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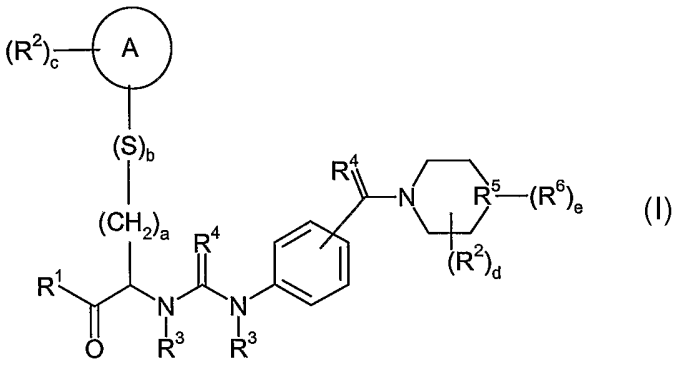
(54) Title: PHENYLUREA COMPOUNDS



(I)

(57) Abstract: The present invention provides compounds of formula (I): pharmaceutical compositions containing the same, processes for preparing the same and their use as pharmaceutical agents.

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PHENYLUREA COMPOUNDS

BACKGROUND OF THE INVENTION

The present invention relates to novel compounds, pharmaceutical formulations comprising these compounds, and the use of these compounds in therapy. More particularly, the present invention relates to novel compounds and methods for treating conditions mediated by Polo-like Kinase, susceptible neoplasms, and other conditions.

Polo-like kinases ("PLK") are evolutionarily conserved serine/threonine kinases that play critical roles in regulating processes in the cell cycle. PLK plays a role in the entry into and the exit from mitosis in diverse organisms from yeast to mammalian cells. PLK includes PLK1, PLK2, and PLK3.

Polo-like kinases are known to be essential for mitosis in yeast, Drosophila, and Xenopus. For example, mutants of the homologous PLK genes in these organisms result in disordered mitotic spindles, and in Drosophila mutations can be embryonic lethal. RNA interference experiments on Drosophila *polo* have shown that ablation of *polo* in S2 cells results in G2/M arrest and apoptosis. PLK1 is the human homolog of Drosophila *polo*. It is believed to be involved in the entry into mitosis through the activation of cdk1 by phosphorylating and activating the phosphatase cdc25C, which in turn removes inhibitory phosphates from cdk1. This sets up an activation loop for cdk1 that leads to mitotic entry. PLK1 also phosphorylates cyclin B1, the cyclin partner of cdk1, resulting in nuclear localization. During mitosis, PLK1 has been shown to play roles in centrosome maturation and microtubule dynamics involved in formation of the mitotic spindle. PLK1 is also involved in the exit of cells from mitosis by phosphorylating and activating subunits of the anaphase-promoting complex (cdc16 and cdc27). PLK1 also phosphorylates cohesin proteins that hold sister chromatids together, exposing separase cleavage sites, and allowing separation of sister chromatids during anaphase.

PLK1 may also play a role in cytokinesis through phosphorylation of the kinesin-like motor protein MKLP1. Inhibition of PLK1 thus has the potential to interfere with several stages of mitosis. Expression and activity of PLK protein increases during the cell cycle, reaching its peak during mitosis when it is also maximally phosphorylated. PLK1 mRNA is highly expressed in cells with a high mitotic index. PLK2 (serum-inducible kinase, SNK) and PLK3 (PRK Proliferation-related kinase Fibroblast Growth Factor-inducible kinase, FNK) were originally identified as immediate-early genes. PLK2 is not very well characterized, but PLK3 appears to be involved in regulation of cell cycle progression through M phase but functions differently from PLK1. Recent published work suggests that PLK3 plays an important role in the regulation of microtubule dynamics and function of the centrosome during mitosis.

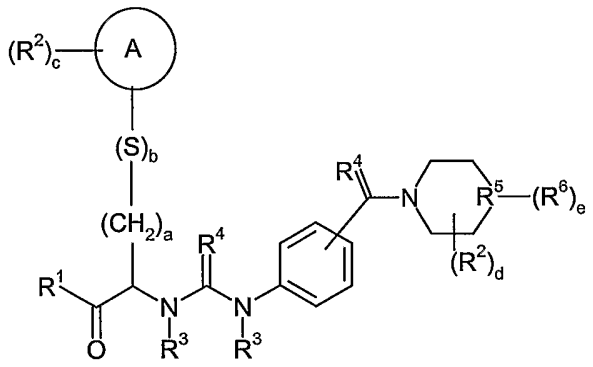
Overexpression of PLK1 appears to be strongly associated with neoplastic cells (including cancers). A published study has shown high levels of PLK1 RNA expression in >80% of lung and breast tumors, with little to no expression in adjacent normal tissue. Several studies have shown correlations between PLK expression, histological grade, and prognosis in several types of cancer. Significant correlations were found between percentages of PLK-positive cells and histological grade of ovarian and endometrial cancer ($P<0.001$). These studies noted that PLK is strongly expressed in invading endometrial carcinoma cells and that this could reflect the degree of malignancy and proliferation in endometrial carcinoma. Using RT-PCR analysis, PLK overexpression was detected in 97% of esophageal carcinomas and 73% of gastric carcinomas as compared to the corresponding normal tissues. Further, patients with high levels of PLK overexpression in esophageal carcinoma represented a significantly poorer prognosis group than those with low levels of PLK overexpression. In head and neck cancers, elevated mRNA expression of PLK1 was observed in most tumors; a Kaplan-Meier analysis showed that those patients with moderate levels of PLK1 expression survived longer than those with high levels of PLK1 expression.

Analysis of patients with non-small cell lung carcinoma showed similar outcomes related to PLK1 expression.

Disruption of mitosis with anti-microtubule drugs has been a successful approach in cancer chemotherapy. The taxanes and vinca alkaloids have been effectively used in the clinic, but they have undesirable side effects. In addition, many tumors appear to have weakened G2/M cell cycle checkpoints; in response to mitotic disruption these tumors attempt to bypass mitosis, leading to mitotic catastrophe and cell death. Several studies suggest that the disruption of mitosis by targeting PLK may be a feasible approach to selective tumor cell destruction. There remains a need in the art for new approaches to the treatment of neoplasms.

BRIEF SUMMARY OF THE INVENTION

According to a first aspect of the invention there is provided a compound of formula (I):



I

wherein:

R^1 is selected from OR^7 and NR^7R^8;

a is 1-6;

b is 0 or 1;

Ring A is phenyl or 5-6 membered heterocycle or heteroaryl containing 1 or 2 N atoms;

c is 0-4;

each R^2 is the same or different and is independently selected from halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, $C(O)R^7$, $C(S)R^7$, CO_2R^7, $CONR^7R^8$, $CSNR^7R^8$, OR^7, SR^7, SO_2R^7 and NR^7R^8;

each R^3 is the same or different and is independently selected from H, alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl;

each R^4 is the same or different and is independently selected from S and O;

d is 0-4;

R^5 is N, O, S or CH;

e is 0 when R^5 is O or S and e is 1 when R^5 is N or CH;

R^6 is selected from H, alkyl, alkenyl, alkynyl, R^9-cycloalkyl, R^9-cycloalkenyl, R^9-Ay, $C(O)R^7$, $C(S)R^7$, CO_2R^7, $C(O)NR^7R^8$, $C(S)NR^7R^8$, C(O)Ay, C(S)Ay, $C(O)N(R^7)Ay$, $C(S)N(R^7)Ay$, $C(O)R^9$-Ay, $C(S)R^9$-Ay, CO_2-R^9-Ay, $C(O)N(R^7)$-R^9-Ay and $C(S)N(R^7)$-R^9-Ay;

each R^7 and R^8 is the same or different and is each independently selected from H, alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl;

R^9 is alkylene or alkenylene; and

Ay is aryl;

or a pharmaceutically acceptable salt or solvate thereof.

In another aspect of the invention there is provided a pharmaceutical composition comprising a compound of formula (I). In one embodiment, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier, diluent or excipient.

In a third aspect of the invention, there is provided a method for treating a condition mediated by PLK in an animal. The method comprises administering to the animal a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

In a fourth aspect of the invention, there is provided a method for treating a susceptible neoplasm in an animal. The method comprises administering to

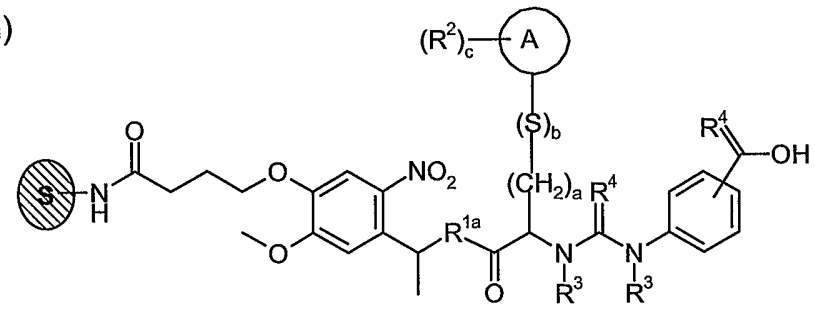
the animal a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof. The susceptible neoplasm may be selected from the group consisting of breast cancer, colon cancer, lung cancer, prostate cancer, lymphoma, leukemia, endometrial cancer, melanoma, pancreatic cancer, ovarian cancer, squamous carcinoma, carcinoma of the head and neck, and esophageal carcinoma.

In a fifth aspect of the invention, there is provided a method for treating a condition characterized by inappropriate cellular proliferation. The method comprises contacting the cell with a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

In a sixth aspect, the present invention provides a method for inhibiting proliferation of a cell. The method comprises contacting the cell with an amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof sufficient to inhibit proliferation of the cell.

In another aspect, the present invention provides a method for inhibiting mitosis in a cell. The method comprises administering to the cell an amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof sufficient to inhibit mitosis in the cell.

In another aspect, there is provided a process for preparing a compound of formula (I) comprising reacting a solid support-bound compound of formula (VIII)



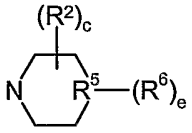
VIII

wherein:

R^{1a} is selected from -O- and -N(R^7)-, and

 represents a solid support;

with a compound of formula (IX)



IX

In another aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof for use in therapy.

In yet another aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof for use in the treatment of a condition mediated by PLK in an animal.

In yet another aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof for use in the treatment of a susceptible neoplasm in an animal.

In another aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof for use in the treatment of a condition characterized by inappropriate cellular proliferation.

In yet another aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof for use in inhibiting proliferation of a cell.

In yet another aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof for use in inhibiting mitosis in a cell.

In yet another aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof for the preparation of a medicament for the treatment of condition mediated by PLK in an animal.

In yet another aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof for the preparation of a medicament for the treatment of a susceptible neoplasm in an animal.

In yet another aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof for the preparation of a medicament for the treatment of a condition characterized by inappropriate cellular proliferation in an animal.

In yet another aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically

functional derivative thereof for the preparation of a medicament for inhibiting proliferation of a cell.

In yet another aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof for the preparation of a medicament for inhibiting mitosis in a cell.

In yet another aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) for use in the treatment of a susceptible neoplasm in an animal.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, "a compound of the invention" or "a compound of formula (I)" means a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

As used herein, the terms "alkyl" (and "alkylene") refer to straight or branched hydrocarbon chains containing from 1 to 8 carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl, and tert-butyl. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, propylene, butylene, and isobutylene. "Alkyl" also includes substituted alkyl. The alkyl groups may be optionally substituted one or more times with a halogen. Thus, the term "alkyl" includes trifluoromethyl and trifluoroethyl, among other halogenated alkyls.

As used herein, the term "alkenyl" refers to straight or branched hydrocarbon chains containing from 2 to 8 carbon atoms (unless a different number of atoms is specified) and at least one and up to three carbon-carbon double bonds. Examples of "alkenyl" as used herein include, but are not limited to

ethenyl and propenyl. "Alkenyl" also includes substituted alkenyl. The alkenyl groups may optionally be substituted one or more times with a halogen.

