HSP90 INHIBITOR COMBINATIONS

[0001] This application claims priority to European Application Nos. 08170279.7, filed November 28, 2008, 08170287.0, filed November 28, 2008, 08170246.6, filed November 28, 2008, 08170230.0, filed November 28, 2008, the contents of all four applications are incorporated by reference.

BACKGROUND OF THE INVENTION

Field of the Invention

[0002] The present invention is directed to a pharmaceutical composition comprising an Hsp90 inhibitor and an mTOR inhibitor, and the uses of such a composition for the treatment of proliferative diseases, more specifically of mammalian target of rapamycin (mTOR) kinase and dependent dieseases.

[0003] In spite of numerous treatment options for proliferative disease patients, there remains a need for effective and safe antiproliferative agents and a need for their use in combination therapy.

[0004] It has now been found that a combination comprising at least one Hsp90 inhibitor compound and at least one mTOR inhibitor, as defined below, has a beneficial effect on proliferative disorders, including without limitation, solid tumors, myelomas, leukemias, psoriasis, restenosis, sclerodermitis and fibrosis.

Description of Related Art

[0005] Heat shock protein 90 (Hsp90) is recognized as an anti-cancer target. Hsp90 is a ubiquitous, highly abundant (1-2% of the total cellular protein), essential protein which functions as a molecular chaperone to ensure the conformational stability, shape and function of client proteins.

[0006] Among the stress proteins, Hsp90 is unique because it is not required for the biogenesis of most polypeptides (Nathan et al., 1997). Its cellular targets, also called client proteins, are conformationally labile signal transducers that play a critical role in growth control, cell survival and tissue development (Pratt and Toft, 2003). Inhibition of its intrinsic ATPase activity of Hsp90 disrupts the Hsp90-client protein interaction resulting in their degradation via the ubiquitin proteasome pathway. A subset of Hsp90 client proteins, such as Raf, AKT, phospho-AKT, CDK4 and the EGFR family including ErbB2 are oncogenic signaling molecules critically involved in cell growth, differentiation and apoptosis, processes which are important in cancer cells. The degradation of one or multiple oncoproteins is believed to produce the anti-tumor effects observed with Hsp90 inhibitors.

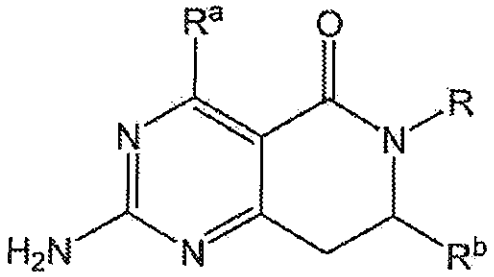
[0007] The Hsp90 family of chaperones is comprised of four members: Hsp90α and Hsp90β both located in the cytosol, GRP94 in the endoplasmic reticulum, and TRAP1 in the mitochondria (Csermely et al., 1998). Hsp90 is the most abundant cellular chaperone, constituting about 1% - 2% of total protein (Jakob and Buchner, 1994).

[0008] Hsp90 chaperones, which possess a conserved ATP-binding site at their N-terminal domain (Chene, 2002) belong to a small ATPase sub-family known as the DNA Gyrase, Hsp90, Histidine Kinase and MutL (GHKL) sub-family (Dutta and Inouye, 2000). The chaperoning (folding) activity of Hsp90 depends on its ATPase activity which is weak for the isolated enzyme. However, it has been shown that the ATPase activity of Hsp90 is enhanced upon its association with proteins known as co-chaperones (Kamal et al., 2003). Therefore, *in vivo*, Hsp90 proteins work as subunits of large, dynamic protein complexes. Hsp90 is essential for eukaryotic cell survival and is overexpressed in many tumors.

[0009] Treatment of cancer cells with an mTOR inhibitor can cause up-regulation of the pro-survival protein phospho-AKT (O'Reilly, 2006). Since phospho-AKT is an Hsp90 client protein, co-treatment of with an Hsp90 inhibitor would prevent or diminish the mTOR inhibitor induced upregulation of phospho-AKT giving rise to an increased anti-tumor effect.

SUMMARY OF THE INVENTION

[0010] In embodiments, a pharmaceutical composition according to the invention comprises, in a pharmaceutically acceptable carrier, components (a) and (b), wherein component (a) is a compound according to Formula (I)



(I)

or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein

R^a is selected from the group consisting of

(1) hydrogen,

(2) halogen,

(3) hydroxyl,

(4) C_1-C_6 alkoxy,

(5) thiol,

(6) C_1-C_6 alkylthiol,

(7) substituted or unsubstituted C_1-C_6 alkyl,

(8) amino or substituted amino,

(9) substituted or unsubstituted aryl,

(10) substituted or unsubstituted heteroaryl, and

(11) substituted or unsubstituted heterocyclyl;

R is selected from the group consisting of

(1) hydrogen,

(2) substituted or unsubstituted C_1-C_6 alkyl,

(3) substituted or unsubstituted C_2-C_6 alkenyl,

(4) substituted or unsubstituted C_2-C_6 alkynyl,

(5) substituted or unsubstituted C_3-C_7 cycloalkyl,

(6) substituted or unsubstituted C_5-C_7 cycloalkenyl,

(7) substituted or unsubstituted aryl,

(8) substituted or unsubstituted heteroaryl, and

(9) substituted or unsubstituted heterocyclyl;

R^6 is selected from the group consisting of

(1) substituted or unsubstituted C_3-C_7 cycloalkyl;

(2) substituted or unsubstituted C_5-C_7 cycloalkenyl,

(3) substituted or unsubstituted aryl,

(4) substituted or unsubstituted heteroaryl, and

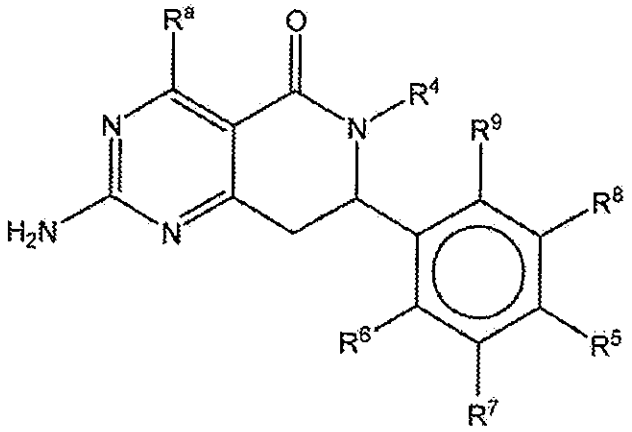
(5) substituted or unsubstituted heterocyclyl; and

with the proviso that when R^a is amino, then R^b is not phenyl, 4-alkyl-phenyl, 4-alkoxy-phenyl, or 4-halo-phenyl, and

component (b) is an mTOR inhibitor.

[0011] The compound according to Formula (I) may be combined with the mTOR inhibitor in a pharmaceutically acceptable carrier. In a method of treating proliferative diseases, an effective amount of the compound according to Formula (I) may be administered to a patient in need thereof in combination with an mTOR inhibitor, together or separately, at the same time, or sequentially.

[0012] In preferred embodiments of the invention, compounds of formula (III) are provided as the first pharmaceutical component in combination with an mTOR inhibitor as the second pharmaceutical component:



(III)

or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein

wherein R^a is selected from the group consisting of

(1) hydrogen,

(2) halogen,

(3) hydroxyl,

(4) C_1-C_6 alkoxy,

(5) thiol,

(6) C_1-C_6 alkylthiol,

(7) substituted or unsubstituted C_1-C_6 alkyl,

(8) amino or substituted amino,

(9) substituted or unsubstituted aryl,

(10) substituted or unsubstituted heteroaryl, and

(11) substituted or unsubstituted heterocyclyl;

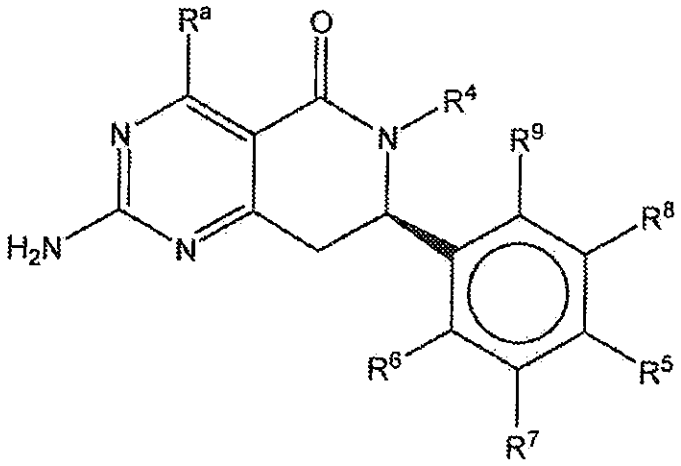
R^4 is hydrogen or substituted or unsubstituted C_1-C_6 alkyl;

R^5 is hydrogen, alkyl, alkoxy, or halo;

each of R^6, R^7, R^8, and R^9 are independently selected from the group consisting of hydrogen, alkyl, alkoxy, halo, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl; or

a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, and with the proviso that when R^a is amino and R^6, R^7, R^8, and R^9 are hydrogen, then R^5 is not hydrogen, alkyl, alkoxy, or halo.

[0013] In some embodiments, compounds of formula (IIIa) are provided:



(IIIa)

or a tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R^a, R^4, R^5, R^6, R^7, R^8, and R^9 are as previously defined for formula (III) and with the proviso that when R^a is amino and R^6, R^7, R^8, and R^9 are hydrogen, then R^5 is not hydrogen, alkyl, alkoxy, or halo.

[0014] In some embodiments, R^a is hydrogen.

[0015] In some embodiments, R^a is substituted or unsubstituted C_1-C_6 alkyl.

[0016] In some embodiments, R^a is C_1-C_6 alkyl or halo C_1-C_6 alkyl. In some such embodiments, R^a is methyl.

[0017] In some embodiments of the invention, R^4 is selected from the group consisting of hydrogen, benzyl, 1-(4-methoxyphenyl)ethyl, methyl, 3-aminopropyl, and 2-methyl-2-morpholinopropyl. In other embodiments, R is selected from the group consisting of methyl, ethyl, allyl, 3-methyl-butyl, and isobutyl.

[0018] In some embodiments, R^5 is hydrogen or fluoro. In some aspects, R^5 is fluoro.

[0019] In some embodiments, R^5 is methyl or methoxy.

[0020] In some embodiments, R^7, R^8, and R^9 are each hydrogen.

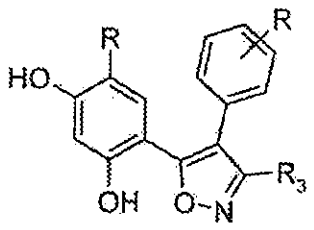
[0021] In some embodiments, R^5 is aryl or heteroaryl substituted with one to two substituents selected from the group consisting of halo, alkoxy, alkyl, amino, alkylamino, haloalkyl, and haloalkoxy.

[0022] In some embodiments R^6 is selected from the group consisting of substituted aryl and substituted heteroaryl, wherein said aryl and heteroaryl is selected from the group consisting of furanyl, pyrrolyl, phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, imidazolyl, triazolyl, indolyl, oxadiazole, thiadiazole, quinolinyl, isoquinolinyl, isoxazolyl, oxazolyl, thiazolyl, and thienyl. In some aspects, the aforementioned groups are substituted with one to two substituents selected from the group consisting of halo, alkoxy, alkyl, amino, alkylamino, haloalkyl, and haloalkoxy.

[0023] In other embodiments R^6 is selected from the group consisting of (2-hydroxy-ethylamino)-pyrazin-2-yl, 1H-pyrazol-4-yl, 1-methyl-1H-pyrazol-4-yl, 1-methyl-1H-pyrazol-4-yl, 2-(5-methyl-pyridin-2-yl)-phenyl, 2,3-difluoro-phenyl, 2,3-dimethoxy-phenyl, 2,4-difluoro-phenyl, 2,4-dimethoxy-phenyl, 2,4-dimethoxy-pyrimidin-5-yl, 2,5-difluoro-phenyl, 2,6-difluoro-phenyl, 2,6-dimethyl-pyridin-3-yl, 2-acetamidophenyl, 2-aminocarbonylphenyl, 2-amino-pyrimidin-5-yl, 2-chloro-4-methoxy-pyrimidin-5-yl, 2-chloro-5-fluoro-pyridin-3-yl, 2-chloro-phenyl, 2-chloro-pyridin-3-yl, 2-chloro-pyridin-4-yl, 2-difluoro-3-methoxyphenyl, 2-ethyl-phenyl, 2-ethoxy-thiazol-4-yl, 2-fluoro-3-methoxy-phenyl, 2-fluoro-3-methylphenyl, 2-fluoro-4-methyl-phenyl, 2-fluoro-5-methoxy-phenyl, 2-fluoro-5-methylphenyl, 2-fluorophenyl, 2-fluoro-pyridin-3-yl, 2-hydroxymethyl-3-methoxyphenyl, 2-hydroxymethylphenyl, 2-isoquinolin-4-yl, 2-methoxy-5-trifluoromethyl-phenyl, 2-methoxy-phenyl, 2-methoxy-pyridin-3-yl, 2-methoxy-pyrimidin-4-yl, 2-methoxy-thiazol-4-yl, 2-methyl-phenyl, 2-methyl-pyridin-3-yl, 2-oxo-1,2-dihydro-pyridin-3-yl, 2-phenoxyphenyl, 2-pyridin-3-yl, 2-pyrimidin-5-yl, 2-trifluoromethoxyphenyl, 2-trifluoromethoxy-phenyl, 3,4-dimethoxy-phenyl, 3,5-dimethyl-isoxazol-4-yl, 3,6-dimethyl-pyrazin-2-yl, 3-acetamidophenyl, 3-aminocarbonylphenyl, 3-bromo-phenyl, 3-chloro-pyrazin-2-yl, 3-cyanophenyl, 3-dimethylaminophenyl, 3-ethoxy-phenyl, 3-ethyl-4-methyl-phenyl, 3-ethynyl-phenyl, 3-fluoro-6-methoxy-pyridin-2-yl, 3-fluorophenyl, 3-fluoro-pyrazin-2-yl, 3-methanesulfonamidophenyl, 3-methoxycarbonylphenyl, 3-methoxyphenyl, 3-methoxy-pyrazin-2-yl, 3-methyl-3H-imidazo[4,5-b]pyrazin-5-yl, 3-methylphenyl, 3-methyl-pyridin-2-yl, 3-trifluoromethoxyphenyl, 3-trifluoromethylphenyl, 4,5-dimethoxy-pyrimidin-2-yl, 4-amino-5-fluoro-pyrimidin-2-yl, 4-chloro-2,5-dimethoxy-phenyl, 4-chloro-2-fluoro-phenyl, 4-chloro-2-methoxy-5-methyl-phenyl, 4-chloro-pyridin-3-yl, 4-difluoro-2-methyl-phenyl, 4-ethoxy-5-fluoro-pyrimidin-2-yl, 4-ethoxy-pyrimidin-2-yl, 4-ethoxy-pyrimidin-5-yl, 4-ethyl-1H-pyrazol-3-yl, 4-fluoro-2-methoxy-phenyl, 4-fluoro-2-methyl-phenyl, 4-fluorophenyl, 4-methoxy-5-methyl-pyrimidin-2-yl, 4-methoxy-pyridin-3-yl, 4-methoxy-pyrimidin-2-yl, 4-methoxy-pyrimidin-5-yl, 4-methyl-phenyl, 4-methyl-pyridin-2-yl, 4-methyl-pyridin-3-yl, 4-pyrrolidin-1-yl-pyrimidin-2-yl, 5,6-dimethoxy-pyrazin-2-yl, 5-acetyl-thiophen-2-

yl, 5-amino-6-ethoxy-pyrazin-2-yl, 5-amino-6-methoxy-3-methyl-pyrazin-2-yl, 5-amino-6-methoxy-pyridin-2-yl, 5-chloro-4-methoxy-pyrimidin-2-yl, 5-chloro-6-methoxy-pyrazin-2-yl, 5-dimethylamino-6-methoxy-pyrazin-2-yl, 5-fluoro-2-methoxyphenyl, 5-fluoro-4-methoxy-pyrimidin-2-yl, 5-fluoro-6-methoxy-pyrazin-2-yl, 5-fluoro-pyridin-2-yl, 5-methoxy-pyridin-3-yl, 5-methoxy-thiophen-2-yl, 5-trifluoromethyl-pyrimidin-2-yl, 6-acetyl-pyridin-2-yl, 6-chloro-pyrazin-2-yl, 6-ethoxy-pyrazin-2-yl, 6-ethoxy-pyridin-2-yl, 6-fluoro-pyridin-2-yl, 6-fluoro-pyridin-3-yl, 6-hydroxy-pyridin-2-yl, 6-methoxy-5-methylamino-pyrazin-2-yl, 6-methoxy-5-methyl-pyrazin-2-yl, 6-methoxy-pyrazin-2-yl, 6-methoxy-pyridin-2-yl, 6-methoxy-pyridin-3-yl, 6-methylamino-pyrazin-2-yl, 6-methyl-pyridin-2-yl, 5-amino-6-(2,2,2-trifluoroethoxy)pyrazin-2-yl, and 6-trifluoromethyl-pyridin-2-yl.

[0024] The present invention also relates to the use of Hsp90 inhibitors such as isoxazole derivatives of formula (D), and regioisomers thereof, and their salts, solvates and hydrates, and prodrugs thereof



(D)

wherein each R independently represents an optional substituent and R3 represents a carboxamide group.

[0025] Combinations of the present invention include compounds which target, decrease or inhibit the activity/function of serine/theronine mTOR kinase. Such compounds will be referred to as "mTOR inhibitors" and include but is not limited to compounds, proteins or antibodies which target/inhibit members of the mTOR kinase family, e.g., RAD, rapamycin (sirolimus) and derivatives/analogs thereof such as everolimus or RAD001. Sirolimus is also known by the name RAPAMUNE and everolimus or RAD001 by the name CERTICAN. Other compounds, proteins or antibodies which target/inhibit members of the mTOR kinase family include CCI-779, ABT578, SAR543, and ascomycin which is an ethyl analog of FK506. Also included are AP23573 and AP23841 from Ariad.

[0026] Preferred mTOR inhibitors are everolimus, rapamycin, ascomycin and rapamycin derivatives.

