 nM is (+), and;

(ii) a microtubule interfering agent.

2. The combination of claim 1, wherein a compound of Formula (I) is selected from the group consisting of:

(+) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-4-methyl-benzamide;

(+) N-(3-Amino-propyl)-N-{1-[5-(4-fluoro-benzyl)-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl]-propyl}-4-methyl-benzamide;

(+) N-(3-Amino-propyl)-N-{1-[5-(3-fluoro-benzyl)-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl]-propyl}-4-methyl-benzamide;

(+) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-4-bromo-benzamide;

(+) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-4-chloro-benzamide;

(+) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-3-fluoro-4-methyl-benzamide;

(+) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-2,3-dichloro-benzamide;

(+) Benzo[b]thiophene-2-carboxylic acid (3-amino-propyl)-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]amide;

(+) N-(2-Amino-ethyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-4-methyl-benzamide;

(+) N-[1-(5-Benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-N-(3-dimethylamino-propyl)-4-methyl-benzamide;

(+) N-[1-(5-Benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-propyl]-N-(3-isopropylamino-propyl)-4-methyl-benzamide;

(+) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isoxazolo[5,4-d]pyrimidin-6-yl)-propyl]-4-methyl-benzamide;

(+) N-(3-Amino-propyl)-N-{1-[5-(4-fluoro-benzyl)-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl]-2-methyl-propyl}-4-methyl-benzamide;
(+) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-methyl-benzamide;
(+) N-(3-Amino-propyl)-N-{1-[5-(3-fluoro-benzyl)-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl]-2-methyl-propyl}-4-methyl-benzamide;
(+) N-(2-Amino-ethyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-bromo-benzamide;
(+) N-(2-Amino-ethyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-methyl-benzamide;
(+) N-(2-Amino-ethyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-3-fluoro-4-methyl-benzamide;
(+) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-3-fluoro-4-methyl-benzamide;
(+) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-bromo-benzamide;
(+) N-[1-(5-Benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-N-(3-dimethylamino-propyl)-4-methyl-benzamide;
(+) N-[1-(5-Benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-N-(3-dimethylamino-propyl)-4-bromo-benzamide;
(+) N-[1-(5-Benzyl-3-methyl-4-oxo-4,5-dihydro-isothiazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-N-(3-dimethylamino-propyl)-3-fluoro-4-methyl-benzamide;
(+) N-(3-Amino-propyl)-N-[1-(5-benzyl-3-methyl-4-oxo-4,5-dihydro-isoxazolo[5,4-d]pyrimidin-6-yl)-2-methyl-propyl]-4-methyl-benzamide;
(+) N-(3-Amino-propyl)-N-{1-[5-(4-fluoro-benzyl)-3-methyl-4-oxo-4,5-dihydro-isoxazolo[5,4-d]pyrimidin-6-yl]-2-methyl-propyl}-4-methyl-benzamide;
(+) N-(3-Amino-propyl)-N-{1-[5-(3-fluoro-benzyl)-3-methyl-4-oxo-4,5-dihydro-isoxazolo[5,4-d]pyrimidin-6-yl]-2-methyl-propyl}-4-methyl-benzamide;
(+) N-(3-Amino-propyl)-N-[1-(6-benzyl-3-methyl-7-oxo-6,7-dihydro-isothiazolo[4,5-d]pyrimidin-5-yl)-propyl]-4-methyl-benzamide;
or a pharmaceutically acceptable salt thereof;

wherein the (+) optical rotation of the enantiomer is measured at a concentration of 1mg/ml in methanol, at 20.0 °C at 589 nM.

3. The combination of either claim 1 or claim 2, wherein the microtubule interfering agent is selected from the group consisting of a taxane, an epothilone and a vinca-alkaloid.

4. The combination of any one of claims 1-3, wherein the microtubule interfering agent is a taxane.

5. The combination of any one of claims 1-3 wherein the taxane is selected from the group consisting of docosahexaenoic acid-paclitaxel conjugate, taxoprexin, docetaxel, milataxel, protaxel, paclitaxel and paclitaxel protein-bound.