As used herein, the term "alkynyl" refers to straight or branched hydrocarbon chains containing from 2 to 8 carbon atoms (unless a different number of atoms is specified) and at least one and up to three carbon-carbon triple bonds. Examples of "alkynyl" as used herein include, but are not limited to ethynyl and propynyl. "Alkynyl" also includes substituted alkynyl. The alkynyl groups may optionally be substituted one or more times with a halogen.

As used herein, the term "cycloalkyl" refers to a non-aromatic monocyclic carbocyclic ring having from 3 to 6 carbon atoms (unless a different number of atoms is specified) and no carbon-carbon double bonds. "Cycloalkyl" includes by way of example cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. "Cycloalkyl" also includes substituted cycloalkyl. The cycloalkyl may optionally be substituted on any available carbon with one or more substituents selected from the group consisting of halo and C_{1-3}alkyl (including haloalkyl, e.g., perfluoroalkyl).

As used herein, the term "cycloalkenyl" refers to a non-aromatic monocyclic carbocyclic ring having from 3 to 6 carbon atoms (unless a different number of atoms is specified) and up to 2 carbon-carbon double bonds. "Cycloalkenyl" includes by way of example cyclobutenyl, cyclopentenyl and cyclohexenyl. "Cycloalkenyl" also includes substituted cycloalkenyl. The cycloalkenyl may optionally be substituted on any available carbon with one or more substituents selected from the group consisting of halo and C_{1-3}alkyl (including haloalkyl, e.g., perfluoroalkyl).

The term "halo" or "halogen" refers to fluorine, chlorine, bromine and iodine.

The term "aryl" refers to monocyclic carbocyclic groups and fused multicyclic carbocyclic groups having from 6 to 13 carbon atoms (unless a different number of atoms is specified) and having at least one aromatic ring. Examples of particular aryl groups include but are not limited to phenyl, naphthyl, fluorene and anthracene. One particular aryl group according to the invention is phenyl.

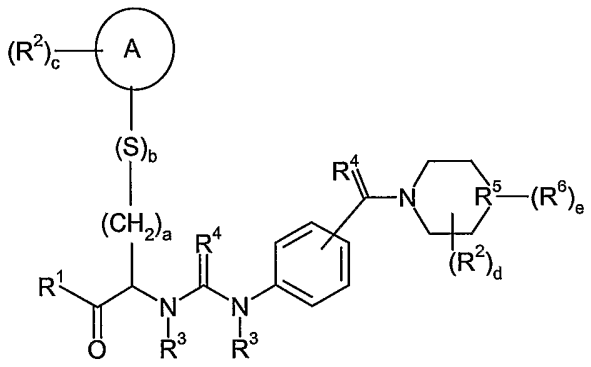
The terms "heterocycle" and "heterocyclic" refer to monocyclic saturated or unsaturated non-aromatic groups and fused bicyclic saturated or unsaturated non-aromatic groups, having the specified number of members and containing 1, 2, 3 or 4 heteroatoms selected from N, O and S (unless a different number of heteroatoms is specified). Examples of particular heterocyclic groups include but are not limited to tetrahydrofuran, dihydropyran, tetrahydropyran, thietane, 1,4-dioxane, 1,3-dioxane, 1,3-dioxalane, piperidine, piperazine, tetrahydropyrimidine, pyrrolidine, morpholine, thiomorpholine, thiazolidine, oxazolidine, tetrahydrothiopyran, tetrahydrothiophene, and the like.

The term "heteroaryl" refers to aromatic monocyclic groups and fused bicyclic groups wherein at least one ring is aromatic, having the specified number of members and containing 1, 2, 3, or 4 heteroatoms selected from N, O and S (unless a different number of heteroatoms is specified). Examples of particular heteroaryl groups include but are not limited to furan, thiophene, pyrrole, imidazole, pyrazole, triazole, tetrazole, thiazole, oxazole, isoxazole, oxadiazole, thiadiazole, isothiazole, pyridine, pyridazine, pyrazine, pyrimidine, quinoline, isoquinoline, benzofuran, benzothiophene, indole, and indazole.

The term "members" (and variants thereof e.g., "membered") in the context of heterocyclic and heteroaryl groups refers to the total atoms, carbon and heteroatoms N, O and/or S, which form the ring. Thus, an example of a 6-membered heterocyclic ring is piperidine and an example of a 6-membered heteroaryl ring is pyridine.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) that occur and events that do not occur.

The present invention provides compounds of formula (I):



I

wherein:

R^1 is selected from OR^7 and NR^7R^8;

a is 1-6;

b is 0 or 1;

Ring A is phenyl or 5-6 membered heterocycle or heteroaryl containing 1 or 2 N atoms;

c is 0-4;

each R^2 is the same or different and is independently selected from halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, $C(O)R^7$, $C(S)R^7$, CO_2R^7, $CONR^7R^8$, $CSNR^7R^8$, OR^7, SR^7, SO_2R^7 and NR^7R^8;

each R^3 is the same or different and is independently selected from H, alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl;

each R^4 is the same or different and is independently selected from S and O;

d is 0-4;

R^5 is N, O, S or CH;

e is 0 when R^5 is O or S and e is 1 when R^5 is N or CH;

R^6 is selected from H, alkyl, alkenyl, alkynyl, R^9-cycloalkyl, R^9-cycloalkenyl, R^9-Ay, $C(O)R^7$, $C(S)R^7$, CO_2R^7, $C(O)NR^7R^8$, $C(S)NR^7R^8$, C(O)Ay, C(S)Ay, $C(O)N(R^7)Ay$, $C(S)N(R^7)Ay$, $C(O)R^9$-Ay, $C(S)R^9$-Ay, CO_2-R^9-Ay, $C(O)N(R^7)$-R^9-Ay and $C(S)N(R^7)$-R^9-Ay;

each R^7 and R^8 is the same or different and is each independently selected from H, alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl;
R^9 is alkylene or alkenylene; and
Ay is aryl;
and pharmaceutically acceptable salts and solvates thereof.

In one embodiment, the present invention provides compounds of formula (I) wherein R^1 is selected from -OH, -O-C_{1-3}alkyl, -NH_2, -N(H)C_{1-3}alkyl and -N(C_{1-3}alkyl)C_{1-3}alkyl, or any subset thereof. In one particular embodiment, R^1 is -OH or -NH_2. In one embodiment, R^1 is -OH. In one embodiment, R^1 is -NH_2.

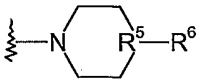
In one embodiment of the present invention, the compounds of formula (I) are defined wherein a is 1, 2 or 3. In one particular embodiment, a is 2.

In one embodiment of the present invention, b is 0.

In one embodiment, the compounds of formula (I) are defined wherein Ring A is phenyl or 5-6 membered heteroaryl containing 1 or 2 N atoms. In one particular embodiment, Ring A is selected from phenyl, pyrrole, imidazole, pyrazole, piperidine, piperazine, pyridine, pyrimidine, pyrazine and morpholine. In one particular embodiment, Ring A is phenyl.

In one embodiment of the present invention, the compounds of formula (I) are defined wherein c is 0, 1 or 2. In one particular embodiment, c is 0.

In one embodiment, the present invention provides compounds of formula (I) wherein each R^2 is the same or different and is independently selected from halo, alkyl, alkenyl, C(O)R^7, CO_2R^7, OR^7 and NR^7R^8, or any subset thereof In one particular embodiment, each R^2 is the same or different and is independently selected from halo, alkyl, OR^7 and NR^7R^8, or any subset thereof.

Specific examples of groups defining R^2 include but are not limited to F, Cl, Br, I, methyl, ethyl, isopropyl, propyl, ethenyl, C(O)H, $C(O)C_{1-3}$alkyl, CO_2H, CO_2C_{1-3}alkyl, OH, OC_{1-3}alkyl, OCF_3, NH_2, $N(H)C_{1-3}$alkyl and $N(C_{1-3}$alkyl$)C_{1-3}$alkyl. More specifically, in one embodiment c is 1 or more and R^2 on ring A is selected from the group consisting of F, Cl, Br, I, methyl, ethyl, isopropyl, propyl, $C(O)C_{1-3}$alkyl, CO_2H, CO_2C_{1-3}alkyl, OH, OC_{1-3}alkyl, NH_2, $N(H)C_{1-3}$alkyl and $N(C_{1-3}$alkyl$)C_{1-3}$alkyl. In one embodiment d is 1 or more and R^2 on N-containing ring, i.e.,  is selected from the group consisting of methyl, ethyl, isopropyl, propyl, ethenyl, $C(O)C_{1-3}$alkyl, CO_2H, CO_2C_{1-3}alkyl, NH_2, $N(H)C_{1-3}$alkyl and $N(C_{1-3}$alkyl$)C_{1-3}$alkyl.

In one embodiment, the compounds of formula (I) are defined wherein each R^3 is the same or different and is independently selected from H, alkyl, alkenyl and cycloalkyl. In one embodiment, each R^3 is the same or different and is independently selected from H and alkyl, more particularly H and C_{1-3}alkyl. In one particular embodiment, each R^3 is the same. In one particular embodiment, each R^3 is the same and is H.

In one embodiment, the compounds of formula (I) are defined wherein each R^4 is the same. In one particular embodiment, the compounds of formula (I) are defined wherein R^4 is O.

In one embodiment of the present invention, d is 0 or 1. In one particular embodiment, d is 0.

In one embodiment of the present invention, R^5 is N or CH. In one particular embodiment R^5 is N.

According to one embodiment of the invention when e is 1, R^6 is selected from H, alkyl, $C(O)R^7$, CO_2R^7, $C(O)NR^7R^8$, C(O)Ay, $C(O)N(R^7)$Ay, $C(O)R^9$-Ay,

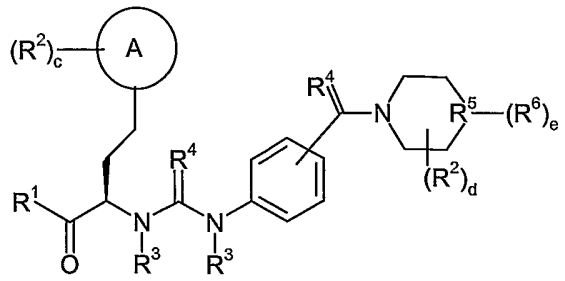
CO_2-R^9-Ay and C(O)N(R^7)-R^9-Ay. In one particular embodiment, R^6 is selected from H, C(O)R^7, CO_2R^7, C(O)NR^7R^8 and CO_2-R^9-Ay.

Specific examples of some groups defining R^6 include but are not limited to H, methyl, ethyl, isopropyl, propyl, ethenyl, C(O)H, C(O)C_{1-3}alkyl, CO_2H, CO_2C_{1-3}alkyl, $C(O)NH_2$, C(O)N(H)C_{1-3}alkyl, C(O)N(C_{1-3}alkyl)C_{1-3}alkyl, C(O)phenyl, C(O)fluorene, C(O)anthracene, C(O)N(H)phenyl, C(O)C_{1-4}alkylene-phenyl, C(O)C_{1-4}alkylene-fluorene, C(O)C_{1-4}alkylene-anthracene, CO_2-phenyl, CO_2-fluorene, CO_2-anthracene, CO_2C_{1-4}alkylene-phenyl, CO_2C_{1-4}alkylene-fluorene, CO_2C_{1-4}alkylene-anthracene, C(O)N(H)C_{1-4}alkylene-phenyl, C(O)N(H)C_{1-4}alkylene-fluorene and C(O)N(H)C_{1-4}alkylene-anthracene. In one particular embodiment, R^6 selected from H, methyl, ethyl, isopropyl, propyl, ethenyl, C(O)H, C(O)C_{1-3}alkyl, $C(O)NH_2$, C(O)N(H)C_{1-3}alkyl, C(O)N(C_{1-3}alkyl)C_{1-3}alkyl, C(O)phenyl, C(O)fluorene, C(O)anthracene, C(O)N(H)phenyl, C(O)C_{1-4}alkylene-phenyl, C(O)C_{1-4}alkylene-fluorene, C(O)C_{1-4}alkylene-anthracene, CO_2C_{1-4}alkylene-phenyl, CO_2C_{1-4}alkylene-fluorene, CO_2C_{1-4}alkylene-anthracene, C(O)N(H)C_{1-4}alkylene-phenyl, C(O)N(H)C_{1-4}alkylene-fluorene and C(O)N(H)C_{1-4}alkylene-anthracene.