SUMMARY OF THE DRAWINGS

[0027] Fig. 1 shows the Akt phosphorylation levels in presence of everolimus (RAD001) and everolimus (RAD001) in combination with compound I in BT474 breast tumor cells.

[0028] Fig. 2 shows the AKT phosphorylation levels in presence of everolimus (RAD001) and everolimus (RAD001) in combination with compound I in MDA-MB-231 breast tumor cells.

DETAILED DESCRIPTION OF THE INVENTION

[0029] The following definitions are provided to better understand the invention.

[0030] "Alkyl" or "unsubstituted alkyl" refers to saturated hydrocarbyl groups that do not contain heteroatoms. Thus the phrase includes straight chain alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the like. The phrase also includes branched chain isomers of straight chain alkyl groups, including but not limited to, the following which are provided by way of example: -$CH(CH_3)_2$, -$CH(CH_3)(CH_2CH_3)$, -$CH(CH_2CH_3)_2$, -$C(CH_3)_3$, -$C(CH_2CH_3)_3$, -$CH_2CH(CH_3)_2$, -$CH_2CH(CH_3)(CH_2CH_3)$, -$CH_2CH(CH_2CH_3)_2$, -$CH_2C(CH_3)_3$, -$CH_2C(CH_2CH_3)_3$, -$CH(CH_3)CH(CH_3)(CH_2CH_3)$, -$CH_2CH_2CH(CH_3)_2$, -$CH_2CH_2CH(CH_3)(CH_2CH_3)$, -$CH_2CH_2CH(CH_2CH_3)_2$, -$CH_2CH_2C(CH_3)_3$, -$CH_2CH_2C(CH_2CH_3)_3$, -$CH(CH_3)CH_2CH(CH_3)_2$, -$CH(CH_3)CH(CH_3)CH(CH_3)_2$, -$CH(CH_2CH_3)CH(CH_3)CH(CH_3)(CH_2CH_3)$, and others. Thus the phrase "alkyl groups" includes primary alkyl groups, secondary alkyl groups, and tertiary alkyl groups. Preferred alkyl groups include straight and branched chain alkyl groups having 1 to 12, 1 to 6, or 1 to 3 carbon atoms.

[0031] "Alkylene" or "unsubstituted alkylene" refers to the same residues as noted above for "alkyl," but having two points of attachment. Exemplary alkylene groups include ethylene (-CH_2CH_2-), propylene (-$CH_2CH_2CH_2$-), and dimethylpropylene (-$CH_2C(CH_3)_2CH_2$-).

[0032] "Alkenyl" or "unsubstituted alkenyl" refers to straight chain and branched, chain hydrocarbyl radicals having one or more carbon-carbon double bonds and from 2 to about 20 carbon atoms. Preferred alkenyl groups include straight chain and branched alkenyl groups having 2 to 12, or 2 to 6 carbon atoms.

[0033] "Alkynyl" or "unsubstituted alkynyl" refers to straight chain and branched chain hydrocarbyl radicals having one or more carbon-carbon triple bonds and from 2 to about 20 carbon atoms. Preferred alkynyl groups include straight chain and branched alkynyl groups having 2 to 12, or 2 to 6 carbon atoms.

[0034] "Cycloalkyl" or "unsubstituted cycloalkyl" refers to a mono- or polycyclic alkyl substituent. Representative cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Preferred cycloalkyl groups have 3 to 7 carbon atoms.

[0035] "Cycloalkenyl" or "unsubstituted cycloalkenyl" refers to a mono- or polycyclic alkyl substituents having at least one ring carbon-carbon double bond. Preferred cycloalkenyl groups have 5 to 7 carbon atoms and include cyclopentenyl and cyclohexenyl.

[0036] "Substituted alkyl" refers to an alkyl group as defined above in which one or more bonds to a carbon(s) or hydrogen(s) are replaced by a bond to non-hydrogen or non-carbon atoms such as, but not limited to, a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, aryloxy groups, and ester groups; a sulfur atom in groups such as thiol groups, alkyl and aryl sulfide, sulfone, sulfonyl, and sulfoxide groups; a nitrogen atom in groups such as amino, amido, alkylamino, arylamino, alkylarylamino, diarylamino, N-oxides, imides, and enamines. Substituted alkyl groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom is replaced by a higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; or nitrogen in groups such as imines, oximes, hydrazones, and nitriles. Substituted alkyl groups further include alkyl groups in which one or more bonds to a carbon(s) or hydrogen(s) atoms is replaced by a bond to an aryl, heteroaryl, heterocyclyl, cycloalkyl, or cycloalkenyl group. Preferred substituted alkyl groups include, among others, alkyl groups in which one or more bonds to a carbon or hydrogen atom is/are replaced by one or more bonds to fluoro, chloro, or bromo group. Another preferred substituted alkyl group is the trifluoromethyl group and other alkyl groups that contain the trifluoromethyl group. Other preferred substituted alkyl groups include those in which one or more bonds to a carbon or hydrogen atom is replaced by a bond to an oxygen atom such that the substituted alkyl group contains a hydroxyl, alkoxy, or aryloxy group. Other preferred substituted alkyl groups include alkyl groups that have an amino, or a substituted or unsubstituted alkylamino, arylamino, heterocyclylamino. Still other preferred substituted alkyl groups include those in which one or more bonds to a carbon(s) or hydrogen(s) atoms is replaced by a bond to an aryl, heteroaryl, heterocyclyl, or cycloalkyl

group. Examples of substituted alkyl are: $-(CH_2)_3NH_2$, $-(CH_2)_3NH(CH_3)$, $-(CH_2)_3NH(CH_3)_2$, $-CH_2C(=CH_2)CH_2NH_2$, $-CH_2C(=O)CH_2NH_2$, $-CH_2S(=O)_2CH_3$, $-CH_2OCH_2NH_2$, $-CH_2CO_2H$. Examples of substituents of substituted alkyl are: $-CH_2OH$, -OH, $-OCH_3$, $-OC_2H_5$, $-OCF_3$, $OC(=O)CH_3$, $-OC(=O)NH_2$, $-OC(=O)N(CH_3)_2$, -CN, $-NO_2$, $-C(=O)CH_3$, $-CO_2H$, $-CO_2CH_3$, $-CONH_2$, $-NH_2$, $-N(CH_3)_2$, $-NHSO_2CH_3$, $-NHCOCH_3$, $-NHC(=O)OCH_3$, $-NHSO_2CH_3$, $-SO_2CH_3$, $-SO_2NH_2$, and halo.

[0037] "Substituted alkenyl" has the same meaning with respect to unsubstituted alkenyl groups that substituted alkyl groups has with respect to unsubstituted alkyl groups. A substituted alkenyl group includes alkenyl groups in which a non-carbon or non-hydrogen atom is bonded to a carbon double bonded to another carbon and those in which one of the non-carbon or non-hydrogen atoms is bonded to a carbon not involved in a double bond to another carbon.

[0038] "Substituted alkynyl" has the same meaning with respect to unsubstituted alkynyl groups that substituted alkyl groups has with respect to unsubstituted alkyl groups. A substituted alkynyl group includes alkynyl groups in which a non-carbon or non-hydrogen atom is bonded to a carbon triple bonded to another carbon and those in which a non-carbon or non-hydrogen atom is bonded to a carbon not involved in a triple bond to another carbon.

[0039] "Substituted cycloalkyl" has the same meaning with respect to unsubstituted cycloalkyl groups that substituted alkyl groups has with respect to unsubstituted alkyl groups.

[0040] "Substituted cycloalkenyl" has the same meaning with respect to unsubstituted cycloalkenyl groups that substituted alkyl groups has with respect to unsubstituted alkyl groups.

[0041] "Aryl" or "unsubstituted aryl" refers to monocyclic and polycyclic aromatic groups that do not contain ring heteroatoms. Such groups can contain from 6 to 14 carbon atoms but preferably 6. Exemplary aryl moieties employed as substituents in compounds of the present invention include phenyl, naphthyl, and the like.

[0042] "Aralkyl" or "arylalkyl" refers to an alkyl group substituted with an aryl group as defined above. Typically, aralkyl groups employed in compounds of the present invention have from 1 to 6 carbon atoms incorporated within the alkyl portion of the aralkyl group. Suitable aralkyl groups employed in compounds of the present invention include, for example, benzyl and the like. "Heteroarylalkyl" or "heteroaralkyl" refers to an alkyl group substituted with a heteroaryl group as defined above. Typically, heteroarylalkyl groups employed in compounds of the present invention have from 1 to 6 carbon atoms

incorporated within the alkyl portion of the aralkyl group. Suitable heteroarylalkyl groups employed in compounds of the present invention include, for example, picolyl and the like.

[0043] "Alkoxy" refers to $R^{20}O$- wherein R^{20} is C_1-C_7 alkyl or substituted alkyl. In some embodiments, R^{20} is C_1-C_6 alkyl. Representative examples of alkoxy groups include methoxy, ethoxy, t-butoxy, trifluoromethoxy, and the like.

[0044] "Amino" refers herein to the group $-NH_2$.

[0045] "Substituted amino" refers to the group $-NR^{60}R^{61}$ where R^{60} and R^{61} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, -SO_2-alkyl, -SO_2-substituted alkyl, and where R^{60} and R^{61} are joined, together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group provided that R^{60} and R^{61} are both not hydrogen. When R^{60} is hydrogen and R^{61} is alkyl, the substituted amino group is sometimes referred to herein as alkylamino. When R^{60} and R^{61} are alkyl, the substituted amino group is sometimes referred to herein as dialkylamino. When referring to a monosubstituted amino, it is meant that either R^{60} and R^{61} is hydrogen but not both. When referring to a disubstituted amino, it is meant that neither R^{60} and R^{61} is hydrogen. The term "alkylamino" refers herein to the group $-NR^{60}R^{61}$ where R^{60} is C_1-C_7 alkyl and R^{61} is hydrogen or C_1-C_7 alkyl. The term "dialkylamino" refers to the group $-NR^{60}R^{61}$ where R^{60} and R^{61} are C_1-C_7 alkyl. The term "arylamino" refers herein to the group $-NR^{60}R^{61}$ where R^{60} is C_5-C_7 aryl and R^{61} is hydrogen, C_1-C_7 alkyl, or C_5-C_7 aryl. The term "aralkylamino" refers herein to the group $-NR^{60}R^{61}$ where R^{60} is aralkyl and R^{61} is hydrogen, C_1-C_7 alkyl, C_5-C_7 aryl, or C_5-C_7 aralkyl.

[0046] "Amidino" refers to the moieties R^{40}-C(=N)-NR^{41}- (the radical being at the "N^{1}" nitrogen) and $R^{40}(NR^{41})C$=N- (the radical being at the "N^{2}" nitrogen), where R^{40} and R^{41} can be hydrogen, C_1-C_7 alkyl, aryl, or C_5-C_7 aralkyl.

[0047] "Alkoxyalkyl" refers to the group $-alk_1$-O-alk_2 where alk_1 is C_1-C_7 alkyl, and alk_2 is C_1-C_7 alkyl. The term "aryloxyalkyl" refers to the group -(C_1-C_7 alkyl)-O-(C_5-C_7 aryl).

[0048] "Alkoxyalkylamino" refers herein to the group $-NR^{27}$-(alkoxyalkyl), where R^{27} is typically hydrogen, C_5-C_7 aralkyl, or C_1-C_7 alkyl.

[0049] "Aminocarbonyl" refers herein to the group $-C(O)-NH_2$. "Substituted aminocarbonyl" refers herein to the group $-C(O)-NR^{28}R^{29}$ where R^{28} is C_1-C_7 alkyl and R^{29} is hydrogen or C_1-C_7 alkyl. The term "arylaminocarbonyl" refers herein to the group -C(O)-$NR^{30}R^{31}$ where R^{30} is C_5-C_7 aryl and R^{31} is hydrogen, C_1-C_7 alkyl or C_5-C_7 aryl. "Aralkylaminocarbonyl" refers

herein to the group -C(O)-$NR^{32}R^{33}$ where R^{32} is C_5-C_7 aralkyl and R^{33} is hydrogen, C_1-C_7 alkyl, C_5-C_7 aryl, or C_5-C_7 aralkyl.

[0050] "Aminosulfonyl" refers herein to the group $-S(O)_2-NH_2$. "Substituted aminosulfonyl" refers herein to the group $-S(O)_2-NR^{34}R^{35}$ where R^{34} is C_1-C_7 alkyl and R^{35} is hydrogen or C_1-C_7 alkyl. The term "aralkylaminosulfonlyaryl" refers herein to the group -(C_5-C_7 aryl)-$S(O)_2$-NH-aralkyl.

[0051] "Aryloxy" refers to $R^{50}O$- wherein R^{50} is aryl.

[0052] "Carbonyl" refers to the divalent group –C(O)-. "Alkylcarbonyl" refers to the group -C(O)alkyl. "Arylcarbonyl" refers to the group –C(O)aryl. Similarly, the term "heteroarylcarbonyl", "aralkylcarbonyl", and "heteroaralkylcarbonyl" refers to -C(O)-R where R is respectively heteroaryl, aralkyl, and heteroaralkyl.

[0053] "Carbonyloxy" refers generally to the group -C(O)-O-. Such groups include esters, -C(O)-O-R^{36}, where R^{36} is C_1-C_7 alkyl, C_3-C_7 cycloalkyl, aryl, or C_5-C_7 aralkyl. The term "arylcarbonyloxy" refers herein to the group -C(O)-O-(aryl). The term "aralkylcarbonyloxy" refers herein to the group –C(O)-O-(C_5-C_7 aralkyl).

[0054] "Cycloalkylalkyl" refers to an alkyl group substituted with a cyloalkyl group as defined above. Typically, cycloalkylalkyl groups have from 1 to 6 carbon atoms incorporated within the alkyl portion of the cycloalkylalkyl group.

[0055] "Carbonylamino" refers to the divalent group -NH-C(O)- in which the hydrogen atom of the amide nitrogen of the carbonylamino group can be replaced C_1-C_7 alkyl, aryl, or C_5-C_7 aralkyl group. Carbonylamino groups include moieties such as carbamate esters (-NH-C(O)-O-R^{28}) and amido –NH-C(O)-R^{28}, where R^{28} is a straight or branched chain C_1-C_7 alkyl, C_3-C_7 cycloalkyl, or aryl or C_5-C_7 aralkyl. The term "alkylcarbonylamino" refers to the group -NH-C(O)-$R^{28'}$ where $R^{28'}$ is alkyl having from 1 to about 7 carbon atoms in its backbone structure. The term "arylcarbonylamino" refers to group -NH-C(O)-R^{29} where R^{29} is C_5-C_7 aryl. Similarly, the term "aralkylcarbonylamino" refers to carbonylamino where R^{29} is C_5-C_7 aralkyl.

[0056] "Guanidino" or "guanidyl" refers to moieties derived from guanidine, H_2N-C(=NH)-NH_2. Such moieties include those bonded at the nitrogen atom carrying the formal double bond (the "2"-position of the guanidine, e.g., diaminomethyleneamino, $(H_2N)_2C$=NH-) and those bonded at either of the nitrogen atoms carrying a formal single bond (the "1-" and/or "3"-positions of the guandine, e.g., H_2N-C(=NH)-NH-). The hydrogen atoms at any of the nitrogens can be replaced with a suitable substituent, such as C_1-C_7 alkyl, aryl, or C_5-C_7 aralkyl.

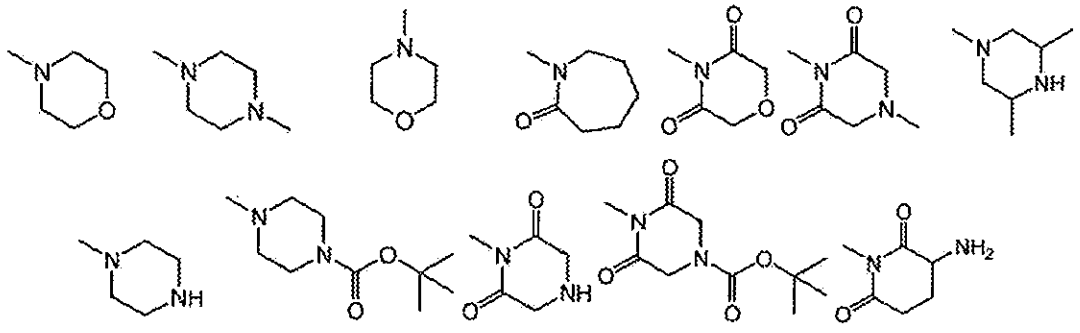
[0057] "Halogen" or "halo" refers to chloro, bromo, fluoro, and iodo groups. The term "haloalkyl" refers to an alkyl radical substituted with one or more halogen atoms. "Haloalkyl" groups include $-CF_3$. The term "haloalkoxy" refers to an alkoxy radical substituted with one or more halogen atoms. "Haloalkoxy" groups include $-OCF_3$ and $-OCH_2CF_3$.

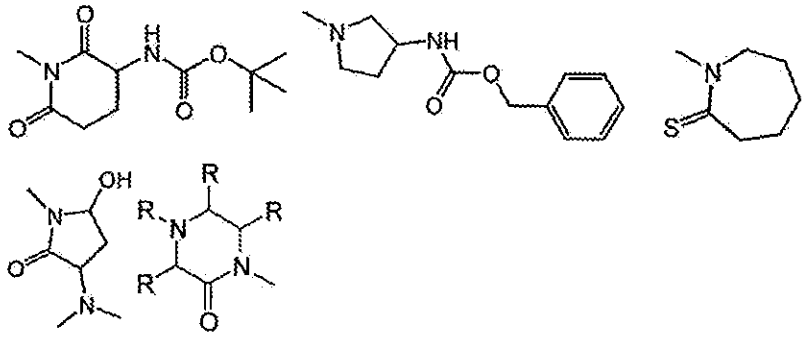
[0058] "Hydroxyl" or "hydroxy" refers to the group -OH.

[0059] "Heterocyclic" or "unsubstituted heterocyclic group," "heterocycle" or "unsubstituted heterocycle," and "heterocyclyl" or "unsubstituted heterocyclyl," "heterocycloalkyl" or "unsubstituted heterocycloalkyl group," as used herein refers to any non-aromatic monocyclic or polycyclic ring compounds containing a heteroatom selected from nitrogen, oxygen, or sulfur. Examples include 3- or 4-membered ring containing a heteroatom selected from nitrogen, oxygen, and sulfur or a 5- or 6-membered ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, or sulfur; wherein the 5-membered ring has 0-1 double bonds and the 6-membered ring has 0-2 double bonds; wherein the nitrogen and sulfur atom maybe optionally oxidized; wherein the nitrogen and sulfur heteroatoms maybe optionally quarternized; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another 5- or 6-membered heterocyclic ring independently defined above provided that the point of attachment is through the heterocyclic ring.