6. The combination of any one of claims 1-5, wherein the Eg5 inhibitor is administered prior to the microtubule interfering agent.

7. The combination of any one of claim 1-5, wherein the microtubule interfering agent is administered prior to the Eg5 inhibitor.

8. A method of treating cancer comprising administering sequentially a therapeutically effective amount of a pharmaceutical combination as defined in any one of claims 1-7 to a patient in need thereof.

9. The method of claim 8, wherein the cancer is breast cancer, colorectal cancer, ovarian cancer, lung (non small cell) cancer, malignant brain tumors, sarcomas, melanoma and lymphoma.

10. Use of the pharmaceutical combination as defined in any one of claims 1-7 in the treatment of cancer, wherein the Eg5 inhibitor and the microtubule interfering agent are administered sequentially, in any order.

11. The use of claim 10, wherein the cancer is breast cancer, colorectal cancer, ovarian cancer, lung (non small cell) cancer, malignant brain tumors, sarcomas, melanoma and lymphoma.

12. A pharmaceutical combination comprising an Eg5 inhibitor, or a pharmaceutically acceptable salt thereof, and a microtubule interfering agent, for use in treating cancer wherein the Eg5 inhibitor and the microtubule interfering agent are administered sequentially, in any order.

13. A kit comprising a preparation of a pharmaceutical composition as defined in any one of claims 1-7, and instructions for the sequential administration of the preparations to a patient in need thereof.

Fig. 1

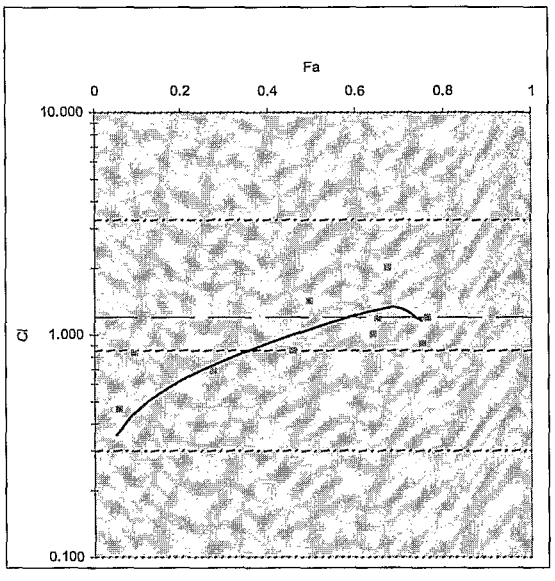


Fig. 2

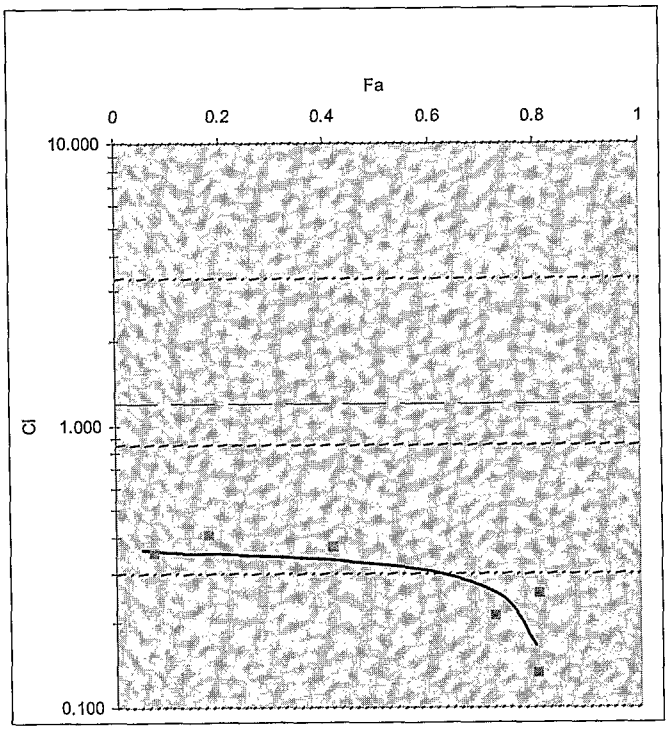


Fig. 3