In one embodiment of the present invention, each R^7 and R^8 is the same or different and is each independently selected from H, alkyl and cycloalkyl. In one particualr embodiment, each R^7 and R^8 is the same or different and is each independently selected from H and C_{1-3}alkyl.

In one embodiment of the present invention, R^9 is alkylene. In one particular embodiment, R^9 is C_{1-3}alkylene.

In another embodiment, the present invention provides compounds of formula (I-A):



I-A

wherein all variables are as defined above.

It is to be understood that the present invention includes all combinations and subsets of the particular groups defined hereinabove.

Specific compounds of formula (I) include but are not limited to those compounds described in the Example section that follows. Some particular compounds of formula (I) include but are not limited to:

Benzyl 4-{3-[({[(1*R*)-1-(aminocarbonyl)-3-phenylpropyl]amino}carbonyl)-amino]benzoyl}piperazine-1-carboxylate;

Ethyl 4-{3-[({[(1*R*)-1-(aminocarbonyl)-3-phenylpropyl]amino}carbonyl)-amino]benzoyl}piperazine-1-carboxylate;

9*H*-Fluoren-9-ylmethyl 4-{3-[({[(1*R*)-1-(aminocarbonyl)-3-phenylpropyl]-amino}carbonyl)amino]benzoyl}piperazine-1-carboxylate;

(2*R*)-2-{[({3-[(4-Acetylpiperazin-1-yl)carbonyl]phenyl}amino)-carbonyl]amino}-4-phenylbutanamide;

(2R)-4-phenyl-2-[({[3-(1-piperazinylcarbonyl)phenyl]amino}carbonyl)amino]-butanamide;

1,1-dimethylethyl 4-({3-[({[(1R)-1-(aminocarbonyl)-3-phenylpropyl]amino}-carbonyl)amino]phenyl}carbonyl)-1-piperazinecarboxylate;

(2S)-4-phenyl-2-[({[3-(1-piperazinylcarbonyl)phenyl]amino}carbonyl)amino]-butanamide;

1,1-dimethylethyl 4-({3-[({[(1S)-1-(aminocarbonyl)-3-phenylpropyl]amino}-carbonyl)-amino]phenyl}carbonyl)-1-piperazinecarboxylate, and

pharmaceutically acceptable salts, solvates and physiologically functional derivatives thereof.

It will be appreciated by those skilled in the art that the compounds of the present invention may also be utilized in the form of a pharmaceutically acceptable salt or solvate or physiologically functional derivative thereof. The pharmaceutically acceptable salts of the compounds of formula (I) include conventional salts formed from pharmaceutically acceptable inorganic or organic acids or bases as well as quaternary ammonium salts. More specific examples of suitable acid salts include hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, perchloric, fumaric, acetic, propionic, succinic, glycolic, formic, lactic, maleic, tartaric, citric, palmoic, malonic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, fumaric, toluenesulfonic, methanesulfonic (mesylate), naphthalene-2-sulfonic, benzenesulfonic hydroxynaphthoic, hydroiodic, malic, steroic, tannic and the like.

Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable salts. More specific examples of suitable basic salts include sodium, lithium, potassium, magnesium, aluminium, calcium, zinc, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine and procaine salts.

The term "solvate" as used herein refers to a complex of variable stoichiometry formed by a solute (a compound of formula (I)) and a solvent. Solvents, by way of example, include water, methanol, ethanol, or acetic acid.

Processes for preparing pharmaceutically acceptable salts and solvates of the compounds of formula (I) are conventional in the art. *See*, e.g., Burger's Medicinal Chemistry And Drug Discovery 5th Edition, Vol 1: Principles And Practice.

As will be apparent to those skilled in the art, in the processes described below for the preparation of compounds of formula (I), certain intermediates, may be in the form of pharmaceutically acceptable salts or solvates of the compound. Those terms as applied to any intermediate employed in the process of preparing compounds of formula (I) have the same meanings as noted above with respect to compounds of formula (I). Processes for preparing pharmaceutically acceptable salts and solvates of such intermediates are known in the art and are analogous to the process for preparing pharmaceutically acceptable salts and solvates of the compounds of formula (I).

Certain compounds of formula (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms or may exhibit *cis-trans* isomerism). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. In one embodiment of the present invention, the compounds of formula (I) are the D- enantiomers. The present invention also covers the individual isomers of the compounds represented by formula (I) as mixtures with isomers thereof in which one or more chiral centres are inverted. Certain compounds of formula (I) may be prepared as a mixture of regioisomers. The present invention covers both the mixture of regioisomers as well as the individual compounds. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

The compounds of the present invention are typically inhibitors of PLK. By PLK inhibitor is meant a compound which exhibits pIC_{50} greater than 4 in the PLK Inhibition assay described below in the examples; more particularly a PLK inhibitor is a compound which exhibits a pIC_{50} greater than 5 using the methods described in the examples below.

The present invention further provides compounds of formula (I) for use in medical therapy in an animal, e.g. a mammal such as a human. In particular, the present invention provides compounds of formula (I) for use in the treatment of a condition mediated by PLK. The present invention also provides compounds of formula (I) for use in the treatment of a susceptible neoplasm. The present invention provides compounds of formula (I) for use in treating a condition characterized by inappropriate cellular proliferation. The present invention also provides compounds of formula (I) for use in inhibiting proliferation of a cell. The present invention also provides compounds of formula (I) for use in inhibiting mitosis in a cell.

The present invention provides methods for the treatment of several conditions or diseases, all of which comprise the step of administering a therapeutically effective amount of a compound of formula (I). As used herein, the term "treatment" refers to alleviating the specified condition, eliminating or reducing the symptoms of the condition, slowing or eliminating the progression of the condition and preventing or delaying the reoccurrance of the condition in a previously afflicted subject.

As used herein, the term "therapeutically effective amount" means an amount of a compound of formula (I) which is sufficient, in the subject to which it is administered, to elicit the biological or medical response of a cell culture, tissue, system, animal (including human) that is being sought, for instance, by a researcher or clinician. For example, a therapeutically effective amount of a compound of formula (I) for the treatment of a condition mediated by PLK is an amount sufficient to treat the PLK mediated condition in the subject. Similarly, a therapeutically effective amount of a compound of formula (I) for the treatment of a susceptible neoplasm is an amount sufficient to treat the susceptible neoplasm in the subject. In one embodiment of the present invention, the therapeutically effective amount of a compound of formula (I) is an amount sufficient to inhibit cell mitosis. In one embodiment of the present

invention, a therapeutically effective amount of a compound of formula (I) is an amount sufficient to regulate, modulate, bind or inhibit PLK.

The precise therapeutically effective amount of the compounds of formula (I) will depend on a number of factors including, but not limited to, the age and weight of the subject being treated, the precise disorder requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physcian or veternarian. Typically, the compound of formula (I) will be given for treatment in the range of 0.1 to 200 mg/kg body weight of recipient (animal) per day and more usually in the range of 1 to 100 mg/kg body weight per day. Acceptable daily dosages, may be from about 0.1 to about 2000 mg/day, and preferably from about 0.1 to about 100 mg/day.

As one aspect, the present invention provides methods of regulating, modulating, binding, or inhibiting PLK for the treatment of conditions mediated by PLK. "Regulating, modulating, binding or inhibiting PLK" refers to regulating, modulating, binding or inhibiting PLK activity, as well as regulating, modulating, binding or inhibiting overexpression of PLK. Such conditions include certain neoplasms (including cancers and tumors) which have been associated with PLK and conditions characterized by inappropriate cellular proliferation.

The present invention provides a method for treating a condition mediated by PLK in an animal such as a mammal (e.g., a human), which method comprises administering to the animal a therapeutically effective amount of the compound of formula (I). Conditions which are mediated by PLK are known in the art and include but are not limited to neoplasms and conditions characterized by inappropriate cellular proliferation.

The present invention also provides a method for treating a susceptible neoplasm (cancer or tumor) in an animal such as a mammal (e.g., a human),

which method comprises administering to the animal a therapeutically effective amount of the compound of formula (I). "Susceptible neoplasm" as used herein refers to neoplasms which are susceptible to treatment with a PLK inhibitor. Neoplasms which have been associated with PLK and are therefor susceptible to treatment with a PLK inhibitor are known in the art, and include both primary and metastatic tumors and cancers. For example, susceptible neoplasms within the scope of the present invention include but are not limited to breast cancer, colon cancer, lung cancer (including small cell lung cancer and non-small cell lung cancer), prostate cancer, lymphoma, leukemia, endometrial cancer, melanoma, ovarian cancer, pancreatic cancer, squamous carcinoma, carcinoma of the head and neck, and esophageal carcinoma. The compounds of formula (I) can be used alone in the treatment of such susceptible neoplasms or can be used to provide additive or synergistic effects with certain existing chemotherapies, and/or be used to restore effectiveness of certain existing chemotherapies and radiation.

The present invention also provides a method for treating a condition characterized by inappropriate cellular proliferation. By "inapproriate cellular proliferation" is meant cellular proliferation resulting from inappropriate cell growth, cellular proliferation resulting from excessive cell division, cellular proliferation resulting from cell division at an accelerated rate, cellular proliferation resulting from inappropriate cell survival, and/or cellular proliferation in a normal cell occurring at a normal rate, which is neverthless undesired. Conditions characterized by inappropriate cellular proliferation include but are not limited to neoplasms, blood vessel proliferative disorders, fibrotic disorders, mesangial cell proliferative disorders and metabolic diseases. Blood vessel proliferative disorders include arthritis and restenosis. Fibrotic disorders include hepatic cirrhosis and atherosclerosis. Mesangial cell proliferative disorders include glomerulonephritis, malignant nephrosclerosis, thrombotic microangiopathy syndromes, organ transplant rejection and glomerulopathies. Metabolic disorders include psoriasis, chronic wound healing, inflammation and neurodegenerative diseases. Osteoarthritis

and other osteoclast proliferation dependent diseases of excess bone resorbtion are examples of conditions characterized by inapproprate cellular proliferation in which the cellular proliferation occurs in normal cells at a normal rate, but is nevertheless undesired.

The present invention also provides a method for inhibiting proliferation of a cell, which method comprises contacting the cell with an amount of a compound of formula (I) sufficient to inhibit proliferation of the cell. In one particular embodiment, the cell is a neoplastic cell. In one particular embodiment, the cell is an inappropriately proliferative cell. The term "inappropriately proliferative cell" as used herein refers to cells that grow inappropriately (abnormally), cells that divide excessively or at an accelerated rate, cells that inappropriately (abnormally) survive and/or normal cells that proliferate at a normal rate but for which proliferation is undesired. Neoplastic cells (including cancer cells) are an example of inappropriately proliferative cells but are not the only inappropriately proliferative cells.

PLK is essential for cellular mitosis and accordingly, the compounds of formula (I) are effective for inhibiting mitosis. "Inhibiting mitosis" refers to inhibiting the entry into the M phase of the cell cycle, inhibiting the normal progression of the M phase of the cell cycle once M phase has been entered and inhibiting the normal exit from the M phase of the cell cycle. Thus, the compounds of the present invention may inhibit mitosis by inhibiting the cell's entry into mitosis, by inhibiting the cell's progression through mitosis or by inhibiting the cell's exit from mitosis. As one aspect, the present invention provides a method for inhibiting mitosis in a cell, which method comprises administering to the cell an amount of a compound of formula (I) sufficient to inhibit mitosis. In one particular embodiment, the cell is a neoplastic cell. In one particular embodiment, the cell is an inappropriately proliferative cell.

The present invention also provides the use of a compound of formula (I) for the preparation of a medicament for the treatment of condition mediated by

PLK in an animal, such as a mammal (e.g., a human). The present invention further provides the use of a compound of formula (I) for the preparation of a medicament for the treatment of a susceptible neoplasm in an animal. The present invention further provides the use of a compound of formula (I) for the preparation of a medicament for the treatment of a condition characterized by inappropriate cellular proliferation. The present invention further provides the use of a compound of formula (I) for the preparation of a medicament for inhibiting proliferation of a cell. The present invention further provides the use of a compound of formula (I) for the preparation of a medicament for inhibiting mitosis in a cell.