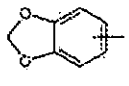
[0060] Heterocyclic moieties can be, for example monosubstituted or disubstituted with various substituents independently selected from but not limited to hydroxy, alkoxy, halo, oxo (C=O), alkylimino ($R^{31}N=$, wherein R^{31} is alkyl or alkoxy group), amino, alkylamino, acylaminoalkyl, alkoxy, thioalkoxy, polyalkoxy, alkyl, cycloalkyl or haloalkyl.

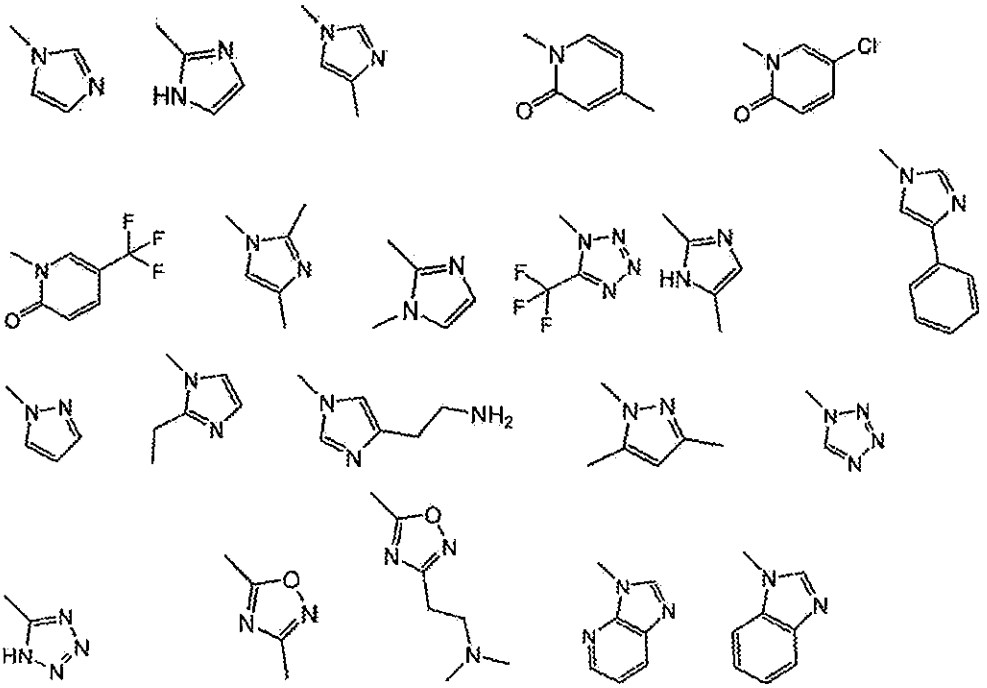
[0061] The heterocyclic groups may be attached at various positions as shown below as will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein.

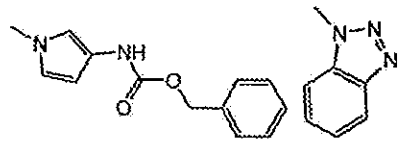




where R is H or a heterocyclic substituent, as described herein.

[0062] "Heteroaryl" or "unsubstituted heteroaryl" refers herein to an aromatic group having from 1 to 4 heteroatoms as ring atoms in an aromatic ring with the remainder of the ring atoms being carbon atoms. The term "heteroaryl" includes rings in which nitrogen is the heteroatom as well as partially and fully-saturated rings in which at least one cyclic structure is aromatic, such as, for example, benzodioxozolo (which has a heterocyclic structure fused to a phenyl group, i.e.,  provided that the point of attachment is through the heteroaryl ring. Heteroaryl groups can be further substituted and may be attached at various positions as will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein. Representative substituted and unsubstituted heteroaryl groups include, for example, those found in the compounds disclosed in this application and in the examples shown below





[0063] Preferred heterocycles and heteroaryls have 3 to 14 ring atoms and include, for example: diazapinyl, pyrroyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazoyl, imidazolidinyl, pyridyl, piperidinyl, pyrazinyl, piperazinyl, azetidinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, triazolyl, quinoxalinyl, phthalazinyl, naphthpyridinyl, indazolyl, and benzothienyl.

[0064] "Heteroarylalkyl" or "heteroaralkyl" refers to an alkyl group substituted with a heteroaryl group as defined above. Typically, heteroarylalkyl groups have from 1 to 6 carbon atoms incorporated within the alkyl portion of the heteroarylalkyl group.

[0065] "Imino" refers to the group =NH.

[0066] "Nitro" refers to the group NO_2.

[0067] "Sulfonyl" refers herein to the group $-SO_2-$. "Alkylsulfonyl" refers to a substituted sulfonyl of the structure $-SO_2R^{52}-$ in which R^{52} is C_1-C_7 alkyl. Alkylsulfonyl groups employed in compounds of the present invention are typically alkylsulfonyl groups having from 1 to 6 carbon atoms in its backbone structure. Thus, typical alkylsulfonyl groups employed in compounds of the present invention include, for example, methylsulfonyl (i.e., where R^{52} is methyl), ethylsulfonyl (i.e., where R^{52} is ethyl), propylsulfonyl (i.e., where R^{52} is propyl), and the like. The term "arylsulfonyl" refers herein to the group $-SO_2$-aryl. The term "heterocyclylsulfonyl" refers herein to the group $-SO_2$-heterocyclyl. The term "aralkylsulfonyl" refers herein to the group $-SO_2$-aralkyl. The term "sulfonamido" refers herein to $-SO_2NH_2$. The term "sulfonamidoalkyl" refers to (alkyl)SO_2NH_2-.

[0068] "Thio" or "thiol" refers to the group –SH. "Alkylthio" or "alkylthiol" refers to a thio group substituted with an alkyl group such as, for example, a C_1-C_6 alkyl group.

[0069] "Thioamido" refers to the group $-C(=S)NH_2$.

[0070] "Optionally substituted" refers to the optional replacement of hydrogen with a monovalent or divalent radical. "Substituted" refers to the replacement of hydrogen with a monovalent or divalent radical. Unless indicated otherwise, suitable substitution groups include, for example, hydroxyl, alkoxy, nitro, amino, imino, cyano, halo, thio, sulfonyl, thioamido, amidino, oxo, oxamidino, methoxamidino, guanidino, sulfonamido, carboxyl, formyl, alkyl, haloalkyl, alkylamino, haloalkylamino, alkoxy, haloalkoxy, alkoxy-alkyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl,

heteroaralkyl-carbonyl, alkylthio, aminoalkyl, cyanoalkyl, aryl and the like. Other suitable substitution groups include those substituents indicated for substituted alkyl. Examples of various suitable substitution groups are also found in reference to the compounds disclosed throughout this application.

[0071] The substitution group can itself be substituted. The group substituted onto the substitution group can be carboxyl, halo, nitro, amino, cyano, hydroxyl, alkyl, alkoxy, aminocarbonyl, -SR^{42}, thioamido, -SO_3H, -SO_2R^{42}, or cycloalkyl, where R^{42} is typically hydrogen, hydroxyl or alkyl.

[0072] When the substituted substituent includes a straight chain group, the substitution can occur either within the chain (e.g., 2-hydroxypropyl, 2-aminobutyl, and the like) or at the chain terminus (e.g., 2-hydroxyethyl, 3-cyanopropyl, and the like). Substituted substituents can be straight chain, branched or cyclic arrangements of covalently bonded carbon or heteroatoms.

[0073] Unless indicated otherwise, the nomenclature of substituents that are not explicitly defined herein are arrived at by naming the terminal portion of the functionality followed by the adjacent functionality toward the point of attachment. For example, the substituent "alkoxyheteroaryl" refers to the group (alkoxy)-(heteroaryl)-.

[0074] Preferred compounds of Formula (I) used in this invention have a total molecular weight less than 1000 Daltons, preferably less than 750 Daltons. Compounds of Formula (I) typically have a minimum molecular weight of at least 150 Daltons. Preferred compounds of Formula (I) have a molecular weight between 150 and 750 Daltons, and in more preferred embodiments, have a molecular weight between 200 and 500 Daltons. Other embodiments of the invention include the use of compounds of Formula (I) with a molecular weight between 300 and 450 Daltons. In another aspect of the invention compounds of Formula (I) used in the invention have a molecular weight between 350 and 400 Daltons.

[0075] Similarly, it is understood that the above definitions are not intended to include impermissible substitution patterns (e.g., methyl substituted with 5 fluoro groups). Such impermissible substitution patterns are well known to the skilled artisan.

[0076] "Carboxy-protecting group" refers to a carbonyl group which has been esterified with one of the commonly used carboxylic acid protecting ester groups employed to block or protect the carboxylic acid function while reactions involving other functional sites of the compound are carried out. In addition, a carboxy protecting group can be attached to a solid support whereby the compound remains connected to the solid support as the carboxylate

until cleaved by hydrolytic methods to release the corresponding free acid. Representative carboxy-protecting groups include, for example, alkyl esters, secondary amides and the like.

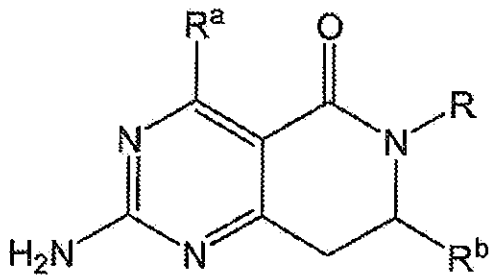
[0077] Certain of the compounds according to Formula (I) comprise asymmetrically substituted carbon atoms. Such asymmetrically substituted carbon atoms can result in the compounds of the invention comprising mixtures of stereoisomers at a particular asymmetrically substituted carbon atom or a single stereoisomer. As a result, racemic mixtures, mixtures of enantiomers, as well as enantiomers of the compounds of the invention are included in the present invention. The terms "S" and "R" configuration, as used herein, are as defined by the IUPAC 1974 "RECOMMENDATIONS FOR SECTION E, FUNDAMENTAL STEREOCHEMISTRY," *Pure Appl. Chem.* 45:13-30, 1976. The terms α and β are employed for ring positions of cyclic compounds. The α-side of the reference plane is that side on which the preferred substituent lies at the lower numbered position. Those substituents lying on the opposite side of the reference plane are assigned β descriptor. It should be noted that this usage differs from that for cyclic stereoparents, in which "α" means "below the plane" and denotes absolute configuration. The terms α and β configuration, as used herein, are as defined by the "Chemical Abstracts Index Guide," Appendix IV, paragraph 203, 1987.

[0078] As used herein, the term "pharmaceutically acceptable salts" refers to the nontoxic acid or alkaline earth metal salts of the 2-amino-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one compounds of the invention. These salts can be prepared *in situ* during the final isolation and purification of the 2-amino-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one compounds, or by separately reacting the base or acid functions with a suitable organic or inorganic acid or base, respectively. Representative salts include, but are not limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemi-sulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-napthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproionate, picrate, pivalate, propionate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl, and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

[0079] Examples of acids that may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulfuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, methanesulfonic acid, succinic acid and citric acid. Basic addition salts can be prepared *in situ* during the final isolation and purification of the 2-amino-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one compounds, or separately by reacting carboxylic acid moieties with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia, or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like.

[0080] The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example by hydrolysis in blood, such an ester. A thorough discussion is provided in Higuchi, T., and V. Stella, "Pro-drugs as Novel Delivery Systems," *A.C.S. Symposium Series 14*, and in "Bioreversible Carriers in Drug Design," in Edward B. Roche (ed.), *American Pharmaceutical Association*, Pergamon Press, 1987, both of which are incorporated herein by reference.

[0081] In embodiments, a pharmaceutical composition according to the invention comprises a first pharmaceutical component and a second pharmaceutical component in a pharmaceutically acceptable carrier. The first component is a compound according to Formula (I)



(I)

or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein

R^a is selected from the group consisting of

(1) hydrogen,

(2) halogen,

(3) hydroxyl,

(4) C_1-C_6 alkoxy,

(5) thiol,

(6) C_1-C_6 alkylthiol,

(7) substituted or unsubstituted C_1-C_6 alkyl,

(8) amino or substituted amino,

(9) substituted or unsubstituted aryl,

(10) substituted or unsubstituted heteroaryl, and

(11) substituted or unsubstituted heterocyclyl;

R is selected from the group consisting of

(1) hydrogen,

(2) substituted or unsubstituted C_1-C_6 alkyl,

(3) substituted or unsubstituted C_2-C_6 alkenyl,

(4) substituted or unsubstituted C_2-C_6 alkynyl,

(5) substituted or unsubstituted C_3-C_7 cycloalkyl,

(6) substituted or unsubstituted C_5-C_7 cycloalkenyl,

(7) substituted or unsubstituted aryl,

(8) substituted or unsubstituted heteroaryl, and

(9) substituted or unsubstituted heterocyclyl;

R^b is selected from the group consisting of

(1) substituted or unsubstituted C_3-C_7 cycloalkyl,

(2) substituted or unsubstituted C_5-C_7 cycloalkenyl,

(3) substituted or unsubstituted aryl,

(4) substituted or unsubstituted heteroaryl, and

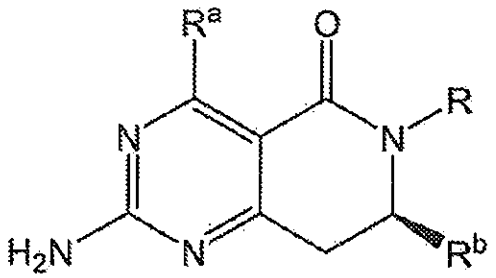
(5) substituted or unsubstituted heterocyclyl; and

with the proviso that when R^a is amino, then R^b is not phenyl, 4-alkyl-phenyl, 4-alkoxy-phenyl, or 4-halo-phenyl.

[0082] The second component is an mTOR inhibitor.

[0083] Preferably, the first component is an Hsp 90 inhibitor.

[0084] In particular embodiments, the first component is a compound according to formula (Ia)



(Ia)

or a tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R, R^a, and R^b are as previously defined for Formula (I) and with the proviso that when R^a is amino, then R^b is not phenyl, 4-alkyl-phenyl, 4-alkoxy-phenyl, or 4-halo-phenyl.

[0085] In some embodiments of the compounds of Formula (I) or (Ia), R^a is hydrogen.

[0086] In other embodiments, R^a is substituted or unsubstituted C_1-C_6 alkyl.

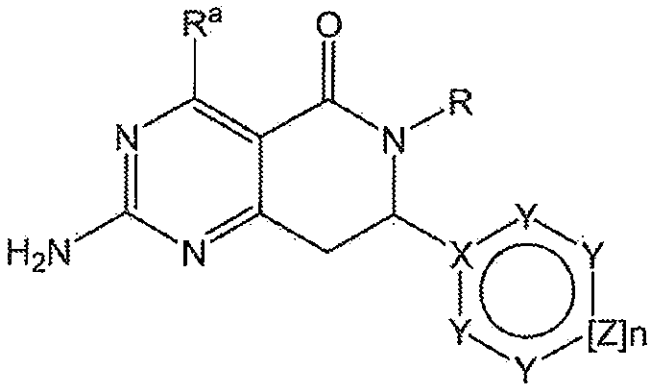
[0087] In some embodiments, R^a is C_1-C_6 alkyl or halo C_1-C_6 alkyl. In some such embodiments, R^a is methyl.

[0088] In some embodiments, R^b is aryl or heteroaryl. In some such embodiments, R^b is selected from the group consisting of phenyl, pyridyl, pyrimidinyl, pyrazinyl, indolyl, thiazolyl, and thienyl, each of which can be substituted or unsubstituted. In some aspects, the invention provides compounds wherein the aforementioned R^b groups are substituted with substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In other aspects the R^b groups are substituted with halo. In still other aspects the R^b groups are substituted with fluoro. In still other aspects, the R^b groups are substituted with alkyl, haloalkyl, alkoxy, and haloalkoxy. In some aspects, the R^b groups are substituted with methyl. In other aspects, the R^b groups are substituted with methoxy.

[0089] In other embodiments, R^b is selected from the group consisting of substituted aryl, substituted heterocyclyl, substituted heteroaryl, substituted C_3-C_7 cycloalkyl, and substituted C_5-C_7 cycloalkenyl, wherein said aryl, heterocyclyl, heteroaryl, C_3-C_7 cycloalkyl, and C_5-C_7 cycloalkenyl is selected from the group consisting of pyrrolyl, phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, imidazolyl, triazolyl, indolyl, oxadiazole, thiadiazole, furanyl, quinolinyl, isoquinolinyl, isoxazolyl, oxazolyl, thiazolyl, morpholino, piperidinyl, pyrrolidinyl, thienyl, cyclohexyl, cyclopentyl, cyclohexenyl, and cyclopentenyl. In some aspects, the aforementioned groups are substituted with one to two substituents selected from the group consisting of halo, alkoxy, alkyl, amino, alkylamino, haloalkyl, and haloalkoxy.

[0090] In some embodiments, R is selected from the group consisting of hydrogen, unsubstituted alkyl, and substituted alkyl. In some such embodiments, R is selected from the group consisting of methyl, ethyl, allyl, 3-methyl-butyl, and isobutyl. In other embodiments, R is selected from the group consisting of hydrogen, benzyl, 1-(4-methoxyphenyl)ethyl, methyl, 3-aminopropyl, and 2-methyl-2-morpholinopropyl. In still other embodiment, R is hydrogen.