While it is possible that, for use in therapy, a therapeutically effective amount of a compound of formula (I) may be administered as the raw chemical, it is typically presented as the active ingredient of a pharmaceutical composition or formulation. Accordingly, the invention further provides a pharmaceutical composition comprising a compound of the formula (I). The pharmaceutical composition may further comprise one or more pharmaceutically acceptable carriers, diluents, and/or excipients. The carrier(s), diluent(s) and/or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of the formula (I) with one or more pharmaceutically acceptable carriers, diluents and/or excipients.

Pharmaceutical formulations may be presented in unit dose form containing a predetermined amount of active ingredient per unit dose. Such a unit may contain a therapeutically effective dose of the compound of formula (I) or a fraction of a therapeutically effective dose such that multiple unit dosage forms might be administered at a given time to achieve the desired therapeutically effective dose. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an

appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules are made by preparing a powder mixture as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of active ingredient. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle.

Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The compounds of formula (I) can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of formula (I) may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include peptides, polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide - phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone,

polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in *Pharmaceutical Research,* **3(6)**:318 (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurised aerosols, nebulizers or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

In the above-described methods of treatment and uses, a compound of formula (I) may be employed alone, in combination with one or more other compounds of formula (I) or in combination with other therapeutic agents. In particular, in methods of treating conditions mediated by PLK and methods of treating susceptible neoplasms, combination with other chemotherapeutic, hormonal and/or antibody agents is envisaged as well as combination with surgical therapy and radiotherapy. The term "chemotherapeutic" as used herein refers to any chemical agent having a therapeutic effect on the subject to which it is administered. "Chemotherapeutic" agents include but are not limited to anti-neoplastic agents, analgesics and anti-emetics. As used herein, "anti-neoplastic agents" include both cytostatic and cytotoxic agents. Combination therapies according to the present invention thus comprise the administration of at least one compound of formula (I) and the use of at least one other cancer treatment method. In one embodiment, combination therapies according to the present invention comprise the administration of at least one compound of formula (I) and at least one other chemotherapeutic agent. In one particular embodiment, the present invention comprises the administration of at least one compound of formula (I) and at least one anti-neoplastic agent. As an additional aspect, the present invention provides the methods of treatment and uses as described above, which comprise administering a compound of formula (I) together with at least one chemotherapeutic agent. In one particular embodiment, the chemotherapeutic agent is an anti-neoplastic agent. In another embodiment, the present invention provides a pharmaceutical composition as described above further comprising at least one other chemotherapeutic agent, more particularly, the chemotherapeutic agent is an anti-neoplastic agent.

Typically, any chemotherapeutic agent that has activity versus a susceptible neoplasm being treated may be utilized in combination with the compounds of formula (I), provided that the particular agent is clinically compatible with therapy employing a compound of formula (I). Typical anti-neoplastic agents useful in the present invention include, but are not limited to, anti-microtubule

agents such as diterpenoids and vinca alkaloids; platinum coordination complexes; alkylating agents such as nitrogen mustards, oxazaphosphorines, alkylsulfonates, nitrosoureas, and triazenes; antibiotic agents such as anthracyclins, actinomycins and bleomycins; topoisomerase II inhibitors such as epipodophyllotoxins; antimetabolites such as purine and pyrimidine analogues and anti-folate compounds; topoisomerase I inhibitors such as camptothecins; hormones and hormonal analogues; signal transduction pathway inhibitors; non-receptor tyrosine kinase angiogenesis inhibitors; immunotherapeutic agents; proapoptotic agents; and cell cycle signaling inhibitors.

Anti-microtubule or anti-mitotic agents are phase specific agents active against the microtubules of tumor cells during M or the mitosis phase of the cell cycle. Examples of anti-microtubule agents include, but are not limited to, diterpenoids and vinca alkaloids. Examples of diterpenoids include, but are not limited to, paclitaxel and its analog docetaxel. Examples of vinca alkaloids include, but are not limited to, vinblastine, vincristine, and vinorelbine.

Platinum coordination complexes are non-phase specific anti-neoplastic agents, which are interactive with DNA. The platinum complexes enter tumor cells, undergo, aquation and form intra- and interstrand crosslinks with DNA causing adverse biological effects to the tumor. Examples of platinum coordination complexes include, but are not limited to, cisplatin and carboplatin.

Alkylating agents are non-phase anti-neoplastic specific agents and strong electrophiles. Typically, alkylating agents form covalent linkages, by alkylation, to DNA through nucleophilic moieties of the DNA molecule such as phosphate, amino, and hydroxyl groups. Such alkylation disrupts nucleic acid function leading to cell death. Examples of alkylating agents include, but are not limited to, nitrogen mustards such as cyclophosphamide, melphalan,

and chlorambucil; alkyl sulfonates such as busulfan; nitrosoureas such as carmustine; and triazenes such as dacarbazine.

Antibiotic chemotherapeutic agents are non-phase specific agents, which bind or intercalate with DNA. Typically, such action results in stable DNA complexes or strand breakage, which disrupts ordinary function of the nucleic acids leading to cell death. Examples of antibiotic anti-neoplastic agents include, but are not limited to, actinomycins such as dactinomycin, anthrocyclins such as daunorubicin and doxorubicin; and bleomycins.

Topoisomerase II inhibitors include, but are not limited to, epipodophyllotoxins. Epipodophyllotoxins are phase specific anti-neoplastic agents derived from the mandrake plant. Epipodophyllotoxins typically affect cells in the S and G_2 phases of the cell cycle by forming a ternary complex with topoisomerase II and DNA causing DNA strand breaks. The strand breaks accumulate and cell death follows. Examples of epipodophyllotoxins include, but are not limited to, etoposide and teniposide.

Antimetabolite neoplastic agents are phase specific anti-neoplastic agents that act at S phase (DNA synthesis) of the cell cycle by inhibiting DNA synthesis or by inhibiting purine or pyrimidine base synthesis and thereby limiting DNA synthesis. Consequently, S phase does not proceed and cell death follows. Examples of antimetabolite anti-neoplastic agents include, but are not limited to, fluorouracil, methotrexate, cytarabine, mecaptopurine and thioguanine.

Camptothecins, including, camptothecin and camptothecin derivatives are available or under development as Topoisomerase I inhibitors. Camptothecins cytotoxic activity is believed to be related to its Topoisomerase I inhibitory activity. Examples of camptothecins include, but are not limited to irinotecan, topotecan, and the various optical forms of 7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20-camptothecin.

Hormones and hormonal analogues are useful compounds for treating cancers in which there is a relationship between the hormone(s) and growth and/or lack of growth of the cancer. Examples of hormones and hormonal analogues believed to be useful in the treatment of neoplasms include, but are not limited to, adrenocorti-costeroids such as prednisone and prednisolone which are useful in the treatment of malignant lymphoma and acute leukemia in children; aminoglutethimide and other aromatase inhibitors such as anastrozole, letrazole, vorazole, and exemestane useful in the treatment of adrenocortical carcinoma and hormone dependent breast carcinoma containing estrogen receptors; progestrins such as megestrol acetate useful in the treatment of hormone dependent breast cancer and endometrial carcinoma; estrogens, androgens, and anti-androgens such as flutamide, nilutamide, bicalutamide, cyproterone acetate and 5α-reductases such as finasteride and dutasteride, useful in the treatment of prostatic carcinoma and benign prostatic hypertrophy; anti-estrogens such as tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene useful in the treatment of hormone dependent breast carcinoma; and gonadotropin-releasing hormone (GnRH) and analogues thereof which stimulate the release of leutinizing hormone (LH) and/or follicle stimulating hormone (FSH) for the treatment prostatic carcinoma, for instance, LHRH agonists and antagagonists such as goserelin acetate and luprolide.

Signal transduction pathway inhibitors are those inhibitors which block or inhibit a chemical process which evokes an intracellular change. As used herein this change is cell proliferation or differentiation. Signal tranduction inhibitors useful in the present invention include inhibitors of receptor tyrosine kinases, non-receptor tyrosine kinases, SH2/SH3 domain blockers, serine/threonine kinases, phosphotidyl inositol-3 kinases, myo-inositol signaling, and Ras oncogenes.

Several protein tyrosine kinases catalyse the phosphorylation of specific tyrosyl residues in various proteins involved in the regulation of cell growth.

Such protein tyrosine kinases can be broadly classified as receptor or non-receptor kinases.

Receptor tyrosine kinases are transmembrane proteins having an extracellular ligand binding domain, a transmembrane domain, and a tyrosine kinase domain. Receptor tyrosine kinases are involved in the regulation of cell growth and are sometimes termed growth factor receptors. Inappropriate or uncontrolled activation of many of these kinases, i.e. aberrant kinase growth factor receptor activity, for example by over-expression or mutation, has been shown to result in uncontrolled cell growth. Accordingly, the aberrant activity of such kinases has been linked to malignant tissue growth. Consequently, inhibitors of such kinases could provide cancer treatment methods. Growth factor receptors include, for example, epidermal growth factor receptor (EGFr, ErbB2 and ErbB4,), platelet derived growth factor receptor (PDGFr), vascular endothelial growth factor receptor (VEGFR), tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains (TIE-2), insulin growth factor-I receptor (IGF-I), macrophage colony stimulating factor (cfms), BTK, ckit, cmet, fibroblast growth factor (FGF) receptors, Trk receptors (TrkA, TrkB, and TrkC), ephrin (eph) receptors, and the RET protooncogene. Several inhibitors of growth factor receptors are under development and include ligand antagonists, antibodies, tyrosine kinase inhibitors, anti-sense oligonucleotides and aptamers. Growth factor receptors and agents that inhibit growth factor receptor function are described, for instance, in Kath, John C., Exp. Opin. Ther. Patents (2000) 10(6):803-818; Shawver et al DDT Vol 2, No. 2 February 1997; and Lofts, F. J. et al, "Growth Factor Receptors as Targets", New Molecular Targets for Cancer Chemotherapy, Ed. Workman, Paul and Kerr, David, CRC Press 1994, London.

Tyrosine kinases, which are not growth factor receptor kinases are termed non-receptor tyrosine kinases. Non-receptor tyrosine kinases useful in the present invention, which are targets or potential targets of anti-neoplastic

drugs, include cSrc, Lck, Fyn, Yes, Jak, cAbl, FAK (Focal adhesion kinase), Brutons tyrosine kinase, and Bcr-Abl. Such non-receptor kinases and agents which inhibit non-receptor tyrosine kinase function are described in Sinh, S. and Corey, S.J., (1999) Journal of Hematotherapy and Stem Cell Research 8 (5): 465 - 80; and Bolen, J.B., Brugge, J.S., (1997) Annual Review of Immunology. 15: 371-404.

SH2/SH3 domain blockers are agents that disrupt SH2 or SH3 domain binding in a variety of enzymes or adaptor proteins including, PI3-K p85 subunit, Src family kinases, adaptor molecules (Shc, Crk, Nck, Grb2) and Ras-GAP. SH2/SH3 domains as targets for anti-cancer drugs are discussed in Smithgall, T.E. (1995), Journal of Pharmacological and Toxicological Methods. 34(3) 125-32.

Inhibitors of Serine/Threonine Kinases including MAP kinase cascade blockers which include blockers of Raf kinases (Rafk), Mitogen or Extracellular Regulated Kinase (MEKs), and Extracellular Regulated Kinases (ERKs); and Protein kinase C family member blockers including blockers of subtypes of PKCs (alpha, beta, gamma, epsilon, mu, lambda, iota, zeta), IkB kinase family (IKKa, IKKb), PKB family kinases, Akt kinase family members, and TGF beta receptor kinases. Such Serine/Threonine kinases and inhibitors thereof are described in Yamamoto, T., Taya, S., Kaibuchi, K., (1999), Journal of Biochemistry. 126 (5) 799-803; Brodt, P, Samani, A., and Navab, R. (2000), Biochemical Pharmacology, 60. 1101-1107; Massague, J., Weis-Garcia, F. (1996) Cancer Surveys. 27:41-64; Philip, P.A., and Harris, A.L. (1995), Cancer Treatment and Research. 78: 3-27, Lackey, K. et al Bioorganic and Medicinal Chemistry Letters, (10), 2000, 223-226; and Martinez-Iacaci, L., et al, Int. J. Cancer (2000), 88(1), 44-52.

Inhibitors of Phosphotidyl Inositol-3 Kinase family members including blockers of PI3-kinase, ATM, DNA-PK, and Ku are also useful in combination with the present invention. Such kinases are discussed in Abraham, R.T. (1996),

Current Opinion in Immunology. 8 (3) 412-8; Canman, C.E., Lim, D.S. (1998), Oncogene 17 (25) 3301-3308; Jackson, S.P. (1997), International Journal of Biochemistry and Cell Biology. 29 (7):935-8; and Zhong, H. et al, Cancer Res, (2000) 60(6), 1541-1545.

Also useful in combination with the present invention are Myo-inositol signaling inhibitors such as phospholipase C blockers and Myoinositol analogues. Such signal inhibitors are described in Powis, G., and Kozikowski A., (1994) New Molecular Targets for Cancer Chemotherapy ed., Paul Workman and David Kerr, CRC Press 1994, London.

Another group of signal transduction pathway inhibitors useful in combination with the present invention are inhibitors of Ras Oncogene. Such inhibitors include inhibitors of farnesyltransferase, geranyl-geranyl transferase, and CAAX proteases as well as anti-sense oligonucleotides, ribozymes and immunotherapy. Such inhibitors have been shown to block Ras activation in cells containing wild type mutant Ras , thereby acting as antiproliferation agents. Ras oncogene inhibition is discussed in Scharovsky, O.G., Rozados, V.R., Gervasoni, S.I. Matar, P. (2000), Journal of Biomedical Science. 7(4) 292-8; Ashby, M.N. (1998), Current Opinion in Lipidology. 9(2)99-102; and BioChim. Biophys. Acta, (1989) 1423(3):19-30.

As mentioned above, antibodies to receptor kinase ligand binding may also serve as signal transduction inhibitors. This group of signal transduction pathway inhibitors includes the use of humanized antibodies to the extracellular ligand binding domain of receptor tyrosine kinases. For example, Imclone C225 EGFR specific antibody (see Green, M.C. et al, Monoclonal Antibody Therapy for Solid Tumors, Cancer Treat. Rev., (2000), 26(4), 269-286); Herceptin® ErbB2 antibody (see Tyrosine Kinase Signaling in Breast Cancer:ErbB Family Receptor Tyrosine Kinases, Breast Cancer Res., 2000, 2(3), 176-183); and 2CB VEGFR2 specific antibody (see Brekken, R.A. et al,

Selective Inhibition of VEGFR2 Activity by a Monoclonal Anti-VEGF Antibody Blocks Tumor Growth in Mice, Cancer Res. (2000) 60, 5117-5124).

Receptor kinase angiogenesis inhibitors may also find use in the present invention. Inhibitors of angiogenesis related VEGFR and TIE2 are discussed above in regard to signal transduction inhibitors (both receptors are receptor tyrosine kinases). Other inhibitors may be used in combination with the compounds of the present invention. For example, anti-VEGF antibodies, which do not recognize VEGFR (the receptor tyrosine kinase), but bind to the ligand; small molecule inhibitors of integrin ($alpha_v$ $beta_3$) that will inhibit angiogenesis; endostatin and angiostatin (non-RTK) may also prove useful in combination with PLK inhibitors.

Agents used in immunotherapeutic regimens may also be useful in combination with the compounds of formula (I).

Agents used in proapoptotic regimens (e.g., bcl-2 antisense oligonucleotides) may also be used in the combination of the present invention. Members of the Bcl-2 family of proteins block apoptosis. Upregulation of bcl-2 has therefore been linked to chemoresistance. Studies have shown that the epidermal growth factor (EGF) stimulates anti-apoptotic members of the bcl-2 family (i.e., mcl-1). Therefore, strategies designed to downregulate the expression of bcl-2 in tumors have demonstrated clinical benefit and are now in Phase II/III trials, namely Genta's G3139 bcl-2 antisense oligonucleotide. Such proapoptotic strategies using the antisense oligonucleotide strategy for bcl-2 are discussed in Water JS et al., *J. Clin. Oncol.* **18**:1812-1823 (2000); and Kitada S et al., *Antisense Res. Dev.* **4**:71-79 (1994).

Cell cycle signaling inhibitors inhibit molecules involved in the control of the cell cycle. Cyclin dependent kinases (CDKs) and their interaction cyclins control progression through the eukaryotic cell cycle. The coordinated activation and inactivation of different cyclin/CDK complexes is necessary for

normal progression through the cell cycle. Several inhibitors of cell cycle signaling are under development. For instance, examples of cyclin dependent kinases, including CDK2, CDK4, and CDK6 and inhibitors for the same are described in, for instance, Rosania, et al., *Exp. Opin. Ther. Patents* **10(2)**:215-230 (2000).

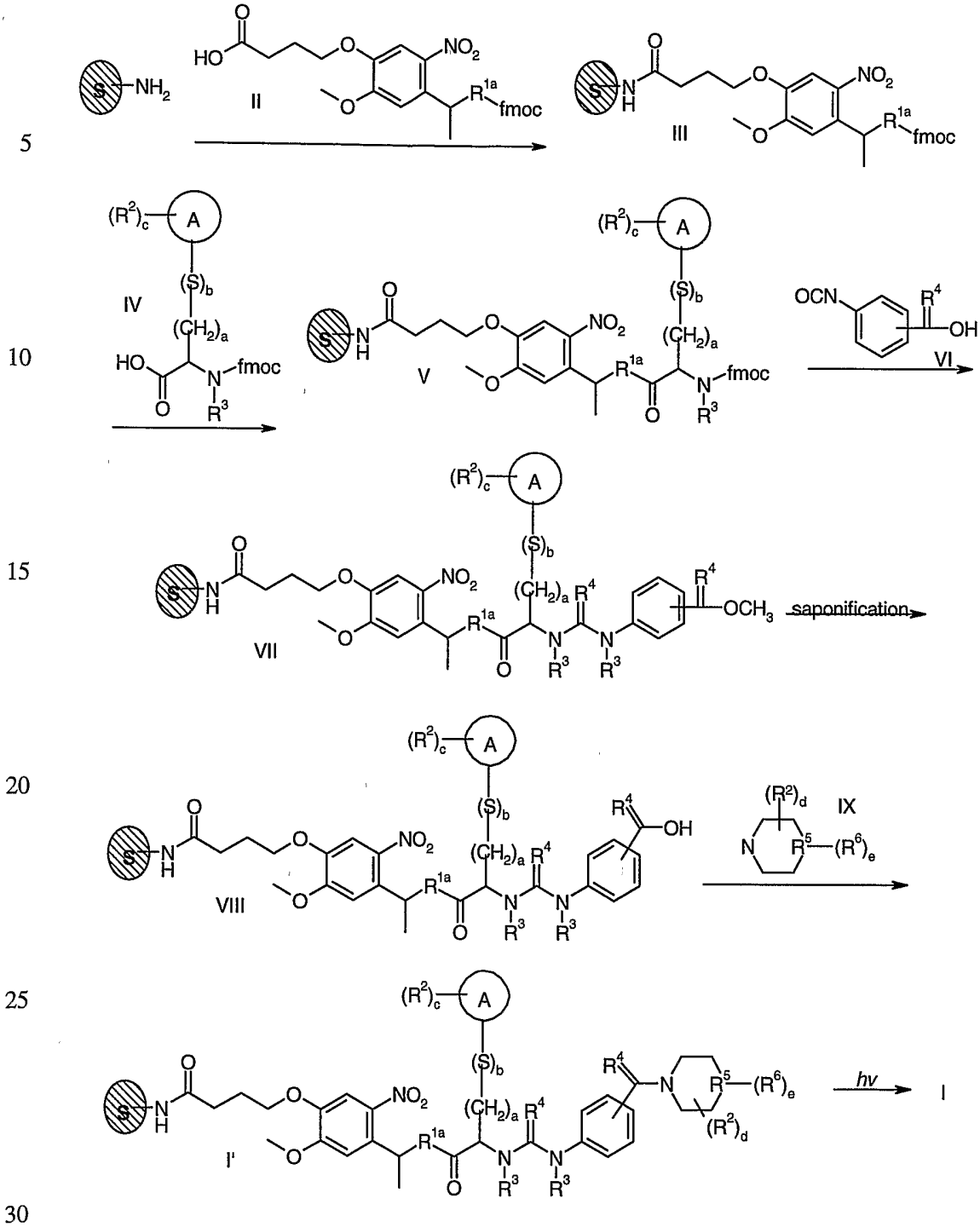
In one embodiment, the methods of the present invention comprise administering to the animal a compound of formula (I) in combination with a signal transduction pathway inhibitor, particularly gefitinib (IRESSA®).

The methods and uses employing these combinations may comprise the administration of the compound of formula (I) and the other chemotherapeutic/anti-neoplastic agent either sequentially in any order or simultaneously in separate or combined pharmaceutical compositions. When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation and may be formulated for administration. When formulated separately they may be provided in any convenient formulation, in such a manner as are known for such compounds in the art.

When a compound of formula (I) is used in combination with a chemotherapeutic agent, the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art. The appropriate dose of the compound(s) of formula (I) and the other therapeutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect, and are within the expertise and discretion of the attendent clinician.

Compounds of formula (I) may be conveniently prepared by the methods outlined in Scheme 1 below.

Scheme 1



wherein:

R^{1a} is selected from -O- and -N(R^7)-

a is 1-6;

b is 0 or 1;

Ring A is phenyl or 5-6 membered heterocycle or heteroaryl containing 1 or 2 N atoms;

c is 0-4;

each R^2 is the same or different and is independently selected from halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, $C(O)R^7$, $C(S)R^7$, CO_2R^7, $CONR^7R^8$, $CSNR^7R^8$, OR^7, SR^7, SO_2R^7 and NR^7R^8;

each R^3 is the same or different and is independently selected from H, alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl;

each R^4 is the same or different and is independently selected from S and O;

d is 0-4;

R^5 is N, O, S or CH;

e is 0 when R^5 is O or S and e is 1 when R^5 is N or CH;

R^6 is selected from H, alkyl, alkenyl, alkynyl, R^9-cycloalkyl, R^9-cycloalkenyl, R^9-Ay, $C(O)R^7$, $C(S)R^7$, CO_2R^7, $C(O)NR^7R^8$, $C(S)NR^7R^8$, C(O)Ay, C(S)Ay, $C(O)N(R^7)Ay$, $C(S)N(R^7)Ay$, $C(O)R^9$-Ay, $C(S)R^9$-Ay, CO_2-R^9-Ay, $C(O)N(R^7)$-R^9-Ay and $C(S)N(R^7)$-R^9-Ay;

each R^7 and R^8 is the same or different and is each independently selected from H, alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl;

R^9 is alkylene or alkenylene;

Ay is aryl;

fmoc is *N*-(9-Fluorenylmethoxycarbonyl); and

 represents a solid support.

In general the process is a solid-phase synthesis carried out using a solid support such as an encoded bead or a lantern, and comprises the steps of:

a) reacting solid support with a protected compound of formula (II) to prepare a solid support-bound compound of formula (III);

b) deprotecting the solid support-bound compound of formula (III) and reacting the deprotected, solid support-bound compound of formula (III)

with a protected compound of formula (IV) to prepare a solid support-bound compound of formula (V);

c) deprotecting the solid support-bound compound of formula (V) and reacting the deprotected, solid support-bound compound of formula (V) with a compound of formula (VI) to prepare a solid support-bound compound of formula (VII);

d) saponifying the the solid support-bound compound of formula (VII) to prepare a solid support-bound compound of formula (VIII);

e) reacting the solid support-bound compound of formula (VIII) with a compound of formula (IX) to prepare a solid support-bound compound of formula (I); and

f) isolating the compound of formula (I).