[0091] In another embodiment, the 2-amino-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one compounds have the formula (II):



(II)

or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein

n is 0 or 1,

wherein R^a is selected from the group consisting of

(1) hydrogen,

(2) halogen,

(3) hydroxyl,

(4) C_1-C_6 alkoxy,

(5) thiol,

(6) C_1-C_6 alkylthiol,

(7) substituted or unsubstituted C_1-C_6 alkyl,

(8) amino or substituted amino,

(9) substituted or unsubstituted aryl,

(10) substituted or unsubstituted heteroaryl, and

(11) substituted or unsubstituted heterocyclyl;

wherein R is selected from the group consisting of

(1) hydrogen,

(2) substituted or unsubstituted C_1-C_6 alkyl,

(3) substituted or unsubstituted C_2-C_6 alkenyl,

(4) substituted or unsubstituted C_2-C_6 alkynyl,

(5) substituted or unsubstituted C_3-C_7 cycloalkyl,

(6) substituted or unsubstituted C_5-C_7 cycloalkenyl,

(7) substituted or unsubstituted aryl,

(8) substituted or unsubstituted heteroaryl, and

(9) substituted or unsubstituted heterocyclyl,

wherein when n is 1, X is C, Y is at each position independently selected from CQ^1 and N, and Z is selected from CR^2 and N with the proviso that no more than 3 Y and Z groups are N, and

wherein when n is 0, X is C or N, Y is at each position independently selected from CQ^1, N, NQ^2, O, and S with the proviso that no more than 4 X and Y groups are N and NQ^2 and no more than 1 Y group is S or O;

wherein Q^1 is at each position independently selected from the group consisting of

(1) hydrogen,

(2) halogen,

(3) substituted or unsubstituted C_1-C_6 alkyl,

(4) substituted or unsubstituted C_2-C_6 alkenyl,

(5) substituted or unsubstituted C_2-C_6 alkynyl,

(6) substituted or unsubstituted C_3-C_7 cycloalkyl,

(7) substituted or unsubstituted C_5-C_7 cycloalkenyl,

(8) substituted or unsubstituted aryl,

(9) substituted or unsubstituted heteroaryl,

(10) substituted or unsubstituted heterocyclyl,

(11) substituted or unsubstituted amino,

(12) $-OR^3$ or $-SR^3$,

(13) $-C(O)R^3$, $-CO_2R^3$, $-C(O)N(R^3)_2$, $-S(O)R^3$, $-SO_2R^3$, or $-SO_2N(R^3)_2$,

(14) $-OC(O)R^3$, $-N(R^3)C(O)R^3$, or $-N(R^3)SO_2R^3$,

(15) –CN, and

(16) $-NO_2$;

wherein Q^2 is at each position independently selected from the group consisting of

(1) hydrogen,

(3) substituted or unsubstituted C_1-C_6 alkyl,

(4) substituted or unsubstituted C_2-C_6 alkenyl,

(5) substituted or unsubstituted C_2-C_6 alkynyl,

(6) substituted or unsubstituted C_3-C_7 cycloalkyl,

(7) substituted or unsubstituted C_5-C_7 cycloalkenyl,

(8) substituted or unsubstituted aryl,

(9) substituted or unsubstituted heteroaryl, and

(10) substituted or unsubstituted heterocyclyl;

wherein R^2 is selected from the group consisting of

(1) hydrogen,

(2) halogen,

(3) substituted or unsubstituted C_1-C_3 alkyl, and

(4) $-OR^3$, $-SR^3$, or $-NHR^3$;

wherein R^3 is at each position independently selected from the group consisting of

(1) hydrogen,

(2) substituted or unsubstituted C_1-C_6 alkyl,

(3) substituted or unsubstituted C_2-C_6 alkenyl,

(4) substituted or unsubstituted C_2-C_6 alkynyl,

(5) substituted or unsubstituted C_3-C_7 cycloalkyl,

(6) substituted or unsubstituted C_5-C_7 cycloalkenyl,

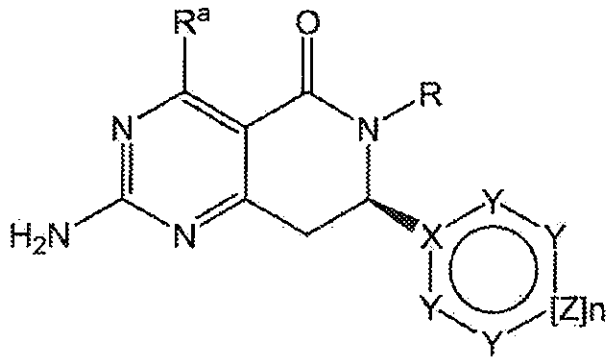
(7) substituted or unsubstituted aryl,

(8) substituted or unsubstituted heteroaryl, and

(9) substituted or unsubstituted heterocyclyl,

with the proviso that when R^a is amino, then X, Y, Z, and n together do not form a phenyl, 4-alkyl-phenyl, 4-alkoxy-phenyl, or 4-halo-phenyl group.

[0092] In other embodiments, the first pharmaceutical component of the invention is described according to formula (IIa):



(IIa)

or a tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R^a, R, X, Y, Z, and n are previously defined for formula (II) and with the proviso that when R^a is amino, then X, Y, Z, and n together do not form a phenyl, 4-alkyl-phenyl, 4-alkoxy-phenyl, or 4-halo-phenyl group.

[0093] In some embodiments when n is 0, X is C, and Y adjacent to X is not O.

[0094] In some embodiments of the compounds of formula (II) or (IIa), R^a is hydrogen.

[0095] In other embodiments, R^a is substituted or unsubstituted C_1-C_6 alkyl.

[0096] In some embodiments, R^a is C_1-C_6 alkyl or halo C_1-C_6 alkyl. In some such embodiments, R^a is methyl.

[0097] For the compounds of Formula (I), (Ia), (II), or (IIa), representative substituted alkyl groups include arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocyclylalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, and sulfonamidoalkyl groups.

[0098] Representative aryl groups include phenyl groups.

[0099] Representative heteroaryl groups include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, indolyl, quinolinyl, isoquinolinyl, furanyl, oxazolyl, thiazolyl, and thienyl groups.

[00100] In one embodiment, one of Q^1 or Q^2 is selected from the group consisting of substituted and unsubstituted phenyl, substituted and unsubstituted pyridyl, substituted and unsubstituted pyrimidinyl, substituted and unsubstituted pyrazinyl, substituted and

unsubstituted indolyl, substituted and unsubstituted thiazolyl, and substituted and unsubstituted thienyl.

[00101] In one embodiment, one of Q^1 or Q^2 is selected from the group consisting of piperidinyl, morpholinyl, pyrrolidinonyl, and benzyl amino.

[00102] In one embodiment, one of Q^1 or Q^2 is selected from the group consisting of cyclohexyl and cyclopentyl.

[00103] In one embodiment, one of Q^1 or Q^2 is selected from the group consisting of cyclohexenyl and cyclopentenyl.

[00104] In one embodiment, one of Q^1 or Q^2 is selected from the group consisting of substituted aryl, substituted heterocyclyl, substituted heteroaryl, substituted C_3-C_7 cycloalkyl, and substituted C_5-C_7 cycloalkenyl, wherein said aryl, heterocyclyl, heteroaryl, C_3-C_7 cycloalkyl, and C_5-C_7 cycloalkenyl is selected from the group consisting of pyrrolyl, phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, imidazolyl, triazolyl, indolyl, oxadiazole, thiadiazole, furanyl, quinolinyl, isoquinolinyl, isoxazolyl, oxazolyl, thiazolyl, morpholino, piperidinyl, pyrrolidinyl, thienyl, cyclohexyl, cyclopentyl, cyclohexenyl, and cyclopentenyl.

[0100] In some aspects, the aforementioned groups are substituted with one to two substituents selected from the group consisting of halo, alkoxy, alkyl, amino, alkylamino, haloalkyl, and haloalkoxy.

[0101] In one embodiment, one of Q^1 or Q^2 is selected from substituted and unsubstituted pyridyl, substituted and unsubstituted pyrazinyl, substituted and unsubstituted phenyl, substituted and unsubstituted isoquinolinyl, substituted and unsubstituted pyrimidinyl, substituted and unsubstituted pyrazolyl, and substituted and unsubstituted furanyl. In some aspects, the aforementioned groups are substituted with one to two substituents selected from the group consisting of halo, alkoxy, alkyl, amino, alkylamino, haloalkyl, and haloalkoxy.

[0102] In other embodiments one of Q^1 or Q^2 is selected from the group consisting of (2-hydroxy-ethylamino)-pyrazin-2-yl, 1H-pyrazol-4-yl, 1-methyl-1H-pyrazol-4-yl, 1-methyl-1H-pyrazol-4-yl, 2-(5-methyl-pyridin-2-yl)-phenyl, 2,3-difluoro-phenyl, 2,3-dimethoxy-phenyl, 2,4-difluoro-phenyl, 2,4-dimethoxy-phenyl, 2,4-dimethoxy-pyrimidin-5-yl, 2,5-difluoro-phenyl, 2,6-difluoro-phenyl, 2,6-dimethyl-pyridin-3-yl, 2-acetamidophenyl, 2-aminocarbonylphenyl, 2-amino-pyrimidin-5-yl, 2-chloro-4-methoxy-pyrimidin-5-yl, 2-chloro-5-fluoro-pyridin-3-yl, 2-chloro-phenyl, 2-chloro-pyridin-3-yl, 2-chloro-pyridin-4-yl, 2-difluoro-3-methoxyphenyl, 2-ethyl-phenyl, 2-

ethoxy-thiazol-4-yl, 2-fluoro-3-methoxy-phenyl, 2-fluoro-3-methylphenyl, 2-fluoro-4-methyl-phenyl, 2-fluoro-5-methoxy-phenyl, 2-fluoro-5-methylphenyl, 2-fluorophenyl, 2-fluoro-pyridin-3-yl, 2-hydroxymethyl-3-methoxyphenyl, 2-hydroxymethylphenyl, 2-isoquinolin-4-yl, 2-methoxy-5-trifluoromethyl-phenyl, 2-methoxy-phenyl, 2-methoxy-pyridin-3-yl, 2-methoxy-pyrimidin-4-yl, 2-methoxy-thiazol-4-yl, 2-methyl-phenyl, 2-methyl-pyridin-3-yl, 2-oxo-1,2-dihydro-pyridin-3-yl, 2-phenoxyphenyl, 2-pyridin-3-yl, 2-pyrimidin-5-yl, 2-trifluoromethoxyphenyl, 2-trifluoromethoxy-phenyl, 3,4-dimethoxy-phenyl, 3,5-dimethyl-isoxazol-4-yl, 3,6-dimethyl-pyrazin-2-yl, 3-acetamidophenyl, 3-aminocarbonylphenyl, 3-bromo-phenyl, 3-chloro-pyrazin-2-yl, 3-cyanophenyl, 3-dimethylaminophenyl, 3-ethoxy-phenyl, 3-ethyl-4-methyl-phenyl, 3-ethynyl-phenyl, 3-fluoro-6-methoxy-pyridin-2-yl, 3-fluorophenyl, 3-fluoro-pyrazin-2-yl, 3-methanesulfonamidophenyl, 3-methoxycarbonylphenyl, 3-methoxyphenyl, 3-methoxy-pyrazin-2-yl, 3-methyl-3H-imidazo[4,5-b]pyrazin-5-yl, 3-methylphenyl, 3-methyl-pyridin-2-yl, 3-trifluoromethoxyphenyl, 3-trifluoromethylphenyl, 4,5-dimethoxy-pyrimidin-2-yl, 4-amino-5-fluoro-pyrimidin-2-yl, 4-chloro-2,5-dimethoxy-phenyl, 4-chloro-2-fluoro-phenyl, 4-chloro-2-methoxy-5-methyl-phenyl, 4-chloro-pyridin-3-yl, 4-difluoro-2-methyl-phenyl, 4-ethoxy-5-fluoro-pyrimidin-2-yl, 4-ethoxy-pyrimidin-2-yl, 4-ethoxy-pyrimidin-5-yl, 4-ethyl-1H-pyrazol-3-yl, 4-fluoro-2-methoxy-phenyl, 4-fluoro-2-methyl-phenyl, 4-fluorophenyl, 4-methoxy-5-methyl-pyrimidin-2-yl, 4-methoxy-pyridin-3-yl, 4-methoxy-pyrimidin-2-yl, 4-methoxy-pyrimidin-5-yl, 4-methyl-phenyl, 4-methyl-pyridin-2-yl, 4-methyl-pyridin-3-yl, 4-pyrrolidin-1-yl-pyrimidin-2-yl, 5,6-dimethoxy-pyrazin-2-yl, 5-acetyl-thiophen-2-yl, 5-amino-6-ethoxy-pyrazin-2-yl, 5-amino-6-methoxy-3-methyl-pyrazin-2-yl, 5-amino-6-methoxy-pyridin-2-yl, 5-chloro-4-methoxy-pyrimidin-2-yl, 5-chloro-6-methoxy-pyrazin-2-yl, 5-dimethylamino-6-methoxy-pyrazin-2-yl, 5-fluoro-2-methoxyphenyl, 5-fluoro-4-methoxy-pyrimidin-2-yl, 5-fluoro-6-methoxy-pyrazin-2-yl, 5-fluoro-pyridin-2-yl, 5-methoxy-pyridin-3-yl, 5-methoxy-thiophen-2-yl, 5-trifluoromethyl-pyrimidin-2-yl, 6-acetyl-pyridin-2-yl, 6-chloro-pyrazin-2-yl, 6-ethoxy-pyrazin-2-yl, 6-ethoxy-pyridin-2-yl, 6-fluoro-pyridin-2-yl, 6-fluoro-pyridin-3-yl, 6-hydroxy-pyridin-2-yl, 6-methoxy-5-methylamino-pyrazin-2-yl, 6-methoxy-5-methyl-pyrazin-2-yl, 6-methoxy-pyrazin-2-yl, 6-methoxy-pyridin-2-yl, 6-methoxy-pyridin-3-yl, 6-methylamino-pyrazin-2-yl, 6-methyl-pyridin-2-yl, 5-amino-6-(2,2,2-trifluoroethoxy)pyrazin-2-yl, and 6-trifluoromethyl-pyridin-2-yl.

[0103] In one embodiment Q^1 is halo.

[0104] In one embodiment Q^1 is alkyl. In some aspects, Q^1 is methyl.

[0105] In one embodiment, R^2 is selected from hydrogen and fluoro. In some aspects, R^2 is fluoro.

[0106] In one embodiment, R^2 is selected from alkyl. In some aspects, R^2 is methyl.

[0107] In one embodiment, R^2 is selected from alkoxy. In some aspects, R^2 is methoxy.

[0108] In one embodiment Q^1 is OR^3.

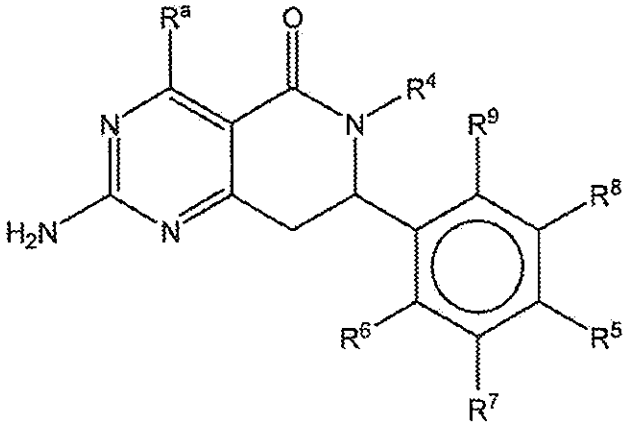
[0109] In one embodiment, R^3 is selected from the group consisting of methyl, ethyl, isopropyl, cyclopentyl, and cyclohexyl.

[0110] In one embodiment, R^3 is selected from substituted and unsubstituted phenyl, substituted and unsubstituted thiazolyl, substituted and unsubstituted pyridyl, substituted and unsubstituted pyrazinyl, and substituted and unsubstituted pyrimidinyl.

[0111] In one embodiment, R^3 is selected from the group consisting of 2-aminoethyl, 2-piperidinylethyl, 2-piperazinylethyl, 2-morpholinylethyl, and 2-(N-methylpiperazinyl)ethyl.

[0112] In some embodiments, R is selected from the group consisting of hydrogen, unsubstituted alkyl, and substituted alkyl. In some such embodiments, R is selected from the group consisting of methyl, ethyl, allyl, 3-methyl-butyl, and isobutyl. In other embodiments, R is selected from the group consisting of hydrogen, benzyl, 1-(4-methoxyphenyl)ethyl, methyl, 3-aminopropyl, and 2-methyl-2-morpholinopropyl.

[0113] In another embodiment of the invention, compounds of formula (III) are provided as the first component, in combination with an mTOR inhibitor as the second component:



(III)

or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein

wherein R^a is selected from the group consisting of

(1) hydrogen,

(2) halogen,

(3) hydroxyl,

(4) C_1-C_6 alkoxy,

(5) thiol,

(6) C_1-C_6 alkylthiol,

(7) substituted or unsubstituted C_1-C_6 alkyl,

(8) amino or substituted amino,

(9) substituted or unsubstituted aryl,

(10) substituted or unsubstituted heteroaryl, and

(11) substituted or unsubstituted heterocyclyl;

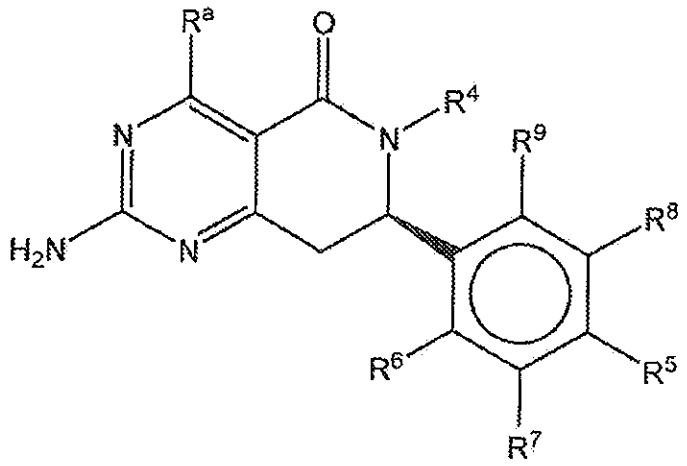
R^4 is hydrogen or substituted or unsubstituted C_1-C_6 alkyl;

R^5 is hydrogen, alkyl, alkoxy, or halo;

each of R^6, R^7, R^8, and R^9 are independently selected from the group consisting of hydrogen, alkyl, alkoxy, halo, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl; or

a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, and with the proviso that when R^a is amino and R^6, R^7, R^8, and R^9 are hydrogen, then R^5 is not hydrogen, alkyl, alkoxy, or halo.