More particularly, a compound of formula (I) may be prepared by isolating the compound from the solid support by cleaving the solid support-bound compound of formula (I) from the substrate using conventional techniques such as photo-cleavage by illumination with >350 nm UV light. C. P. Holmes and D. G. Jones, J. Org. Chem., 1995, 60, 2318-2319.

The solid support-bound compound of formula (I) is prepared by using solid phase synthesis to react a solid support-bound compound of formula (VIII) with a compound of formula (IX). Typically, the reaction is carried out in the presence of suitable coupling agent(s) capable of facilitating amide bond formation. Such coupling agents are well known in the art. Specific examples of suitable coupling agents include but are not limited to 1-hydroxybenzotriazole (0.70 g, 4.5 mmol), 1,3-diisopropylcarbo-diimide. The reaction may be carried out in a suitable solvent such as, for example dimethylformamide (DMF), dimethylsulphoxide (DMSO), N-methylpyrrolidone (NMP), dichloromethane (DCM) and mixtures thereof. Compounds of formula (IX) are commercially available or my be synthesized using conventional materials and techniques.

The solid support-bound compound of formula (VIII) can be prepared by saponifying a solid support-bound compound of formula (VII). The solid support-bound compound of formula (VII) is reacted with a suitable saponifying agent such as lithium hydroxide (LiOH), typically will stirring. The reaction may be carried out in a polar solvent such as p-dioxane or tetrahydrofuran (THF).

The solid support-bound compound of formula (VII) may be prepared by reacting a solid support-bound and deprotected compound of formula (V) with a compound of formula (VI). The solid support-bound and deprotected compound of formula (V) is reacted with a solution of the compound of formula (VI) in a suitable solvent. Suitable solvents include but are not limited to dichloromethane (DCM). The fmoc protecting group may be removed from the solid-support bound compound of formula (V) using conventional deprotection techniques such as reaction with suitable base (e.g., piperidine). The compounds of formula (VI) are commercially available or may be prepared using conventional materials and techniques.

The solid support-bound compound of formula (V) may be prepared by reacting a solid support-bound and deprotected compound of formula (III) with a compound of formula (IV). This reaction is carried out using the same general procedures described above for the deprotection of the solid support-bound compound of formula (V) and the reaction of the solid support-bound compound of formula (VIII) with the compound of formula (IX). The protected compounds of formula (IV) are commercially available or may be prepared using conventional materials and techniques.

The solid support-bound compound of formula (III) may be prepared by reacting a substrate with a protected compound of formula (II). Suitable substrates include encoded beads such as encoded peptide substrates and lanterns, such as Mimotopes SynPhase crowns. Examples of encoded beads are commercially available. One such encoded bead is available from

ChemCodes, Inc. of Durham, North Carolina. Other examples of suitable encoded beads are described in M. Geyson, et al., Nature Reviews Drug Discovery, 2003, 2, 222-230. Lanterns are also commercially available. The protected compounds of formula (II) are commercially available or may be prepared using conventional materials and techniques. C. P. Holmes and D. G. Jones, J. Org. Chem., 1995, 60, 2318-2319.

The present invention also provides radiolabeled compounds of formula (I) and biotinylated compounds of formula (I) and solid-support-bound versions thereof. Radiolabeled compounds of formula (I) and biotinylated compounds of formula (I) can be prepared using conventional techniques. For example, radiolabeled compounds of formula (I) can be prepared by reacting the compound of formula (I) with tritium gas in the presence of an appropriate catalyst to produce radiolabeled compounds of formula (I).

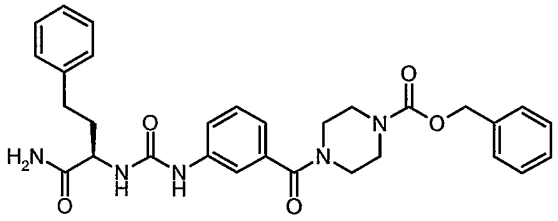
In one embodiment, the compounds of formula (I) are tritiated.

The radiolabeled compounds of formula (I) and biotinylated compounds of formula (I) are useful in assays for the identification of compounds which inhibit PLK, for the identification of compounds for the treatment of a condition mediated by PLK, for the treatment of susceptible neoplasms, for the treatment of conditions characterized by inappropriate proliferation, for the inhibition of proliferation of a cell and for the inhitibion of mitosis in a cell. Accordingly, the present invention provides an assay method for identifying such compounds, which method comprises the step of specifically binding the radiolabeled compound of formula (I) or the biotinylated compound of formula (I) to the target protein or cellular homogenates. More specifically, suitable assay methods will include competition binding assays. The radiolabeled compounds of formula (I) and biotinylated compounds of formula (I) and solid-support-bound verstions thereof, can be employed in assays according to the methods conventional in the art.

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way, the invention being defined by the claims which follow.

Reagents are commercially available or are prepared according to procedures in the literature.

Example 1: Benzyl 4-{3-[({[(1*R*)-1-(aminocarbonyl)-3-phenylpropyl]amino}carbonyl)amino]benzoyl}piperazine-1-carboxylate

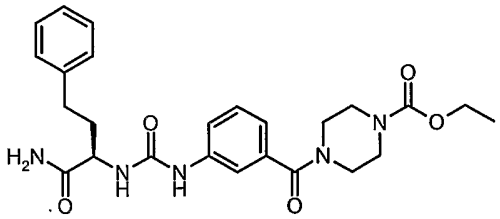


Mimotopes SynPhase™, D-Series Lanterns (50 used: 35micromoles per lantern, 1.75 mmoles total) with the Rink Amide linker (Fmoc protected) are soaked in dimethylformamide (DMF) (30 mL) for 30 minutes then drained. The lanterns are treated with a solution of 20% piperidine/DMF (30 mL) for 30 minutes, then washed with DMF (30 mL x 6). The lanterns are then treated with DMF (30 mL), Fmoc-D-Homophenylalanine-OH (2.80 g, 7.0 mmol), 1-hydroxybenzotriazole (2.2 g, 14.0 mmol) and 1,3-diisopropylcarbodiimide (2.2 mL, 14.0 mmol) and shaken for 18 hrs, then washed with DMF (30 mL x 6), methanol (MeOH) (30 mL x 3) and dichloromethane (DCM) (30 mL x 2). The lanterns are then treated with a solution of 20% piperidine/DMF (30 mL) for 30 minutes, then washed with DMF (30 mL x 6) and DCM (30 mL x 6). The lanterns are then treated with DCM (30 mL) and methyl-3-isocyanatobenzoate (2.0 g, 11.3 mmol) and shaken for 16 hrs, then washed with DCM (30 mL x 3), DMF (30 mL x 3), and DCM (30 mL x 3) and dried under high vacuum. The lanterns are then soaked in tetrahydrofuran (THF) (30 mL) for 15 mins, drained, then treated with 1M LiOH in 4:1 THF/H_2O (50 mL) and shaken for 72 hrs. The lanterns are then washed with 1:1 THF/H_2O (30 mL x 3), 1:1:1

THF/H_2O/1.0 M HCl in Et_2O (30 mL x 3), 1:1 THF/H_2O (30 mL x 2) and THF (30 mL x 3).

Three of the lanterns (0.105 mmol) are then treated with DMF (3 mL), benzyl 1-piperazine carboxylate (330 mg, 1.50 mmol), 1-hydroxybenzotriazole (350 mg, 2.25 mmol) and 1,3-diisopropylcarbodiimide (0.36 mL, 2.25 mmol) and shaken for 23 hrs, then washed with DMF (30 mL x 3), MeOH (30 mL x 3) and DCM (30 mL x 3). The lanterns are then treated with 9:1 trifluoroacetic acid (TFA)/H_2O (10 mL) for 1 hr. The lanterns are removed from the TFA/H_2O solution and the solution is concentrated under vacuum to give an oil that is purified by PREP reverse-phase HPLC and lyopholization to give benzyl 4-{3-[({[(1*R*)-1-(aminocarbonyl)-3-phenylpropyl]amino}carbonyl)amino]-benzoyl}piperazine-1-carboxylate (21 mg, 37%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (s, 1H), 7.55 (m, 2H), 7.24-7.37 (m, 9H), 7.13-7.19 (m, 4H), 6.91 (d, J = 7.32 Hz, 1H), 6.53-6.58 (m, 1H), 5.09 (s, 2H), 4.19-4.25 (m, 1H), 3.35-3.65 (m, 8H), 2.55-2.60 (m, 2H), 1.90-2.01 (m, 1H), 1.75-1.85 (m, 1H). MS m/z 543 (M+1).

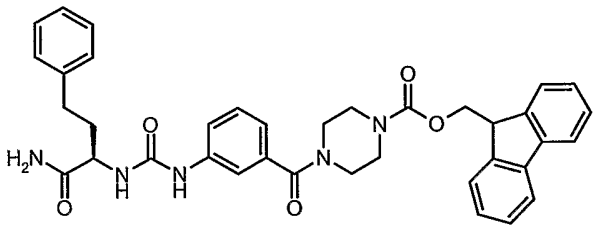
Example 2: Ethyl 4-{3-[({[(1*R*)-1-(aminocarbonyl)-3-phenylpropyl]amino}carbonyl)-amino]benzoyl}piperazine-1-carboxylate



In a similar manner as described in **Example 1** from ethyl 1-piperazine carboxylate (240 mg, 1.50 mmol) is obtained ethyl 4-{3-[({[(1*R*)-1-(aminocarbonyl)-3-phenylpropyl]amino}carbonyl)amino]benzoyl}piperazine-1-carboxylate (22 mg, 43%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1H), 7.55 (m, 2H), 7.24-7.36 (m, 4H), 7.14-7.19 (m, 4H), 6.91 (d, J = 7.14 Hz, 1H), 6.54-6.59 (m, 1H), 4.19-4.25 (m, 1H), 4.04 (q, J = 7.02 Hz, 2H),

3.35-3.65 (m, 8H), 2.58 (t, J = 8.15 Hz, 2H), 1.90-2.01 (m, 1H), 1.75-1.85 (m, 1H), 1.17 (t, J = 6.96 Hz, 3H). MS m/z 481 (M+1).

Example 3: 9*H*-Fluoren-9-ylmethyl 4-{3-[({[(1*R*)-1-(aminocarbonyl)-3-phenylpropyl]amino}carbonyl)amino]benzoyl}piperazine-1-carboxylate



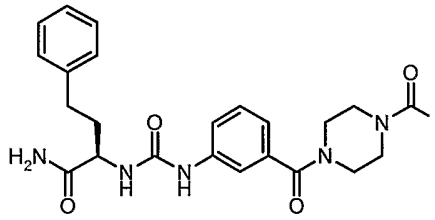
Mimotopes SynPhase™, D-Series Lanterns (50 used: 35micromoles per lantern, 1.75 mmoles total) with the Rink Amide linker(Fmoc protected) are soaked in DMF (30 mL) for 30 minutes then drained. The lanterns are treated with a solution of 20% piperidine/DMF (30 mL) for 30 minutes, then washed with DMF (30 mL x 6). The lanterns are then treated with DMF (30 mL), Fmoc-D-Homophenylalanine-OH (2.80 g, 7.0 mmol), 1-hydroxybenzotriazole (2.2 g, 14.0 mmol) and 1,3-diisopropylcarbodiimide (2.2 mL, 14.0 mmol) and shaken for 18 hrs, then washed with DMF (30 mL x 6), MeOH (30 mL x 3) and DCM (30 mL x 2). The lanterns are then treated with a solution of 20% piperidine/DMF (30 mL) for 30 minutes, then washed with DMF (30 mL x 6) and DCM (30 mL x 6). The lanterns are then treated with DCM (30 mL) and methyl-3-isocyanatobenzoate (2.0 g, 11.3 mmol) and shaken for 16 hrs, then washed with DCM (30 mL x 3), DMF (30 mL x 3), and DCM (30 mL x 3) and dried under high vacuum. The lanterns are then soaked in THF (30 mL) for 15 mins, drained, then treated with 1M LiOH in 4:1 THF/H_2O (50 mL) and shaken for 72 hrs. The lanterns are then washed with 1:1 THF/H_2O (30 mL x 3), 1:1:1 THF/H_2O/1.0 M HCl in Et_2O (30 mL x 3), 1:1 THF/H_2O (30 mL x 2) and THF (30 mL x 3).