[0114] In some embodiments, compounds of formula (IIIa) are provided as the first component:



(IIIa)

or a tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R^a, R^4, R^5, R^6, R^7, R^8, and R^9 are as previously defined for formula (III) and with the proviso that when R^a is amino and R^6, R^7, R^8, and R^9 are hydrogen, then R^5 is not hydrogen, alkyl, alkoxy, or halo.

[0115] In some embodiments, R^a is hydrogen.

[0116] In some embodiments, R^a is substituted or unsubstituted C_1-C_6 alkyl.

[0117] In some embodiments, R^a is C_1-C_6 alkyl or halo C_1-C_6 alkyl. In some such embodiments, R^a is methyl.

[0118] In some embodiments of the invention, R^4 is selected from the group consisting of hydrogen, benzyl, 1-(4-methoxyphenyl)ethyl, methyl, 3-aminopropyl, and 2-methyl-2-morpholinopropyl. In other embodiments, R is selected from the group consisting of methyl, ethyl, allyl, 3-methyl-butyl, and isobutyl.

[0119] In some embodiments, R^5 is hydrogen or fluoro. In some aspects, R^5 is fluoro.

[0120] In some embodiments, R^5 is methyl or methoxy.

[0121] In some embodiments, R^7, R^8, and R^9 are each hydrogen.

[0122] In some embodiments, R^6 is aryl or heteroaryl substituted with one to two substituents selected from the group consisting of halo, alkoxy, alkyl, amino, alkylamino, haloalkyl, and haloalkoxy.

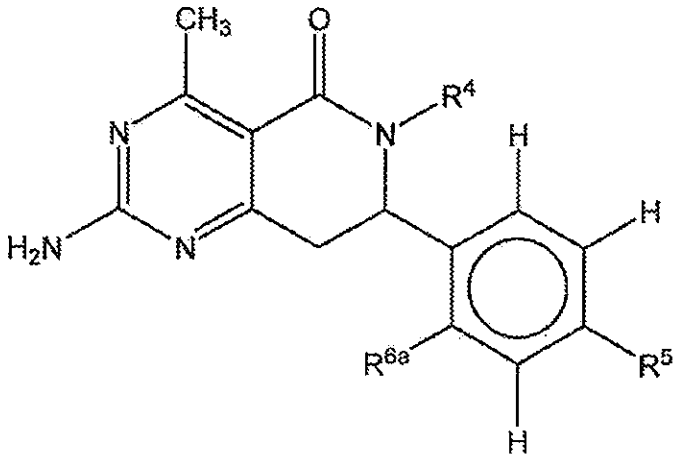
[0123] In some embodiments R^6 is selected from the group consisting of substituted aryl and substituted heteroaryl, wherein said aryl and heteroaryl is selected from the group consisting of furanyl, pyrrolyl, phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, imidazolyl, triazolyl, indolyl, oxadiazole, thiadiazole, quinolinyl, isoquinolinyl, isoxazolyl, oxazolyl, thiazolyl, and thienyl. In some aspects, the aforementioned groups are substituted with one to two substituents selected from the group consisting of halo, alkoxy, alkyl, amino, alkylamino, haloalkyl, and haloalkoxy.

[0124] In other embodiments R^6 is selected from the group consisting of (2-hydroxy-ethylamino)-pyrazin-2-yl, 1H-pyrazol-4-yl, 1-methyl-1H-pyrazol-4-yl, 1-methyl-1H-pyrazol-4-yl, 2-(5-methyl-pyridin-2-yl)-phenyl, 2,3-difluoro-phenyl, 2,3-dimethoxy-phenyl, 2,4-difluoro-phenyl, 2,4-dimethoxy-phenyl, 2,4-dimethoxy-pyrimidin-5-yl, 2,5-difluoro-phenyl, 2,6-difluoro-phenyl, 2,6-dimethyl-pyridin-3-yl, 2-acetamidophenyl, 2-aminocarbonylphenyl, 2-amino-pyrimidin-5-yl, 2-chloro-4-methoxy-pyrimidin-5-yl, 2-chloro-5-fluoro-pyridin-3-yl, 2-chloro-phenyl, 2-chloro-pyridin-3-yl, 2-chloro-pyridin-4-

yl, 2-difluoro-3-methoxyphenyl, 2-ethyl-phenyl, 2-ethoxy-thiazol-4-yl, 2-fluoro-3-methoxy-phenyl, 2-fluoro-3-methylphenyl, 2-fluoro-4-methyl-phenyl, 2-fluoro-5-methoxy-phenyl, 2-fluoro-5-methylphenyl, 2-fluorophenyl, 2-fluoro-pyridin-3-yl, 2-hydroxymethyl-3-methoxyphenyl, 2-hydroxymethylphenyl, 2-isoquinolin-4-yl, 2-methoxy-5-trifluoromethyl-phenyl, 2-methoxy-phenyl, 2-methoxy-pyridin-3-yl, 2-methoxy-pyrimidin-4-yl, 2-methoxy-thiazol-4-yl, 2-methyl-phenyl, 2-methyl-pyridin-3-yl, 2-oxo-1,2-dihydro-pyridin-3-yl, 2-phenoxyphenyl, 2-pyridin-3-yl, 2-pyrimidin-5-yl, 2-trifluoromethoxyphenyl, 2-trifluoromethoxy-phenyl, 3,4-dimethoxy-phenyl, 3,5-dimethyl-isoxazol-4-yl, 3,6-dimethyl-pyrazin-2-yl, 3-acetamidophenyl, 3-aminocarbonylphenyl, 3-bromo-phenyl, 3-chloro-pyrazin-2-yl, 3-cyanophenyl, 3-dimethylaminophenyl, 3-ethoxy-phenyl, 3-ethyl-4-methyl-phenyl, 3-ethynyl-phenyl, 3-fluoro-6-methoxy-pyridin-2-yl, 3-fluorophenyl, 3-fluoro-pyrazin-2-yl, 3-methanesulfonamidophenyl, 3-methoxycarbonylphenyl, 3-methoxyphenyl, 3-methoxy-pyrazin-2-yl, 3-methyl-3H-imidazo[4,5-b]pyrazin-5-yl, 3-methylphenyl, 3-methyl-pyridin-2-yl, 3-trifluoromethoxyphenyl, 3-trifluoromethylphenyl, 4,5-dimethoxy-pyrimidin-2-yl, 4-amino-5-fluoro-pyrimidin-2-yl, 4-chloro-2,5-dimethoxy-phenyl, 4-chloro-2-fluoro-phenyl, 4-chloro-2-methoxy-5-methyl-phenyl, 4-chloro-pyridin-3-yl, 4-difluoro-2-methyl-phenyl, 4-ethoxy-5-fluoro-pyrimidin-2-yl, 4-ethoxy-pyrimidin-2-yl, 4-ethoxy-pyrimidin-5-yl, 4-ethyl-1H-pyrazol-3-yl, 4-fluoro-2-methoxy-phenyl, 4-fluoro-2-methyl-phenyl, 4-fluorophenyl, 4-methoxy-5-methyl-pyrimidin-2-yl, 4-methoxy-pyridin-3-yl, 4-methoxy-pyrimidin-2-yl, 4-methoxy-pyrimidin-5-yl, 4-methyl-phenyl, 4-methyl-pyridin-2-yl, 4-methyl-pyridin-3-yl, 4-pyrrolidin-1-yl-pyrimidin-2-yl, 5,6-dimethoxy-pyrazin-2-yl, 5-acetyl-thiophen-2-yl, 5-amino-6-ethoxy-pyrazin-2-yl, 5-amino-6-methoxy-3-methyl-pyrazin-2-yl, 5-amino-6-methoxy-pyridin-2-yl, 5-chloro-4-methoxy-pyrimidin-2-yl, 5-chloro-6-methoxy-pyrazin-2-yl, 5-dimethylamino-6-methoxy-pyrazin-2-yl, 5-fluoro-2-methoxyphenyl, 5-fluoro-4-methoxy-pyrimidin-2-yl, 5-fluoro-6-methoxy-pyrazin-2-yl, 5-fluoro-pyridin-2-yl, 5-methoxy-pyridin-3-yl, 5-methoxy-thiophen-2-yl, 5-trifluoromethyl-pyrimidin-2-yl, 6-acetyl-pyridin-2-yl, 6-chloro-pyrazin-2-yl, 6-ethoxy-pyrazin-2-yl, 6-ethoxy-pyridin-2-yl, 6-fluoro-pyridin-2-yl, 6-fluoro-pyridin-3-yl, 6-hydroxy-pyridin-2-yl, 6-methoxy-5-methylamino-pyrazin-2-yl, 6-methoxy-5-methyl-pyrazin-2-yl, 6-methoxy-pyrazin-2-yl, 6-methoxy-pyridin-2-yl, 6-methoxy-pyridin-3-yl, 6-methylamino-pyrazin-2-yl, 6-methyl-pyridin-2-yl, 5-amino-6-(2,2,2-trifluoroethoxy)pyrazin-2-yl, and 6-trifluoromethyl-pyridin-2-yl.

[0125] The first component and the second component may be provided in a pharmaceutically acceptable carrier to form a pharmaceutical composition.

[0126] In another embodiment of the invention, compounds of formula (IV) are provided as the first component:



(IV)

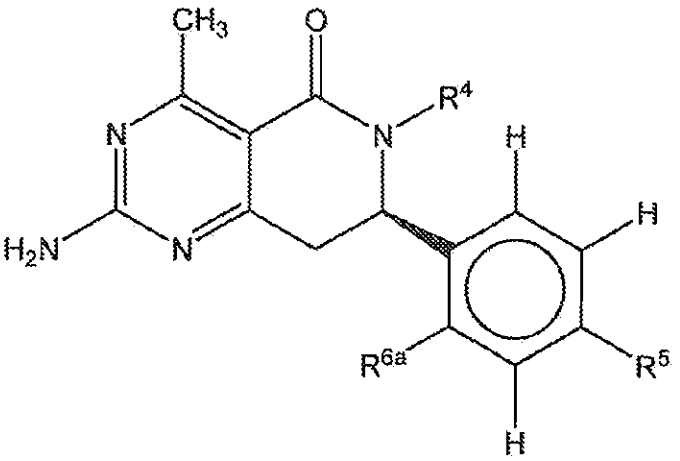
or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein

R^4 is hydrogen or substituted or unsubstituted C_1-C_6 alkyl,

R^5 is hydrogen or halo,

R^{6a} is selected from the group consisting of halo, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0127] In some embodiments compounds of formula (IVa) are provided as the first component:



(IVa)

or a tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein R^4, R^5, and R^{6a} are as previously defined for formula (IV).

[0128] In some embodiments of the compounds of formula (IV) or (IVa), R^4 is selected from the group consisting of hydrogen, benzyl, 1-(4-methoxyphenyl)ethyl, methyl, 3-aminopropyl, and 2-methyl-2-morpholinopropyl. In other embodiments, R is selected from the group consisting of methyl, ethyl, allyl, 3-methyl-butyl, and isobutyl.

[0129] In some embodiments, R^5 is hydrogen or fluoro. In some aspects R^5 is fluoro.

[0130] In some aspects, R^{6a} is aryl or heteroaryl substituted with one to two substituents selected from the group consisting of halo, alkoxy, alkyl, amino, alkylamino, haloalkyl, and haloalkoxy.

[0131] In some embodiments R^{6a} is selected from the group consisting of substituted aryl and substituted heteroaryl, wherein said aryl and heteroaryl is selected from the group consisting of furanyl, pyrrolyl, phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, imidazolyl, triazolyl, indolyl, oxadiazole, thiadiazole, quinolinyl, isoquinolinyl, isoxazolyl, oxazolyl, thiazolyl, and thienyl. In some aspects, the aforementioned groups are substituted with one to two substituents selected from the group consisting of halo, alkoxy, alkyl, amino, alkylamino, haloalkyl, and haloalkoxy.

[0132] In some embodiments, R^{6a} is selected from the group consisting of (2-hydroxy-ethylamino)-pyrazin-2-yl, 1H-pyrazol-4-yl, 1-methyl-1H-pyrazol-4-yl, 1-methyl-1H-pyrazol-4-yl, 2-(5-methyl-pyridin-2-yl)-phenyl, 2,3-difluoro-phenyl, 2,3-dimethoxy-phenyl, 2,4-difluoro-phenyl, 2,4-dimethoxy-phenyl, 2,4-dimethoxy-pyrimidin-5-yl, 2,5-difluoro-phenyl, 2,6-difluoro-phenyl, 2,6-dimethyl-pyridin-3-yl, 2-acetamidophenyl, 2-aminocarbonylphenyl, 2-amino-pyrimidin-5-yl, 2-chloro-4-methoxy-pyrimidin-5-yl, 2-chloro-5-fluoro-pyridin-3-yl, 2-chloro-phenyl, 2-chloro-pyridin-3-yl, 2-chloro-pyridin-4-yl, 2-difluoro-3-methoxyphenyl, 2-ethyl-phenyl, 2-ethoxy-thiazol-4-yl, 2-fluoro-3-methoxy-phenyl, 2-fluoro-3-methylphenyl, 2-fluoro-4-methyl-phenyl, 2-fluoro-5-methoxy-phenyl, 2-fluoro-5-methylphenyl, 2-fluorophenyl, 2-fluoro-pyridin-3-yl, 2-hydroxymethyl-3-methoxyphenyl, 2-hydroxymethylphenyl, 2-isoquinolin-4-yl, 2-methoxy-5-trifluoromethyl-phenyl, 2-methoxy-phenyl, 2-methoxy-pyridin-3-yl, 2-methoxy-pyrimidin-4-yl, 2-methoxy-thiazol-4-yl, 2-methyl-phenyl, 2-methyl-pyridin-3-yl, 2-oxo-1,2-dihydro-pyridin-3-yl, 2-phenoxyphenyl, 2-pyridin-3-yl, 2-pyrimidin-5-yl, 2-trifluoromethoxyphenyl, 2-trifluoromethoxy-phenyl, 3,4-dimethoxy-

phenyl, 3,5-dimethyl-isoxazol-4-yl, 3,6-dimethyl-pyrazin-2-yl, 3-acetamidophenyl, 3-aminocarbonylphenyl, 3-bromo-phenyl, 3-chloro-pyrazin-2-yl, 3-cyanophenyl, 3-dimethylaminophenyl, 3-ethoxy-phenyl, 3-ethyl-4-methyl-phenyl, 3-ethynyl-phenyl, 3-fluoro-6-methoxy-pyridin-2-yl, 3-fluorophenyl, 3-fluoro-pyrazin-2-yl, 3-methanesulfonamidophenyl, 3-methoxycarbonylphenyl, 3-methoxyphenyl, 3-methoxy-pyrazin-2-yl, 3-methyl-3H-imidazo[4,5-b]pyrazin-5-yl, 3-methylphenyl, 3-methyl-pyridin-2-yl, 3-trifluoromethoxyphenyl, 3-trifluoromethylphenyl, 4,5-dimethoxy-pyrimidin-2-yl, 4-amino-5-fluoro-pyrimidin-2-yl, 4-chloro-2,5-dimethoxy-phenyl, 4-chloro-2-fluoro-phenyl, 4-chloro-2-methoxy-5-methyl-phenyl, 4-chloro-pyridin-3-yl, 4-difluoro-2-methyl-phenyl, 4-ethoxy-5-fluoro-pyrimidin-2-yl, 4-ethoxy-pyrimidin-2-yl, 4-ethoxy-pyrimidin-5-yl, 4-ethyl-1H-pyrazol-3-yl, 4-fluoro-2-methoxy-phenyl, 4-fluoro-2-methyl-phenyl, 4-fluorophenyl, 4-methoxy-5-methyl-pyrimidin-2-yl, 4-methoxy-pyridin-3-yl, 4-methoxy-pyrimidin-2-yl, 4-methoxy-pyrimidin-5-yl, 4-methyl-phenyl, 4-methyl-pyridin-2-yl, 4-methyl-pyridin-3-yl, 4-pyrrolidin-1-yl-pyrimidin-2-yl, 5,6-dimethoxy-pyrazin-2-yl, 5-acetyl-thiophen-2-yl, 5-amino-6-ethoxy-pyrazin-2-yl, 5-amino-6-methoxy-3-methyl-pyrazin-2-yl, 5-amino-6-methoxy-pyridin-2-yl, 5-chloro-4-methoxy-pyrimidin-2-yl, 5-chloro-6-methoxy-pyrazin-2-yl, 5-dimethylamino-6-methoxy-pyrazin-2-yl, 5-fluoro-2-methoxyphenyl, 5-fluoro-4-methoxy-pyrimidin-2-yl, 5-fluoro-6-methoxy-pyrazin-2-yl, 5-fluoro-pyridin-2-yl, 5-methoxy-pyridin-3-yl, 5-methoxy-thiophen-2-yl, 5-trifluoromethyl-pyrimidin-2-yl, 6-acetyl-pyridin-2-yl, 6-chloro-pyrazin-2-yl, 6-ethoxy-pyrazin-2-yl, 6-ethoxy-pyridin-2-yl, 6-fluoro-pyridin-2-yl, 6-fluoro-pyridin-3-yl, 6-hydroxy-pyridin-2-yl, 6-methoxy-5-methylamino-pyrazin-2-yl, 6-methoxy-5-methyl-pyrazin-2-yl, 6-methoxy-pyrazin-2-yl, 6-methoxy-pyridin-2-yl, 6-methoxy-pyridin-3-yl, 6-methylamino-pyrazin-2-yl, 6-methyl-pyridin-2-yl, 5-amino-6-(2,2,2-trifluoroethoxy)pyrazin-2-yl, and 6-trifluoromethyl-pyridin-2-yl.