Ten of the lanterns (0.135 mmol) are then treated with DMF (10 mL), Fmoc-piperazine hydrochloride (1.75 g, 5.0 mmol), 1-hydroxybenzotriazole (1.2 g, 7.50 mmol) and 1,3-diisopropylcarbodiimide (1.2 mL, 7.50 mmol) and shaken

for 23 hrs, then washed with DMF (30 mL x 3), MeOH (30 mL x 3) and DCM (30 mL x 3).

Three of the lanterns (0.105 mmol) are then treated with 9:1 trifluoroacetic acid/H_2O (10 mL) for 1 hr. The lanterns are removed from the TFA/H_2O solution and the solution is concentrated under vacuum to give an oil that is purified by PREP reverse-phase HPLC and lyopholization to give 9*H*-fluoren-9-ylmethyl 4-{3-[({[(1*R*)-1-(aminocarbonyl)-3-phenylpropyl]amino}carbonyl)-amino]benzoyl}piperazine-1-carboxylate (25 mg, 38%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.94 (s, 1H), 7.89 (m, 2H), 7.52-7.65 (m, 4H), 7.24-7.43 (m, 8H), 7.14-7.19 (m, 4H), 6.91 (d, J = 7.51 Hz, 1H), 6.59-6.65 (m, 1H), 4.38 (d, J = 6.41 Hz, 2H), 4.19-4.29 (m, 2H), 3.35-3.65 (m, 8H), 2.55-2.61 (m, 2H), 1.91-2.01 (m, 1H), 1.75-1.86 (m, 1H). MS m/z 631 (M+1).

Example 4: (2*R*)-2-{[({3-[(4-Acetylpiperazin-1-yl)carbonyl]phenyl}amino)-carbonyl]amino}-4-phenylbutanamide



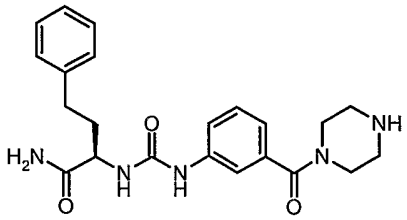
Mimotopes SynPhase™, D-Series Lanterns (50 used: 35micromoles per lantern, 1.75 mmoles total) with the Rink Amide linker(Fmoc protected) are soaked in DMF (30 mL) for 30 minutes then drained. The lanterns are treated with a solution of 20% piperidine/DMF (30 mL) for 30 minutes, then washed with DMF (30 mL x 6). The lanterns are then treated with DMF (30 mL), Fmoc-D-Homophenylalanine-OH (2.80 g, 7.0 mmol), 1-hydroxybenzotriazole (2.2 g, 14.0 mmol) and 1,3-diisopropylcarbodiimide (2.2 mL, 14.0 mmol) and shaken for 18 hrs, then washed with DMF (30 mL x 6), MeOH (30 mL x 3) and DCM (30 mL x 2). The lanterns are then treated with a solution of 20% piperidine/DMF (30 mL) for 30 minutes, then washed with DMF (30 mL x 6) and DCM (30 mL x 6). The lanterns are then treated with DCM (30 mL) and methyl-3-isocyanatobenzoate (2.0 g, 11.3 mmol) and shaken for 16 hrs, then

washed with DCM (30 mL x 3), DMF (30 mL x 3), and DCM (30 mL x 3) and dried under high vacuum. The lanterns are then soaked in THF (30 mL) for 15 mins, drained, then treated with 1M LiOH in 4:1 THF/H_2O (50 mL) and shaken for 72 hrs. The lanterns are then washed with 1:1 THF/H_2O (30 mL x 3), 1:1:1 THF/H_2O/1.0 M HCl in Et_2O (30 mL x 3), 1:1 THF/H_2O (30 mL x 2) and THF (30 mL x 3).

Ten of the lanterns (0.135 mmol) are then treated with DMF (10 mL), Fmoc-piperazine hydrochloride (1.75 g, 5.0 mmol), 1-hydroxybenzotriazole (1.2 g, 7.50 mmol) and 1,3-diisopropylcarbodiimide (1.2 mL, 7.50 mmol) and shaken for 23 hrs, then washed with DMF (30 mL x 3), MeOH (30 mL x 3) and DCM (30 mL x 3).

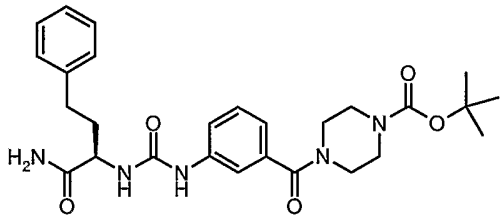
Three of the lanterns (0.105 mmol) are then treated with DMF (10 mL) for 15 minutes, drained, then treated with 20% piperidine/DMF (10 mL) and shaken for 30 minutes. The lanterns were then washed with DMF (30 mL x 6). The lanterns are then treated with 30% acetic anhydride/DMF (10 mL) and diisopropylethylamine (0.50 mL, 2.87 mmol) and shaken for 18 hrs. The lanterns are then washed with DMF (15 mL x 4), MeOH (15 mL x 4), DCM (15 mL x 4) and dried under vacuum. The lanterns are then treated with 9:1 trifluoroacetic acid/H_2O (10 mL) for 1 hr. The lanterns are removed from the TFA/H_2O solution and the solution was concentrated under vacuum to give an oil that is purified by PREP reverse-phase HPLC and lyopholization to give (2*R*)-2-{[({3-[(4-acetylpiperazin-1-yl)carbonyl]phenyl}amino)carbonyl]amino}-4-phenylbutanamide (15 mg, 32%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 7.56 (m, 2H), 7.24-7.36 (m, 4H), 7.14-7.19 (m, 4H), 6.92 (d, J = 7.32 Hz, 1H), 6.52 (d, J = 8.06 Hz, 1H), 4.19-4.26 (m, 1H), 3.35-3.65 (m, 8H), 2.55-2.61 (m, 2H), 1.90-2.05 (m, 4H), 1.75-1.85 (m, 1H). MS m/z 451 (M+1).

Example 5: (2R)-4-phenyl-2-[({[3-(1-piperazinylcarbonyl)phenyl]amino}-carbonyl)amino]butanamide



To a solution of 1,1-dimethylethyl 4-({3-[({[(1R)-1-(aminocarbonyl)-3-phenylpropyl]amino}carbonyl)amino]phenyl}carbonyl)-1-piperazine-carboxylate (10 mg, 0.019 mmol) in DCM (2.0 mL) is added a solution of trifluoroacetic acid in water (2.0 mL of 95:5 TFA/H_2O). The solution is stirred for 1.0 hour, then concentrated under vacuum to give (2*R*)-4-phenyl-2-[({[3-(piperazin-1-ylcarbonyl)phenyl]-amino}carbonyl)amino]butanamide (9.0 mg, 90%) as a clear oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95 (s, 3H), 7.60 (s, 1H), 7.54 (s, 1H), 7.12-7.36 (m, 6H), 6.95-6.98 (m, 1H), 6.62 (d, j = 7.87 Hz 1H), 4.18-4.24 (m, 1H), 3.145-3.81 (m, 8H), 2.55-2.60 (m, 2H), 1.90-2.01 (m, 1H), 1.75-1.85 (m, 1H). MS m/z 409 (M+H).

Example 6: 1,1-Dimethylethyl 4-({3-[({[(1R)-1-(aminocarbonyl)-3-phenylpropyl]amino}carbonyl)amino]phenyl}carbonyl)-1-piperazinecarboxylate



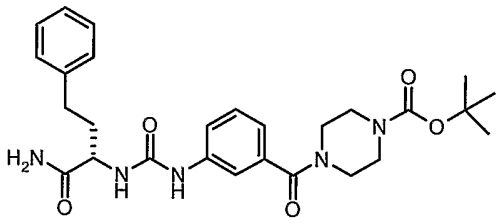
Encoded resin from ChemCodes Inc. (Batch DK-13-26-3, Code 5321, 0.25 mmol/gram) is placed into a shaker (2.0g resin, 0.5 mmol). The resin is treated with 20% piperidine/DMF (20 mL) and shaken for 45 minutes, then drained and washed with DMF (10 mL x 8). The resin is then treated with DMF (12 mL), Affymax aminomethyl photo-linker (1.6 g, 3.0 mmol), 1-

hydroxybenzotriazole (0.90 g, 6.00 mmol) and 1,3-diisopropylcarbodiimide (1.0 mL, 6.4 mmol), shaken for 36 hrs, then washed with DMF (25 mL x 8). The resin is then treated with 20% piperidine/DMF (20 mL) and shaken for 45 minutes, then drained and washed with DMF (25 mL x 8). The resin is then treated with DMF (12 mL), Fmoc-D-Homophenylalanine-OH (1.2 g, 3.0 mmol), 1-hydroxybenzotriazole (0.90 g, 6.00 mmol) and 1,3-diisopropylcarbodiimide (1.0 mL, 6.4 mmol), shaken for 18 hrs, then washed with DMF (25 mL x 8). The resin is then treated with 20% piperidine/DMF (20 mL) and shaken for 45 minutes, then drained and washed with DMF (25 mL x 8). The resin is then treated with a 0.28M solution of methyl isocyanatobenzoate in dichloromethane (10 mL) and shaken for 18 hrs. The resin is then washed with DCM (25 mL x 4), DMF (25 mL x 3), 1:1:1 DMF/MeOH/H_2O (25 mL x 2) and THF (25 mL x3). The resin is then treated with a 0.5M solution of of LiOH in 5:1 THF/H_2O (10 mL) and shaken for 15 hrs. and washed with 1:1 THF/H_2O (25 mL x 5), DMF (25 mL x 3) and THF (25 mL x 3). The resin is then treated with DMF (9 mL), 1-hydroxybenzotriazole (0.70 g, 4.5 mmol), 1,3-diisopropylcarbodiimide (0.7 mL, 4.5 mmol), and t-butyl-piperazine carboxylate (560 mg, 3.0 mmol), then shaken for 16 hrs and washed with DMF (25 mL x 4), 1:1:1 DMF/H_2O/MeOH (25 mL x 4), and THF (25 mL x 4) and dried under vacuum.

The resin is suspended in 40 mL of trifluoroethanol (5 mM in ethanolamine) and transferred from a shaker flask to a Teflon tray. The resin-suspension is irradiated for 1 h. The suspension is filtered and the resin was washed with DCM. The combined organic filtrates are combined and the solvent is removed in vacuo to give 38.3 mg (15% yield). To improve the recovery the resin is further subjected to the photocleavage conditions. At this point the resin is divided into six equal portions and each portion is placed in a separate petri dish. To each petri dish is added trifluorethanol (10 mL, 5 mM in ethanolamine) to create a bead suspension. After irradiating for 30 min an additional aliquot of trifluorethanol (10 mL, 5 mM in ethanolamine) is added and the photocleavage is allowed to run for an additional 30 min. The resin

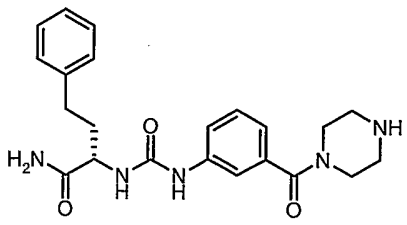
from the 6 petri dishes is combined, filtered and washed with DCM. The filtrates are combined and the solvent removed in vacuo to give a brown oil that is purified by PREP reverse-phase HPLC and lyopholization to give 62 mg (24% yield) of 1,1-dimethylethyl 4-({3-[({[(1R)-1-(aminocarbonyl)-3-phenylpropyl]amino}-carbonyl)amino]phenyl}carbonyl)-1-piperazine-carboxylate as a white solid. Total isolated yield from the two photocleavage runs is 100 mg (39% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 1H), 7.51-7.59 (m, 2H), 7.24-7.37 (m, 4H), 7.13-7.19 (m, 4H), 6.89-6.92 (m, 1H), 6.50-6.53(m, 1H), 4.19-4.25 (m, 1H), 3.10-3.65 (m, 8H), 2.55-2.60 (m, 2H), 1.90-2.01 (m, 1H), 1.75-1.85 (m, 1H), 1.39 (s, 9H). MS m/z 509 (M+H).