[0133] Preferred Hsp90 inhibitor compounds used as the first component of combination according to the invention include:

[0134] (R)-2-amino-7-[2-(2-fluoro-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0135] (S)-2-amino-6-benzyl-7-[4-fluoro-2-(2-fluoro-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0136] (R)-2-amino-7-[4-fluoro-2-(2-fluoro-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0137] (R)-2-amino-7-(2-bromo-4-fluoro-phenyl)-6-[(S)-1-(4-methoxy-phenyl)-ethyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0138] (R)-2-amino-7-[2-(6-methoxy-pyridin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0139] (R)-2-amino-7-[4-fluoro-2-(6-methoxy-pyridin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0140] 2-amino-7-[4-fluoro-2-(6-methoxy-pyridin-2-yl)-phenyl]-4,6-dimethyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0141] 2-amino-7-[4-fluoro-2-(2-fluoro-pyridin-3-yl)-phenyl]-4,6-dimethyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0142] 2-amino-7-[4-fluoro-2-(6-methoxypyridin-2-yl)phenyl]-4-methyl-7,8-dihydropyrido[4,3-d]pyrimidin-5(6H)-one;

[0143] 2-amino-7-[2-(6-methoxy-pyrazin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0144] (R)-2-amino-7-[4-fluoro-2-(6-methoxy-pyrazin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0145] 2-amino-7-[4-fluoro-2-(6-methoxy-pyrazin-2-yl)-phenyl]-4,6-dimethyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0146] 2-amino-7-[2-(2-methoxy-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0147] 2-amino-7-(5,2'-difluoro-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0148] 2-amino-7-(5-fluoro-2'-trifluoromethoxy-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0149] 2-amino-7-[2-(2-chloro-pyridin-3-yl)-4-fluoro-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0150] 2-amino-7-[4-fluoro-2-(6-fluoro-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0151] 2-amino-7-(4-fluoro-2-isoquinolin-4-yl-phenyl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0152] 2-amino-7-(5,3'-difluoro-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0153] 2-amino-7-[2-(4-chloro-pyridin-3-yl)-4-fluoro-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0154] 2-amino-7-(5,2'-difluoro-3'-methoxy-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0155] 2-amino-7-(5,4'-difluoro-2'-methyl-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0156] 2-amino-7-(5-fluoro-2'-methoxy-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0157] 2-amino-7-(4-fluoro-2-pyrimidin-5-yl-phenyl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0158] 2-amino-7-[4-fluoro-2-(2-methoxy-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0159] 2-amino-7-(5-fluoro-3'-methoxy-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0160] (R)-2-amino-6-(3-amino-propyl)-7-[4-fluoro-2-(6-methoxy-pyridin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0161] 2-amino-7-(4-fluoro-2-pyridin-3-yl-phenyl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0162] 2-amino-7-(5,2'-difluoro-4'-methyl-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0163] 2-amino-7-[4-fluoro-2-(1-methyl-1H-pyrazol-4-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0164] 2-amino-7-[4-fluoro-2-(1H-pyrazol-4-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0165] 2-amino-4-methyl-7-(5,2',3'-trifluoro-biphenyl-2-yl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0166] 2-amino-7-(2-bromo-4-fluoro-phenyl)-4-methyl-6-(2-methyl-2-morpholin-4-yl-propyl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0167] 2-amino-7-(3'-dimethylamino-5-fluoro-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0168] 2-amino-7-[2-(2,4-dimethoxy-pyrimidin-5-yl)-4-fluoro-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0169] 2-amino-7-[4-fluoro-2-(5-methoxy-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0170] 2-amino-7-(4-fluoro-2-pyrimidin-5-yl-phenyl)-4-methyl-6-(2-methyl-2-morpholin-4-yl-propyl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0171] 2-amino-7-[4-fluoro-2-(2-methoxy-pyridin-3-yl)-phenyl]-4-methyl-6-(2-methyl-2-morpholin-4-yl-propyl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0172] 2-amino-7-(5-fluoro-3'-methoxy-biphenyl-2-yl)-4-methyl-6-(2-methyl-2-morpholin-4-yl-propyl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

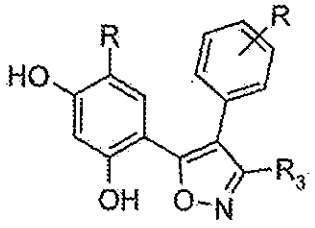
[0173] (R)-2-amino-7-[4-fluoro-2-(4-methoxy-5-methyl-pyrimidin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

[0174] 2-amino-7-(4-fluoro-2-furan-3-yl-phenyl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one, and

[0175] stereoisomers, tautomers, and pharmaceutically acceptable salts or prodrugs thereof.

[0176] Examples of the foregoing Hsp90 inhibitor compounds of Formula (I) and methods of making the same are disclosed in U.S. Patent Application Publication No. 2007-0123546 A1, published May 31, 2007, which is incorporated herein by reference in its entirety.

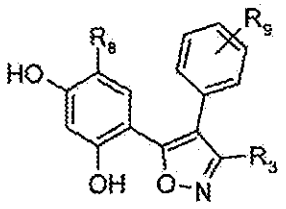
[0177] Other suitable Hsp90 inhibitors include isoxazole derivatives of formula (D), and regioisomers thereof, and their salts, solvates and hydrates, and prodrugs thereof



(D)

[0178] wherein each R independently represents an optional substituent and R3 represents a carboxamide group.

[0179] Preferably the present invention relates to the use of compounds consisting of those of formula (E), and regioisomers thereof, and their salts, solvates and hydrates, and prodrugs thereof:



(E)

[0180] wherein R_3 represents a carboxamide group (such as ethylaminocarbonyl $CH_3CH_2NHC(=O)$-, or isopropylaminocarbonyl $(CH_3)_2CHNHC(=O)$-); R_9 represents $-CH_2NR^{10}R^{11}$ or $-NR^{10}R^{11}$ wherein the substituted amino group $-NR^{10}R^{11}$ is a solubilising group, (such as morpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, ethylamino, isopropylamino, diethylamino, cyclohexylamino, cyclopentylamino, methoxyethylamino, piperidin-4-yl, N-acetylpiperazinyl, N-methylpiperazinyl, methylsulfonylamino, thiomorpholinyl, thiomorpholinyl-dioxide, 4-hydroxyethylpiperidinyl, and 4-hydroxypiperidinyl); and R_8 represents an optional substituent, especially a small lipophilic group (such as ethyl, isopropyl, bromo, or chloro).

[0181] In such 5-substituted, 2,4-diyhdroxy phenyl compounds of the invention, the hydroxyl groups may be protected by groups which are cleaved in the body to release the hydroxyl groups. Known prodrug-type groups of this kind which are cleaved to hydroxyls include alkylcarbonyloxy groups such as methylcarbonyloxy, and alkylaminocarbonyloxy groups such as dialkylamino- or isopropylamino-carbonyloxy.

[0182] Specific compounds with which the invention is concerned include particularly the following, and their salts, N-oxides, hydrates and solvates, and prodrugs thereof:

[0183] 5-(2,4-Dihydroxy-5-isopropyl-phenyl)-4-(4-morpholin-4-ylmethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide

[0184] 5-(2,4-Dihydroxy-5-isopropyl-phenyl)-4-(4-piperidin-1-ylmethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide

[0185] 4-(4-Diethylaminomethyl-phenyl)-5-(2,4-dihydroxy-5-isopropyl-phenyl)-isoxazole-3-carboxylic acid ethylamide

[0186] 5-(2,4-Dihydroxy-5-isopropyl-phenyl)-4-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-isoxazole-3-carboxylic acid ethylamide

[0187] 5-(2,4-Dihydroxy-5-isopropyl-phenyl)-4-(4-ethylaminomethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide

[0188] 5-(2,4-Dihydroxy-5-isopropyl-phenyl)-4-[4-(isopropylamino-methyl)-phenyl]-isoxazole-3-carboxylic acid ethylamide

[0189] 4-(4-Cyclohexylaminomethyl-phenyl)-5-(2,4-dihydroxy-5-isopropyl-phenyl)-isoxazole-3-carboxylic acid ethylamide

[0190] 4-[4-(tert-Butylamino-methyl)-phenyl]-5-(2,4-dihydroxy-5-isopropyl-phenyl)-isoxazole-3-carboxylic acid ethylamide

[0191] 5-(2,4-Dihydroxy-5-isopropyl-phenyl)-4-{4-[(2-methoxy-ethylamino)-methyl]-phenyl}-isoxazole-3-carboxylic acid ethylamide

[0192] 5-(2,4-Dihydroxy-5-isopropyl-phenyl)-4-(4-morpholin-4-ylmethyl-phenyl)-isoxazole-3-carboxylic acid isopropylamide

[0193] 5-(2,4-Dihydroxy-5-isopropyl-phenyl)-4-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-isoxazole-3-carboxylic acid isopropylamide

[0194] 5-(5-tert-Butyl-2,4-dihydroxy-phenyl)-4-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-isoxazole-3-carboxylic acid ethylamide

[0195] 5-(5-tert-Butyl-2,4-dihydroxy-phenyl)-4-(4-piperidin-1-ylmethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide

[0196] 5-(2,4-Dihydroxy-5-isobutyl-phenyl)-4-(4-morpholin-4-ylmethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide

[0197] 5-(2,4-Dihydroxy-5-isobutyl-phenyl)-4-(4-piperidin-1-ylmethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide

[0198] 5-(5-tert-Butyl-2,4-dihydroxy-phenyl)-4-(4-morpholin-4-ylmethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide

[0199] 5-(5-tert-Butyl-2,4-dihydroxy-phenyl)-4-(4-diethylaminomethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide

[0200] 3-(5-Chloro-2,4-dihydroxy-phenyl)-4-(4-morpholin-4-ylmethyl-phenyl)-isoxazole-5-carboxylic acid ethylamide

[0201] 4-(4-Diethylaminomethyl-phenyl)-5-(4,6-dihydroxy-2'-methyl-biphenyl-3-yl)-isoxazole-3-carboxylic acid ethylamide

[0202] 4-(4-Diethylaminomethyl-phenyl)-5-(4'-fluoro-4,6-dihydroxy-biphenyl-3-yl)-isoxazole-3-carboxylic acid ethylamide

[0203] 4-(4-Diethylaminomethyl-phenyl)-5-(4,6-dihydroxy-biphenyl-3-yl)-isoxazole-3-carboxylic acid ethylamide

[0204] 5-(2'-Fluoro-4,6-dihydroxy-biphenyl-3-yl)-4-(4-pyrrolidin-1-ylmethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide

[0205] 5-(4,6-Dihydroxy-biphenyl-3-yl)-4-(4-morpholin-4-ylmethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide

[0206] 5-(2,4-Dihydroxy-5-phenethyl-phenyl)-4-(4-morpholin-4-ylmethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide

[0207] 5-(5-Chloro-2,4-dihydroxy-phenyl)-4-(4-piperidin-1-ylmethyl-phenyl)-isoxazole-3-carboxylic acid isopropylamide

[0208] 4-(4-Diethylaminomethyl-phenyl)-5-(5-ethyl-2,4-dihydroxy-phenyl)-isoxazole-3-carboxylic acid ethylamide

[0209] 5-(5-Ethyl-2,4-dihydroxy-phenyl)-4-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-isoxazole-3-carboxylic acid ethylamide

[0210] 5-(5-Ethyl-2,4-dihydroxy-phenyl)-4-(4-morpholin-4-ylmethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide

[0211] 5-(5-Chloro-2,4-dihydroxy-phenyl)-4-(4-diethylaminomethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide

[0212] 5-(5-Chloro-2,4-dihydroxy-phenyl)-4-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-isoxazole-3-carboxylic acid ethylamide

[0213] 5-(5-Chloro-2,4-dihydroxy-phenyl)-4-(4-morpholin-4-ylmethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide

[0214] Compounds within the scope of formula (D) or formula (E) and the process for their manufacture are disclosed in WO 04/072051 published on August 26, 2004 which is hereby incorporated into the present application by reference. A preferred compound is 5-(2,4-Dihydroxy-5-isopropyl-phenyl)-4-(4-morpholin-4-ylmethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide.

[0215] Suitable mTOR inhibitors include for example:

[0216] I. Rapamycin which is an immunosuppressive lactam macrolide that is produced by *Streptomyces hygroscopicus*.

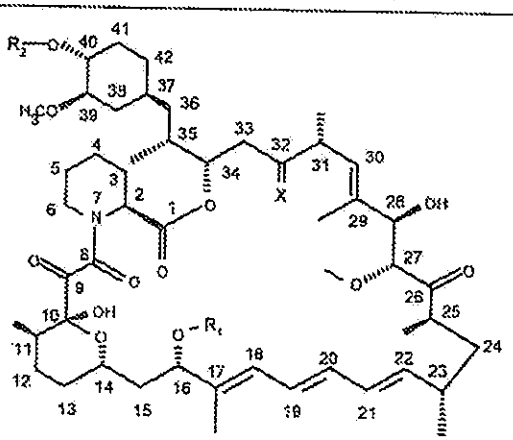
[0217] II. Rapamycin derivatives such as:

a. substituted rapamycin e.g. a 40-O-substituted rapamycin e.g. as described in US 5,258,389, WO 94/09010, WO 92/05179, US 5,118,677, US 5,118,678, US 5,100,883, US 5,151,413, US 5,120,842, WO 93/11130, WO 94/02136, WO 94/02485 and WO 95/14023 all of which are incorporated herein by reference;

b. a 16-O-substituted rapamycin, such as disclosed in WO 94/02136, WO 95/16691 and WO 96/41807, the contents of which are incorporated herein by reference;

c. a 32-hydrogenated rapamycin, such as described in WO 96/41807 and US 5,256,790, incorporated herein by reference.

d. Preferred rapamycin derivatives are compounds of formula I'



I'

wherein

R_1 is CH_3 or C_{3-6}alkynyl,

R_2 is H or $-CH_2-CH_2-OH$, 3-hydroxy-2-(hydroxymethyl)-2-methyl-propanoyl or tetrazolyl, and X is =O, (H,H) or (H,OH)

provided that R_2 is other than H when X is =O and R_1 is CH_3,

or a prodrug thereof when R_2 is $-CH_2-CH_2-OH$, e.g. a physiologically hydrolysable ether thereof.

[0218] Compounds of formula I' are disclosed, for example, in WO 94/09010, WO 95/16691 or WO 96/41807, which are incorporated herein by reference. They may be prepared as disclosed or by analogy to the procedures described in these references

[0219] Preferred mTOR inhibitor compounds are 32-deoxorapamycin, 16-pent-2-ynyloxy-32-deoxorapamycin, 16-pent-2-ynyloxy-32(S)-dihydro-rapamycin, 16-pent-2-ynyloxy-32(S)-dihydro-40-O-(2-hydroxyethyl)-rapamycin and, more preferably, 40-O-(2-hydroxyethyl)-rapamycin, disclosed as Example 8 in WO 94/09010.

[0220] Particularly preferred rapamycin derivatives of formula I' are 40-O-(2-hydroxyethyl)-rapamycin, 40-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]-rapamycin (also called CCI779), 40-epi-(tetrazolyl)-rapamycin (also called ABT578), 32-deoxorapamycin, 16-pent-2-ynyloxy-32(S)-dihydro rapamycin, or TAFA-93.

[0221] e. Rapamycin derivatives also include so-called rapalogs, e.g. as disclosed in WO 98/02441 and WO 01/14387, e.g. AP23573, AP23464, or AP23841.

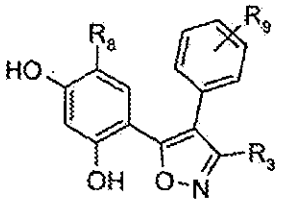
[0222] Rapamycin and derivatives thereof have, on the basis of observed activity, e.g. binding to macrophilin-12 (also known as FK-506 binding protein or FKBP-12),

e.g. as described in WO 94/09010, WO 95/16691 or WO 96/41807, been found to be useful e.g. as immunosuppressant, e.g. in the treatment of acute allograft rejection.

[0223] The present invention provides

[0224] A pharmaceutical combination comprising:

[0225] a) a compound of formula (E)



(E)

[0226] wherein

[0227] R_3 is selected from ethylaminocarbonyl $CH_3CH_2NHC(=O)$- or isopropylaminocarbonyl $(CH_3)_2CHNHC(=O)$-),

[0228] R_8 is selected from ethyl, isopropyl, bromo, or chloro; and

[0229] R_9 is selected from morpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, ethylamino, isopropylamino, diethylamino, cyclohexylamino, cyclopentylamino, methoxyethylamino, piperidin-4-yl, N-acetylpiperazinyl, N-methylpiperazinyl, methylsulfonylamino, thiomorpholinyl, thiomorpholinyl-dioxide, 4-hydroxyethylpiperidinyl or 4-hydroxypiperidinyl; and

[0230] b) at least one mTOR inhibitor

[0231] The compound of formula (E) may be a Hsp90 inhibitor.

[0232] The compound of formula (E) may be 5-(2,4-Dihydroxy-5-isopropyl-phenyl)-4-(4-morpholin-4-ylmethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide.

[0233] In another aspect the present invention provides the use of a compound of formula (E) or 5-(2,4-Dihydroxy-5-isopropyl-phenyl)-4-(4-morpholin-4-ylmethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide and at least one mTOR inhibitor for the manufacture of a medicament for the treatment or prevention of a proliferative disease.

[0234] In a further aspect the present invention provides a compound of formula (E) or 5-(2,4-Dihydroxy-5-isopropyl-phenyl)-4-(4-morpholin-4-ylmethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide and at least one mTOR inhibitor for use in treating or preventing a proliferative disease.

[0235] In another aspect the present invention provides a method of treating or preventing a proliferative disease by administering a compound of formula (E) or 5-(2,4-

Dihydroxy-5-isopropyl-phenyl)-4-(4-morpholin-4-ylmethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide and at least one mTOR inhibitor.

[0236] The mTOR inhibitor used according to the present invention may be selected from RAD rapamycin (sirolimus) and derivatives/analogs thereof such as everolimus or RAD001; CCI-779, ABT578, SAR543, ascomycin (an ethyl analog of FK506), AP23573, AP23841, AZD08055 and OSI027. Particularly preferred mTOR inhibitors in accordance with the present invention are sirolimus and/or everolimus.

[0237] III. Ascomycin, which is an ethyl analog of FK506.

[0238] In each case where citations of patent applications are given above, the subject matter relating to the compounds is hereby incorporated into the present application by reference. Comprised are likewise the pharmaceutically acceptable salts thereof, the corresponding racemates, diastereoisomers, enantiomers, tautomers, as well as the corresponding crystal modifications of above disclosed compounds where present, e.g. solvates, hydrates and polymorphs, which are disclosed therein. The compounds used as active ingredients in the combinations of the invention can be prepared and administered as described in the cited documents, respectively. Also within the scope of this invention is the combination of more than two separate active ingredients as set forth above, i.e., a pharmaceutical combination within the scope of this invention could include three active ingredients or more.

[0239] In embodiments, the mTOR inhibitor used according to the present invention may be selected from RAD rapamycin (sirolimus) and derivatives/analogs thereof such as everolimus or RAD001; CCI-779, ABT578, SAR543, ascomycin (an ethyl analog of FK506), AP23573 and AP23841.

[0240] The term "mTOR kinase dependent diseases" includes but is not restricted to the following symptoms:

- Organ or tissue transplant rejection, e.g. for the treatment of recipients of e.g. heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants; graft-versus-host disease, such as following bone marrow transplantation;
- Restenosis
- Hamartoma syndromes, such as tuberous sclerosis or Cowden Disease
- Lymphangioleiomyomatosis
- Retinitis pigmentosis

- Autoimmune diseases including encephalomyelitis, insulin-dependent diabetes mellitus, lupus, dermatomyositis, arthritis and rheumatic diseases
- Steroid-resistant acute Lymphoblastic Leukaemia
- Fibrotic diseases including scleroderma, pulmonary fibrosis, renal fibrosis, cystic fibrosis
- Pulmonary hypertension
- Immunomodulation
- Multiple sclerosis
- VHL syndrome
- Carney complex
- Familial adenonamtous polyposis
- Juvenile polyposis syndrome
- Birt-Hogg-Duke syndrome
- Familial hypertrophic cardiomyopathy
- Wolf-Parkinson-White syndrome
- Neurodegenarative disorders such as Parkinson's, Huntingtin's, Alzheimer's and dementias caused by tau mutations, spinocerebellar ataxia type 3, motor neuron disease caused by SOD1 mutations, neuronal ceroid lipofucinoses/Batten disease (pediatric neurodegeneration)
- wet and dry macular degeneration
- muscle wasting (atrophy, cachexia) and myopathies such as Danon's disease.
- bacterial and viral infections including M. tuberculosis, group A streptococcus, HSV type I, HIV infection
- Neurofibromatosis including Neurofibromatosis type 1,
- Peutz-Jeghers syndrome

[0241] Furthermore, "mTOR kinase dependent diseases" include cancers and other related malignancies. A non-limiting list of the cancers associated with pathological mTOR signaling cascades includes breast cancer, renal cell carcinoma, gastric tumors, neuroendocrine tumors, lymphomas and prostate cancer.

[0242] Examples for a proliferative disease the can be treated with a combination of Hsp90 inhibitor and mTOR or another pharmaceul agent of the present invention are other are for instance benign or malignant tumor, carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina or thyroid, genitourinary area, melanoma, glioma,

sarcoma, glioblastomas, multiple myeloma or gastrointestinal cancer, especially colon carcinoma or colorectal adenoma or a tumor of the neck and head, an epidermal hyperproliferation, psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, neuroblastoma, lymphomas, a mammary carcinoma, or a leukemia.

[0243] In particular, the inventive compositions are particularly useful for treating:

[0244] a breast tumor; an epidermoid tumor, such as an epidermoid head and/or neck tumor or a mouth tumor; a lung tumor, e.g., a small cell or non-small cell lung tumor; a gastrointestinal tumor, e.g., a colorectal tumor; or a genitourinary tumor, e.g., a prostate tumor (especially a hormone-refractory prostate tumor); or

[0245] (ii) a proliferative disease that is refractory to the treatment with other chemotherapeutics; or

[0246] (iii) a tumor that is refractory to treatment with other chemotherapeutics due to multidrug resistance.

[0247] In a broader sense of the invention, a proliferative disease may furthermore be a hyperproliferative condition, such as leukemias e.g. acute myeloid leukemia, e.g. chronic myeloid leukemia, e.g. chronic lymphatic leukemia, e.g. acute lymphatic leukemia, e.g. multiple myeloma e.g. lymphomas, and/or for use in treatment of myelodysplastic syndrome, systemic mastocytosis, hyperplasias, fibrosis (especially pulmonary, but also other types of fibrosis, such as renal fibrosis), angiogenesis, psoriasis, atherosclerosis, smooth muscle proliferation in the blood vessels, such as stenosis or restenosis following angioplasty, von Hippel-Lindau syndrome, multicentric Castleman disease and/or psioriasis

[0248] The combination of the present invention can also be used to prevent or treat diseases that are triggered by persistent angiogenesis, such as psoriasis; Kaposi's sarcoma; restenosis, e.g., stent-induced restenosis; endometriosis; Crohn's disease; Hodgkin's disease; leukemia; arthritis, such as rheumatoid arthritis; hemangioma; angiofibroma; eye diseases, such as diabetic retinopathy and neovascular glaucoma; renal diseases, such as glomerulonephritis; diabetic nephropathy; malignant nephrosclerosis; thrombotic microangiopathic syndromes; transplant rejections and glomerulopathy; fibrotic diseases, such as cirrhosis of the liver; mesangial cell-proliferative diseases; arteriosclerosis; injuries of the nerve tissue; and for inhibiting the re-occlusion of vessels after balloon catheter treatment, for use in vascular prosthetics or after inserting mechanical devices for holding vessels open, such as,

e.g., stents, as immunosuppressants, as an aid in scar-free wound healing, and for treating age spots and contact dermatitis.

[0249] Combinations of the present invention include use for the treatment, prevention or inhibition of diseases characterized by cell proliferation and infiltration of inflammatory cells such as inflammation, RHA, asthma, chronic bronchitis, artheroschlerosis, and transplant rejection.

[0250] Where a tumor, a tumor disease, a carcinoma or a cancer are mentioned, also metastasis in the original organ or tissue and/or in any other location are implied alternatively or in addition, whatever the location of the tumor and/or metastasis.

[0251] In another embodiment the present invention provides the use of the first pharmaceutical component of the present invention in combination with a mTOR inhibitor for the manufacture of a medicament for the treatment or prevention of a proliferative disease.

[0252] In a further embodiment the present invention provides the first pharmaceutical component of the present invention in combination with a mTOR inhibitor for use in treating or preventing a proliferative disease.

[0253] Suitable clinical studies may be, for example, open label, dose escalation studies in patients with proliferative diseases. Such studies prove in particular the synergism of the active ingredients of the combination of the invention. The beneficial effects on proliferative diseases may be determined directly through the results of these studies which are known as such to a person skilled in the art. Such studies may be, in particular, suitable to compare the effects of a monotherapy using the active ingredients and a combination of the invention. Preferably, the dose of agent (a) is escalated until the Maximum Tolerated Dosage is reached, and agent (b) is administered with a fixed dose. Alternatively, the agent (a) may be administered in a fixed dose and the dose of agent (b) may be escalated. Each patient may receive doses of the agent (a) either daily or intermittent. The efficacy of the treatment may be determined in such studies, e.g., after 12, 18 or 24 weeks by evaluation of symptom scores every 6 weeks.

[0254] The administration of a pharmaceutical combination of the invention may result not only in a beneficial effect, e.g. a synergistic therapeutic effect, e.g. with regard to alleviating, delaying progression of or inhibiting the symptoms, but also in further surprising beneficial effects, e.g. fewer side-effects, an improved quality of life

or a decreased morbidity, compared with a monotherapy applying only one of the pharmaceutically active ingredients used in the combination of the invention.

[0255] A further benefit may be that lower doses of the active ingredients of the combination of the invention may be used, for example, that the dosages need not only often be smaller but may also be applied less frequently, which may diminish the incidence or severity of side-effects. This is in accordance with the desires and requirements of the patients to be treated.

[0256] It is one objective of this invention to provide a pharmaceutical combination, such as composition comprising a quantity of a first component and a second component as previously described, which may be jointly therapeutically effective at targeting or preventing proliferative diseases. These first and second components may be provided for administration in a fixed combination, i.e. in a single galenical composition, which may be prepared in a manner known per se, suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including humans in combination with one or more pharmaceutically acceptable carriers or diluents, especially suitable for enteral or parenteral application.

[0257] Alternatively, the combination is a first component and the second component that can be provided as a combination that are separate pharmaceutical doses, including compositions in a kit or pharmaceutical doses not sold as a kit.

[0258] The pharmaceutical compositions for separate administration of the first component and the second component may be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including humans. Each such composition for separate administration comprises a therapeutically effective amount of at least one pharmacologically active component in combination with one or more pharmaceutically acceptable carriers or diluents.

[0259] The term pharmaceutical component is used synonymously as the terms pharmaceutical agent or active ingredient.

[0260] Suitable pharmaceutical compositions may contain, for example, from about 0.1 % to about 99.9%, preferably from about 1 % to about 60 %, of the active ingredient(s). Pharmaceutical preparations for the combination therapy for enteral or parenteral administration are, for example, those in unit dosage forms, such as sugar-coated tablets, tablets, capsules or suppositories, or ampoules. If not indicated

otherwise, these are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. It will be appreciated that the unit content of a pharmaceutical component contained in an individual dose of each dosage form need not in itself constitute an effective amount since the necessary effective amount may be reached by administration of a plurality of dosage units.

[0261] In a method of treating proliferative disease, the first component and the second component may be administered together, sequentially or separately. The first and second components may be delivered in one combined unit dosage form or in multiple separate unit dosage forms.

[0262] In particular, a therapeutically effective amount of each of the pharmaceutical components of the invention may be administered simultaneously or sequentially and in any order, and the components may be administered separately or as a fixed combination. For example, the method of preventing or treating proliferative diseases according to the invention may comprise (i) administration of the first component in free or pharmaceutically acceptable salt form and (ii) administration of the second component in free or pharmaceutically acceptable salt form, simultaneously or sequentially in any order, in jointly therapeutically effective amounts, preferably in synergistically effective amounts, e.g. in daily or intermittently dosages corresponding to the amounts described herein. The individual combination components of the combination of the invention may be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. Furthermore, the term administering also encompasses the use of a pro-drug of a combination component that convert *in vivo* to the combination partner as such. The instant invention is therefore to be understood as embracing all such regimens of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

[0263] The effective dosage of each of the components employed in the combination of the invention may vary depending on the particular compound or pharmaceutical composition employed, the mode of administration, the condition being treated, the severity of the condition being treated. Thus, the dosage regimen of the combination of the invention is selected in accordance with a variety of factors including the route of administration and the renal and hepatic function of the patient. A clinician or physician of ordinary skill can readily determine and prescribe the effective amount of

the single active ingredients required to alleviate, counter or arrest the progress of the condition. Optimal precision in achieving concentration of the active ingredients within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the active ingredients' availability to target sites.

[0264] The amount of active ingredient that may be combined with carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy. The therapeutically effective amount for a given situation can be readily determined by routine experimentation and is within the skill and judgment of the ordinary clinician.

[0265] For purposes of the present invention, a therapeutically effective dose will generally be a total daily dose administered to a host in single or divided doses may be in amounts, for example, of from 0.001 to 1000 mg/kg body weight daily and more preferred from 1.0 to 30 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

[0266] The compounds according to Formula (I), the mTOR inhibitors and the pharmaceutical compositions comprising these active ingredients, may be administered orally, parenterally, sublingually, by aerosolization or inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or ionophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

[0267] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are

conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or di-glycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0268] Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols, which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

[0269] Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

[0270] Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, cyclodextrins, and sweetening, flavoring, and perfuming agents.

[0271] The compounds according to Formula (I), mTOR inhibitors and pharmaceutical compositions described herein can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott (ed.), "Methods in Cell Biology," Volume XIV, Academic Press, New York, 1976, p. 33 *et seq.*

[0272] In addition to being combine with mTOR inhibitors, the Hsp90 compounds of the present invention can be combine with one or more other pharmaceutical agents. These agents can be an ACE inhibitor; an adenosine-kinase-inhibitor; an adjuvant; an

adrenal cortex antagonist; AKT pathway inhibitor; an alkylating agent; an angiogenesis inhibitor; an angiostatic steroid; an anti-androgen; an anti-estrogen; an anti-hypercalcemia agent; an anti-leukemic compound; an anti-metabolite; an anti-proliferative antibody; an apoptosis inducer; an AT1 receptor antagonist; an aurora kinase inhibitor; an aromatase inhibitor; a biological response modifier; a bisphosphonate; a Bruton's Tyrosine Kinase (BTK) inhibitor; a calcineurin inhibitor; a CaM kinase II inhibitor; a CD45 tyrosine phosphatase inhibitor; a CDC25 phosphatase inhibitor; a CHK kinase inhibitor; a compound targeting/decreasing a protein or lipid kinase activity or a protein or lipid phosphatase activity, a further anti-angiogenic compound or a compound which induces cell differentiation processes; a controlling agent for regulating genistein, olomucine and/or tyrphostins; a cyclooxygenase inhibitor; a cRAF kinase inhibitor; a cyclin dependent kinase inhibitor; a cysteine protease inhibitor; a DNA intercalator; a DNA strand breaker; an E3 Ligase inhibitor; an EDG binder; an endocrine hormone; a farnesyltransferase inhibitor; a Flk-1 kinase inhibitor; a compound which targets, decreases or inhibits the activity of Flt-3; a gonadorelin agonist; a Glycogen synthase kinase-3 (GSK3) inhibitor; a heparanase inhibitor; an agent used in the treatment of hematologic malignancies; a histone deacetylase (HDAC) inhibitor; an implant containing corticosteroids; a I-kappa B-alpha kinase inhibitor (IKK); an insulin receptor tyrosine kinase inhibitor; a c-Jun N-terminal kinase (JNK) kinase inhibitor; a microtubule binding agent; a Mitogen-activated protein (MAP) kinase-inhibitor; a MDM2 inhibitor; a MEK inhibitor; a methionine aminopeptidase inhibitor; a matrix metalloproteinase (MMP) inhibitor; a monoclonal antibody; a NGFR tyrosine-kinase-inhibitor; a p38 MAP kinase inhibitor, including a SAPK2/p38 kinase inhibitor; a p56 tyrosine kinase inhibitor; a PDGFR tyrosine kinase inhibitor; a phosphatidylinositol 3-kinase inhibitor; a phosphatase inhibitor; photodynamic therapy; a platinum agent; a protein phosphatase inhibitor, including a PP1 and PP2 inhibitor and a tyrosine phosphatase inhibitor; a PKC inhibitor and a PKC delta kinase inhibitor; a polyamine synthesis inhibitor; a proteosome inhibitor; a PTP1B inhibitor; a protein tyrosine kinase inhibitor including a SRC family tyrosine kinase inhibitor; a Syk tyrosine kinase inhibitor; and a JAK-2 and/or JAK-3 tyrosine kinase inhibitor; an inhibitor of Ras oncogenic isoforms; a retinoid; a ribonucleotide reductase inhibitor; a RNA polymerase II elongation inhibitor; an S-adenosylmethionine decarboxylase inhibitor; a serine/threonine kinase inhibitor; a somatostatin receptor antagonist; a sterol biosynthesis inhibitor; a telomerase inhibitor; a topoisomerase inhibitor; tumor cell

damaging approaches; a monoclonal antibody of VEGF or VEGFR; VEGFR tyrosine kinase inhibitor; or a RANKL inhibitor.

[0273] Specifc examples of compounds that can be combine with an Hsp90 inhibitor of the present invention are CIBACEN; benazepril; enazepril; captopril; enalapril; fosinopril; lisinopril; moexipril; quinapril; ramipril; perindopril; trandolapril; 5-Iodotubercidin; Leucovorin; Levamisole; Mitotane; Deguelin; Trciribine; Chlorambucil; cyclophosphamide; Dacarbazine; Lomustine; Procarbazine; Thiotepa; Melphalan; Temozolomide; Carmustine; Ifosfamide; Mitomycin; Altretamine; Busulfan; Machlorethamine hydrochloride; nitrosourea; Streptozocin; estramustine; Fumagillin; Shikonin; Tranilast; ursolic acid; suramin; thalidomide; anecortave; triamcinolone; hydrocortisone; 11-[illegible]-epihydrocotisol; cortexolone; 17[illegible]-hydroxyprogesterone; corticosterone; desoxycorticosterone; testosterone; estrone; dexamethasone; Nilutamide; bicalutamide; Toremifene; Letrozole; Testolactone; Anastrozole; Bicalutamide; Flutamide; Tamoxifen Citrate; Exemestane; Fulestrant; tamoxifen; fulvestrant; raloxifene; raloxifene hydrochloride; gallium (III) nitrate hydrate; pamidronate disodium; Ara-C; hypoxanthine; 6-mercaptopurine (6-MP); fludarabine phosphate; Cytarabine; Fludarabine; Flexuridine; Fluorouracil; Capecitabine; Raltitrexed; Methotrexate; Cladribine; Gemcitabine; Gemcitabine hydrochloride; Thioguanine; Hydroxyurea; 5-azacytidine; decitabine; edatrexate; pemetrexed;; bevacizumab; rituximab; PRO64553; ethanol, 2-[[3-(2,3-dichlorophenoxy)propyl]amino]-(9CI); gambogic acid; Embelin; Arsenic Trioxide; DIOVAN; Binucleine 2; atamestane; exemestane; formestane; aminoglutethimide; roglethimide; pyridoglutethimide; trilostane; testolactone; ketokonazole; vorozole; fadrozole; anastrozole; letrozole; lymphokine; interferon γ; etridonic; clodronic; tiludronic; pamidronic; alendronic; ibandronic; risedronic; zoledronic acid; terreic acid; Cypermethrin; Deltamethrin; Fenvalerate; Tyrphostin 8; 5-Isoquinolinesulfonic acid, 4-[(2S)-2-[(5-isoquinolinylsulfonyl)methylamino]-3-oxo-3-(4-phenyl-1-piperazinyl)propyl]phenyl ester (9CI); benzenesulfonamide, N-[2-[[[3-(4-chlorophenyl)-2-propenyl]methyl]amino]methyl]phenyl]-N-(2-hydroxyethyl)-4-methoxy-(9CI); Phosphonic acid, [[2-(4-bromophenoxy)-5-nitrophenyl]hydroxymethyl]-(9CI); 1,4-naphthalenedione, 2,3-bis[(2-hydroyethyl)thio]-(9CI); Debromohymenialdisine; 7H-pyrrolo[2,3-d]pyrimidine derivatives, including {6-[4-(4-ethyl-piperazine-1-ylmethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrinidinpyrimidin-4-yl]-((R)-1-phenyl-ethyl)-amine; BAY 43-9006; (4-tert-butyl-phenyl)-94-pyridin-4-ylmethyl-isoquinolin-1-yl)-amine; imatinib;