Example 7: 1,1-Dimethylethyl 4-({3-[({[(1S)-1-(aminocarbonyl)-3-phenylpropyl]amino}carbonyl)amino]phenyl}carbonyl)-1-piperazinecarboxylate



The title compound is prepared according to the process of **Example 6** except that Fmoc-L-Homophenylalanine-OH is used instead of Fmoc-D-Homophenylalanine-OH. A total of 94 mg (37% yield) of 1,1-dimethylethyl 4-({3-[({[(1S)-1-(aminocarbonyl)-3-phenylpropyl]amino}carbonyl)-amino]phenyl}carbonyl)-1-piperazinecarboxylate is isolated as a white solid.

Example 8: (2S)-4-Phenyl-2-[({[3-(1-piperazinylcarbonyl)phenyl]amino}carbonyl)-amino]butanamide



The title compound is prepared by removing the protecting group on the compound prepared according to **Example 7**.

Example 9: Biological Example

I. Assay for inhibition of PLK1

A. Preparation of 6x N-terminal His-tagged PLK kinase domain

6x N-terminal His-tagged PLK kinase domain (amino acids 21-346 preceded by MKKGHHHHHHD (**SEQ ID No. 1**)) was prepared from baculovirus infected T. ni cells under polyhedrin promoter control. All procedures were performed at 4°C. Cells were lysed in 25 mM HEPES, 200 mM NaCl, 25 mM imidazole; pH 8.0. The homogenate was centrifuged at 14K rpm in a SLA-1500 rotor for 40 min and the supernatant filtered through a 1.2 micron filter. The supernatant was loaded onto a Nickel chelating Sepharose (Amersham Pharmacia) column and washed with 25 mM HEPES, 500 mM NaCl, 25 mM imidazole; pH 8.0. The column was then washed with a 16.6%B step where buffer B is 25 mM HEPES, 500 mM NaCl, 300 mM imidazole; pH 8.0. Protein was eluted using a 10-column volume linear gradient from 16.6%B to 100%B. Fractions containing PLK were determined by SDS-PAGE. PLK was concentrated using a 10 kDa molecular weight cutoff membrane and then loaded onto a Superdex 75 gel filtration (Amersham Pharmacia) column equilibrated in 25 mM HEPES, 1 mM DTT, 500 mM NaCl; pH 8.0. Fractions containing PLK were determined by SDS-PAGE. PLK was pooled, aliquoted and stored at -80°C. Samples were quality controlled using mass spectrometry.

B. Enzyme activity +/- inhibitors was determined as follows: Compounds were added to the plate (1μl in 100% DMSO). DMSO (2% final) and EDTA (55.5mM final) were used as controls. Reaction Mix A is prepared as follows at 4°C:

Reaction Mix A (substrate Mix):

25mM HEPES, pH 7.2

15mM MgCl2

2μM ATP

0.1μCi/well ^{33}P-γ ATP (10Ci/mMol)

2μM substrate peptide (Biotin-Ahx-SFNDTLDFD)

Reaction Mix B is prepared as follows at 4°C:

Reaction Mix B (Enzyme Mix)

25mM HEPES, pH 7.2

15mM $MgCl_2$

0.15mg/ml BSA

2mM DTT

2-10 nM PLK1 kinase domain

Reaction Mix A (20μl) is added per well. Reaction Mix B (20μl) is added per well. Incubate 1.5hrs. at RT. The enzymatic reaction is stopped with 175μl of SPA/EDTA bead mix (29mM EDTA, 2.5 mg/ml Streptavidin-coated SPA in Standard Dulbecco's PBS (without Mg^{2+} and Ca^{2+}), 60μM ATP). Plates are sealed spun (after a 1 hr incubation at RT) at 1,000 x g for 7 min or settled overnight, then plates counted in Packard TopCount for 30 seconds/well.

C. Results

The data obtained is reported in **Table 1** below. In Table 1, + = pIC50 <5; ++ = pIC50 5-7; +++ = pIC50 >7.

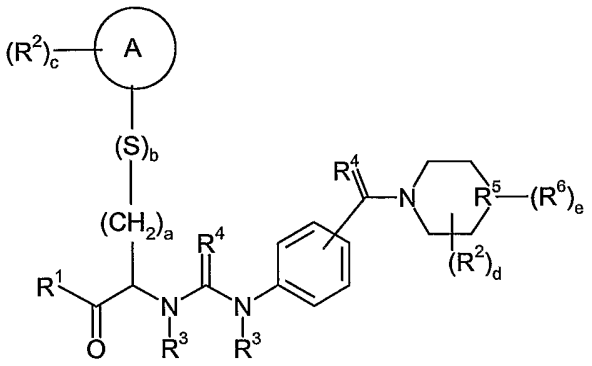
Table 1

Example	Ave pIC50 PLK Enzyme Inhibition
1	++
2	++
3	++
4	++
5	+
6	++

Example	Ave pIC50 PLK Enzyme Inhibition
7	+
8	+

CLAIMS

1. A compound of formula (I):



I

wherein:

R^1 is selected from OR^7 and NR^7R^8;

a is 1-6;

b is 0 or 1;

Ring A is phenyl or 5-6 membered heterocycle or heteroaryl containing 1 or 2 N atoms;

c is 0-4;

each R^2 is the same or different and is independently selected from halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, $C(O)R^7$, $C(S)R^7$, CO_2R^7, $CONR^7R^8$, $CSNR^7R^8$, OR^7, SR^7, SO_2R^7 and NR^7R^8;

each R^3 is the same or different and is independently selected from H, alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl;

each R^4 is the same or different and is independently selected from S and O;

d is 0-4;

R^5 is N, O, S or CH;

e is 0 when R^5 is O or S and e is 1 when R^5 is N or CH;

R^6 is selected from H, alkyl, alkenyl, alkynyl, R^9-cycloalkyl, R^9-cycloalkenyl, R^9-Ay, $C(O)R^7$, $C(S)R^7$, CO_2R^7, $C(O)NR^7R^8$, $C(S)NR^7R^8$, C(O)Ay, C(S)Ay, $C(O)N(R^7)Ay$, $C(S)N(R^7)Ay$, $C(O)R^9$-Ay, $C(S)R^9$-Ay, CO_2-R^9-Ay, $C(O)N(R^7)$-R^9-Ay and $C(S)N(R^7)$-R^9-Ay;

each R^7 and R^8 is the same or different and is each independently selected from H, alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl;

R^9 is alkylene or alkenylene; and
Ay is aryl;
or a pharmaceutically acceptable salt or solvate thereof.

2. The compound according to claim 1, wherein R^1 is -OH or $-NH_2$.

3. The compound according to any of claims 1-2, wherein a is 1, 2 or 3.

4. The compound according to any of claims 1-3, wherein b is 0.

5. The compound according to any of claims 1-4, wherein Ring A is phenyl or 5-6 membered heteroaryl containing 1 or 2 N atoms.

6. The compound according to any of claims 1-4, wherein Ring A is phenyl.

7. The compound according to any of claims 1-6, wherein c is 0, 1 or 2.

8. The compound according to any of claims 1-7, wherein each R^2 is the same or different and is independently selected from halo, alkyl, alkenyl, $C(O)R^7$, CO_2R^7, OR^7 and NR^7R^8.

9. The compound according to any of claims 1-8, wherein each R^3 is the same or different and is independently selected from H, alkyl, alkenyl and cycloalkyl.

10. The compound according to any of claims 1-9, wherein each R^4 is the same.

11. The compound according to any of claims 1-10, wherien R^4 is O.

12. The compound according to any of claims 1-11, wherein d is 0 or 1.

13. The compound according to any of claims 1-12, wherein R^5 is N or CH.

14. The compound according to any of claims 1-12, wherein R^5 is N.

15. The compound according to any of claims 1-14, wherein R^6 is selected from H, alkyl, $C(O)R^7$, CO_2R^7, $C(O)NR^7R^8$, C(O)Ay, $C(O)N(R^7)Ay$, $C(O)R^9$-Ay, CO_2-R^9-Ay and $C(O)N(R^7)$-R^9-Ay.

16. A compound selected from:

Benzyl 4-{3-[({[(1*R*)-1-(aminocarbonyl)-3-phenylpropyl]amino}carbonyl)-amino]benzoyl}piperazine-1-carboxylate;

Ethyl 4-{3-[({[(1*R*)-1-(aminocarbonyl)-3-phenylpropyl]amino}carbonyl)-amino]benzoyl}piperazine-1-carboxylate;

9*H*-Fluoren-9-ylmethyl 4-{3-[({[(1*R*)-1-(aminocarbonyl)-3-phenylpropyl]-amino}carbonyl)amino]benzoyl}piperazine-1-carboxylate;

(2*R*)-2-{[({3-[(4-Acetylpiperazin-1-yl)carbonyl]phenyl}amino)-carbonyl]amino}-4-phenylbutanamide;

(2R)-4-phenyl-2-[({[3-(1-piperazinylcarbonyl)phenyl]amino}carbonyl)amino]-butanamide;

1,1-dimethylethyl 4-({3-[({[(1R)-1-(aminocarbonyl)-3-phenylpropyl]amino}-carbonyl)amino]phenyl}carbonyl)-1-piperazinecarboxylate;

(2S)-4-phenyl-2-[({[3-(1-piperazinylcarbonyl)phenyl]amino}carbonyl)amino]-butanamide;

1,1-dimethylethyl 4-({3-[({[(1S)-1-(aminocarbonyl)-3-phenylpropyl]amino}-carbonyl)-amino]phenyl}carbonyl)-1-piperazinecarboxylate; and

pharmaceutically acceptable salts, solvates and physiologically functional derivatives thereof.

17. A pharmaceutical composition comprising a compound according to any of claims 1-16.

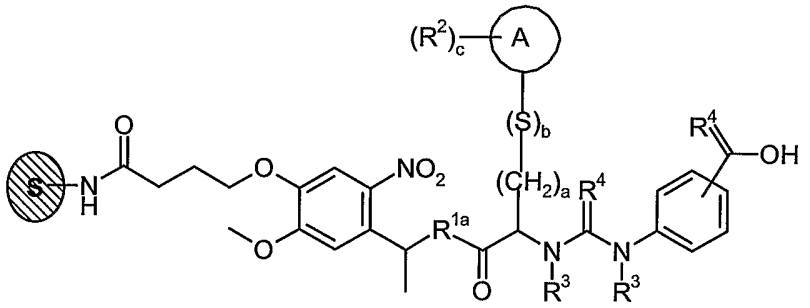
18. The pharmaceutical composition according to claim 17 further comprising a pharmaceutically acceptable carrier, diluent or excipient.

19. The pharmaceutical composition according to claim 17 further comprising a chemotherapeutic agent.

20. A method for treating a condition mediated by PLK in an animal, said method comprising administering to the animal a therapeutically effective amount of a compound according to any of claims 1-16.

21. A method for treating a susceptible neoplasm in an animal, said method comprising administering to the animal a therapeutically effective amount of a compound according to any of claims 1-16.

22. A process for preparing a compound according to any of claims 1-16, said process comprising reacting a solid support-bound compound of formula (VIII)



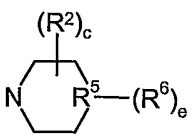
VIII

wherein:

R^{1a} is selected from -O- and -N(R^7)-, and

S represents a solid support;

with a compound of formula (IX)



IX

23. A compound according to any of Claims 1-16 for use in therapy.

24. A compound according to any of Claims 1-16 for use in the treatment of a condition mediated by PLK in an animal.

25. A compound according to any of claims 1-16 for use in the treatment of a susceptible neoplasm in an animal.

26. The use of a compound according to any of claims 1-16 for the preparation of a medicament for the treatment of condition mediated by PLK in an animal.

27. The use of a compound according to any of claims 1-16 for the preparation of a medicament for the treatment of a susceptible neoplasm in an animal.

28. A pharmaceutical composition comprising a compound according to any of claims 1-16 for use in the treatment of a susceptible neoplasm in an animal.

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