SU101; SU6668; GFB-111; 4-amino-5-phenyl-7-cyclobutyl-pyrrolo[2,3-d]pyrimidine derivatives (AEW541); PD180970; AG957; NSC 680410; PD173955; BMS354825; midostaurin; UCN-01; safingol; BAY 43-9006; Bryostatin 1; Perifosine; Ilmofosine; RO 318220; RO 320432; GO 6976; Isis 3521; LY333531/LY379196; PD184352; QAN697; imatinib mesylate (GLEEVEC); tyrphostin or pyrymidylaminobenzamide and derivatives thereof; Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556; AG957 and adaphostin (4-{[(2,5-dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester, NSC 680410, adaphostin); phosphatase 1; phosphatase 2A; PTEN; okadaic acid; TNP-470; retinoic acid, □,□or □-tocopherol or □,□or □-tocotrienol; Daidzein; Iso-Olomoucine; Tyrphostin 1; 1H-indole-3-acetamide, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-N-(2-phenylethyl)-(9Cl); 5-alkyl substituted 2-arylaminophenylacetic acid; celecoxib; rofecoxib; etoricoxib; valdecoxib; 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid, lumiracoxib; 3-(3,5-dibromo-4-hydroxybenzylidene)-5-iodo-1,3-dihydroindol-2-one; benzamide, 3-(dimethylamino)-N-[3-[(4-hydroxybenzoyl)amino]-4-methylphenyl]-(9Cl); N9-Isopropyl-Olomoucine; Olomoucine; Purvalanol B; Roascovitine; Indirubin; Kenpaullone; purvalanol A; Indirubin-3'-monooxime; 4-morpholinecarboxamide,N-[(1S)-3-fluoro-2-oxo-1-(2-phenylethyl)propyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-(9Cl); Plicamycin; Dactinomycin; Bleomycin; N-((3,3,3-trifluoro-2-trifluoromethyl)propionyl)sulfa nilamide; FTY720; Leuprolide; megestrol acetate; ; Tyrphostin 23; Tyrphostin 25; Tyrphostin 47; Tyrphostin 51; Tyrphostin AG 825; 2-propenamide, 2-cyano-3-(3,4-dihydroxyphenyl)-N-phenyl-,(2E)-(9Cl); Tyrphostin Ag 1478; Lavendustin A; 3-pyridineacetonitrile, α-[(3,5-dichlorophenyl)methylene]-, (αZ)-(9Cl); Tyrphostin 46; a-hydroxyfarnesylphosphonic acid; butanoic acid, 2-[[(2S)-2-[[(2S,3S)-2-[[(2R)-2-amino-3-mercaptopropyl]amino]-3-methylpentyl]oxy]-1-oxo-3-phenylpropyl]amino]-4-(methylsulfonyl)-,1-methylethyl ester, (2S)-(9cl); Manumycin A; 2-propenamide, 2-cyano-3-[4-hydroxy-3,5-bis(1-methylethyl)phenyl]-N-(3-phenylpropyl)-,(2E)-(9Cl); N-benzoyl-staurosporine (PKC412); midostaurin; SU11248; MLN518; abarelix; goserelin; goserelin acetate; indirubin-3'-monooxime; PI-88; 1-b-D-arabinofuransylcytosine; bisulfan; N-hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, and N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2E-2-propenamide and pharmaceutically acceptable salts thereof (LBH589); Suberoylanilide hydroxamic acid; [4-(2-amino-

phenylcarbamoyl)-benzyl]-carbamic acid pyridine-3-ylmethyl ester and derivatives thereof; butyric acid; pyroxamide; trichostatin A; Oxamflatin; apicidin; Depsipeptide; depudecin; trapoxin; depudecin; HC Toxin; sodium phenylbutyrate; suberoyl bis-hydroxamic acid; Trichostatin A; 17-allylamino,17-demethoxygeldanamycin (17AAG); geldanamycin,17-demethoxy-17-(2-propenylamino)-(9Cl); Geldanamycin; fluocinolone; dexamethasone; 2-propenenitrile, 3-[(4-methylphenyl)sulfonyl]-, (2E)-(9Cl); hydroxyl-2-naphthalenylmethylphosphonic acid; pyrazoleanthrone; epigallocatechin gallate; Vinblastine Sulfate; Vincristine Sulfate; Vindesine; Vinorelbine; Docetaxel; Paclitaxel; vinorelbine; discodermolides; cochicine; epothilone derivatives; epothilone B; Epotholine A; benzenesulfonamide, N-[2-[[[3-(4-chlorophenyl)-2-propenyl]methyl]amino]methyl]phenyl]-N-(2-hydroxyethyl)-4-methoxy-(9Cl); trans-4-iodo, 4'-boranyl-chalcone; butanedinitrile, bis[amino[2-aminophenyl)thio]methylene]-(9Cl); bengamide or a derivative thereof; Actinonin; epigallocatechin gallate; marimastat; prinomastat; metastat; BMS-279251; BAY 12-9566; TAA211; MMI270B; AAJ996; bevacizumab; Ibritumomab tiuxetan; tositumomab; iodine I 131; Tyrphostin AG 879; Phenol, 4-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]-(9Cl); benzamide, 3-(dimethylamino)-N-[3-[(4-hydroxybenzoyl)amino]-4-methylphenyl]-(9Cl); damnacanthal; Tyrphostin 46; Tyrphostin AG 1296; Tyrphostin 9; 1,3-butadiene-1,1,3-tricarbonitrile,2-amino-4-(1H-indol-5-yl)-(9Cl); Wortmannin; Quercetin Dihydrate; cantharidic acid; cantharidin; L-leucinamide, N-[4-(2-carboxyethenyl)benzoyl]glycyl-L-α-glutamyl-,(E)-(9Cl); VISUDYNE; porfimer sodium; Carboplatin; Cisplatin; Oxaliplatin; cisplatinum; Satraplatin; such as ZD0473; cantharidic acid; cantharidin; L-P-bromotetramisole oxalate; 2(5H)-furanone,4-hydroxy-5-(hydroxymethyl)-3-(1-oxohexadecyl)-, (5R)-(9Cl); benzylphosphonic acid; 1-H-pyrrolo-2,5-dione,3-[1-[3-(dimethylamino)propyl]-1H-indol-3-yl]-4-(1H-indol-3-yl)-(9Cl); Bisindolylmaleimide IX; Sphingosine; staurosporine; tyrphostin 51; Hypericin; Rottlerin; DMFO; aclacinomycin A; gliotoxin; PS-341; MLN 341; bortezomib; Velcade; L-leucinamide, N-[4-(2-carboxyethenyl)benzoyl]glycyl-L-α-glutamyl-,(E)-(9Cl); Tyrphostin AG 126; Tyrphostin Ag 1288; Tyrphostin Ag 1295; Geldanamycin; Genistein; PP1; PP2; 1,2-Benzenediol, 4-[(1E)-2-(3,5-dihydroxyphenyl)ethenyl]- (9Cl); Tyrphostin AG 490; 2-naphthyl vinyl ketone; L-744832; DK8G557; R115777; Isotretinoin; Tretinoin; fludarabine; ara-C; 6-thioguanine; 5-FU; cladribine; 6-mercaptopurine; pentostatin; 5,6-dichloro-1-beta-D-ribofuranosylbenzimidazole; 2-aminopurine; terbinadine; telomestatin; topotecan;

gimatecan; irinotecan; camptothecin; 9-nitrocamptothecin; PNU-166148; 10-hydroxycamptothecin acetate salt; etoposide; idarubicin hydrochloride; irinotecan hydrochloride; teniposide; topotecan hydrochloride; doxorubicin; epirubicin hydrochloride; mitoxantrone hydrochloride; daunorubicin hydrochloride; doxorubicin; epirubicin; idarubicin; nemorubicin; losoxantrone; teniposide; etoposide; mitoxantrone; 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof; ZD4190; ZD6474; SU5416; SU6668; bevacizumab; rhuMAb; RHUFab; Macugon; Angiozyme Avastan; 3-(4-dimethylaminobenzylidenyl)-2-indolinone; denosumab.

[0274] The term "ACE inhibitor" as used herein, includes, but is not limited to CIBACEN, benazepril, enazepril (LOTENSIN), captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, ramipril, perindopril and trandolapril.

[0275] The term "an adenosine-kinase-inhibitor", as used herein, relates to a compound which targets, decreases or inhibits nucleobase, nucleoside, nucleotide and nucleic acid metabolisms. An example of an adenosine-kinase-inhibitor includes, but is not limited to, 5-Iodotubercidin, which is also known as 7H-pyrrolo[2,3-d]pyrimidin-4-amine, 5-iodo-7-β-D-ribofuranosyl-(9Cl).

[0276] The term "an adjuvant", as used herein, refers to a compound which enhances the 5-FU-TS bond as well as a compound which targets, decreases or inhibits, alkaline phosphatase. Examples of an adjuvant include, but are not limited to, Leucovorin, and Levamisole.

[0277] The term "an adrenal cortex antagonist", as used herein, relates to a compound which targets, decreases or inhibits the activity of the adrenal cortex and changes the peripheral metabolism of corticosteroids, resulting in a decrease in 17-hydroxycorticosteroids. An example of an adrenal cortex antagonist includes, but is not limited to, Mitotane.

[0278] The term "AKT pathway inhibitor", as used herein, relates to a compound which targets, decreases or inhibits cell proliferation. Akt, also known as protein kinase B (PKB), a serine/threonine kinase, is a critical enzyme in several signal transduction pathways involved in diabetes. The principal role of Akt in the cell is to facilitate growth factor-mediated cell survival and to block apoptotic cell death. A target of the AKT pathway inhibitor includes, but is not limited to, PI3K/AKT. Examples of an AKT pathway inhibitor, include, but are not limited to, Deguelin, which is also known as 3H-bis[1]benzopyrano[3,4-b:6',5'-e]pyran-7(7aH)-one, 13, 13a-dihydro-9,10-dimethoxy-3,3-

dimethyl-, (7aS, 13aS)-(9CI); and Trciribine, which is also known as 1,4,5,6,8-pentaazaacenaphthylen-3-amine, 1,5-dihydro-5-methyl-1-β-D-ribofuranosyl-(9CI).

[0279] The term "an alkylating agent", as used herein, relates to a compound which causes alkylation of DNA and results in breaks in the DNA molecules as well as cross-linking of the twin strands, thus interfering with DNA replication and transcription of RNA. Examples of an alkylating agent include, but are not limited to, Chlorambucil, cyclophosphamide, Dacarbazine, Lomustine, Procarbazine, Thiotepa, Melphalan, Temozolomide (TEMODAR), Carmustine, Ifosfamide, Mitomycin, Altretamine, Busulfan, Machlorethamine hydrochloride, nitrosourea (BCNU or Gliadel), Streptozocin, and estramustine. Cyclophosphamide can be administered, e.g., in the form as it is marketed, e.g., under the trademark CYCLOSTIN; and ifosfamide as HOLOXAN.

[0280] The term "an angiogenesis inhibitor", as used herein, relates to a compound which targets, decreases or inhibits the production of new blood vessels. Targets of an angiogenesis inhibitor include, but are not limited to, methionine aminopeptidase-2 (MetAP-2), macrophage inflammatory protein-1 (MIP-1alpha), CCL5, TGF-beta, lipoxygenase, cyclooxygenase, and topoisomerase. Indirect targets of an angiogenesis inhibitor include, but are not limited to, p21, p53, CDK2, and collagen synthesis. Examples of an angiogenesis inhibitor include, but are not limited to, Fumagillin, whichis known as 2,4,6,8-Decatetraenedioic acid, mono[(3R,4S,5S,6R)-5-methoxy-4-[(2R,3R)-2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl] ester, (2E,4E,6E,8E)-(9CI); Shikonin, which is also known as 1,4-Naphthalenedione, 5,8-dihydroxy-2-[(1R)-1-hydroxy-4-methyl-3-pentenyl]- (9CI); Tranilast, which is also known as benzoic acid, 2-[[3-(3,4-dimethoxyphenyl)-1-oxo-2-propenyl]amino]-(9CI); ursolic acid; suramin; and thalidomide.

[0281] The term "angiostatic steroid", as used herein, includes, but is not limited to agents which block or inhibit angiogenesis, such as, e.g., anecortave, triamcinolone, hydrocortisone, 11-α-epihydrocotisol, cortexolone, 17α-hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone and dexamethasone.

[0282] The term "an anti-androgen", as used herein, relates to a compound which blocks the action of androgens of adrenal and testicular origin which stimulate the growth of normal and malignant prostatic tissue. Examples of an anti-androgen include, but are not limited to, Nilutamide; bicalutamide (CASODEX), which can be formulated, e.g., as disclosed in U.S. Patent No. 4,636,505.

[0283] The term "an anti-estrogen", as used herein, relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. Examples of an anti-estrogen include, but are not limited to, Toremifene; Letrozole; Testolactone; Anastrozole; Bicalutamide; Flutamide; Tamoxifen Citrate; Exemestane; Fulestrant; tamoxifen; fulvestrant; raloxifene and raloxifene hydrochloride. Tamoxifen can be administered in the form as it is marketed, e.g., NOLVADEX; and raloxifene hydrochloride is marketed as EVISTA. Fulvestrant can be formulated as disclosed in U.S. Patent No. 4,659,516 and is marketed as FASLODEX. A combination of the invention comprising a pharmaceutically active agent which is an anti-estrogen is particularly useful for the treatment of estrogen receptor positive tumors, e.g., breast tumors.

[0284] The term "an anti-hypercalcemia agent", as used herein, refers to compounds which are used to treat hypercalcemia. Examples of an anti-hypercalcemia agent include, but are not limited to, gallium (III) nitrate hydrate; and pamidronate disodium.

[0285] The term "anti-leukemic compound" as used herein, includes, but is not limited to Ara-C, a pyrimidine analog, which is the 2'-α-hydroxy ribose (arabinoside) derivative of deoxycytidine. Also included is the purine analog of hypoxanthine, 6-mercaptopurine (6-MP) and fludarabine phosphate.

[0286] The term "an anti-metabolite", as used herein, relates to a compound which inhibits or disrupts the synthesis of DNA resulting in cell death. Examples of an antimetabolite include, but are not limited to, 6-mercaptopurine; Cytarabine; Fludarabine; Flexuridine; Fluorouracil; Capecitabine; Raltitrexed; Methotrexate; Cladribine; Gemcitabine; Gemcitabine hydrochloride; Thioguanine; Hydroxyurea; DNA de-methylating agents, such as 5-azacytidine and decitabine; edatrexate; and folic acid antagonists such as, but not limited to, pemetrexed. Capecitabine can be administered, e.g., in the form as it is marketed, e.g., under the trademark XELODA; and gemcitabine as GEMZAR.

[0287] The term "an antiproliferative antibody" as used herein, includes, but is not limited to, bevacizumab (AVASTIN), rituximab (RITUXAN), PRO64553 (anti-CD40) and 2C4 Antibody. By antibodies is meant e.g. intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least 2 intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity.

[0288] The term "an apoptosis inducer", as used herein, relates to a compound which induces the normal series of events in a cell that leads to its death. The apoptosis inducer of the present invention may selectively induce the X-linked mammalian inhibitor of apoptosis protein XIAP. The apoptosis inducer of the present invention may downregulate BCL-xL. Examples of an apoptosis inducer include, but are not limited to, ethanol, 2-[[3-(2,3-dichlorophenoxy)propyl]amino]-(9CI); gambogic acid; Embelin, which is also known as 2,5-Cyclohexadiene-1,4-dione, 2,5-dihydroxy-3-undecyl- (9CI); and Arsenic Trioxide.

[0289] The term "AT1 receptor antagonist" as used herein, includes, but is not limited to agents, such as DIOVAN.

[0290] The term "an aurora kinase inhibitor", as used herein, relates to a compound which targets, decreases or inhibits later stages of the cell cycle from the G2/M check point all the way through to the mitotic checkpoint and late mitosis. An example of an aurora kinase inhibitor includes, but is not limited to Binucleine 2, which is also known as Methanimidamide, N'-[1-(3-chloro-4-fluorophenyl)-4-cyano-1H-pyrazol-5-yl]-N,N-dimethyl- (9CI).

[0291] The term "aromatase inhibitor", as used herein, relates to a compound which inhibits the estrogen production, i.e., the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to, steroids, especially atamestane, exemestane and formestane; and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole and letrozole. Exemestane is marketed as AROMASIN; formestane as LENTARON; fadrozole as AFEMA; anastrozole as ARIMIDEX; letrozole as FEMARA or FEMAR; and aminoglutethimide as ORIMETEN. A combination of the invention comprising a pharmaceutically active agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, e.g., breast tumors.

[0292] The term "biological response modifier", as used herein, includes, but is not limited to lymphokine or interferons, e.g., interferon γ.

[0293] The term "bisphosphonates", as used herein, includes, but is not limited to, etridonic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid. "Etridonic acid" can be administered, e.g., in the form as it is marketed, e.g., DIDRONEL; "clodronic acid" as BONEFOS; "tiludronic acid" as SKELID;

"pamidronic acid" as AREDIA; "alendronic acid" as FOSAMAX; "ibandronic acid" as BONDRANAT; "risedronic acid" as ACTONEL; and "zoledronic acid" as ZOMETA.

[0294] The term "a Bruton's Tyrosine Kinase (BTK) inhibitor", as used herein, relates to a compound which targets, decreases or inhibits human and murine B cell development. An example of a BTK inhibitor includes, but is not limited to terreic acid.

[0295] The term "a calcineurin inhibitor", as used herein, relates to a compound which targets, decreases or inhibits the T cell activation pathway. A target of a calcineurin inhibitor includes protein phosphatase 2B. Examples of a calcineurin inhibitor include, but are not limited to Cypermethrin, which is also known as cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-,cyano(3-phenoxyphenyl)methyl ester (9CI); Deltamethrin, which is also known as cyclopropanecarboxylic aci, 3-(2,2-dibromoethenyl)-2,2-dimethyl-(S)-cyano(3-phenoxyphenyl)methyl ester, (1R,3R)-(9CI); Fenvalerate, which is also known as benzeneacetic acid, 4-chloro-α-(1-methylethyl)-,cyano(3-phenoxyphenyl)methyl ester (9CI); and Tyrphostin 8.

[0296] The term "a CaM kinase II inhibitor", as used herein, relates to a compound which targets, decreases or inhibits CaM Kinases. CaM Kinases constitute a family of structurally related enzymes that include phosphorylase kinase, myosin light chain kinase, and CaM kinases I-IV. CaM Kinase II, one of the best-studied multifunctional enzymes, is found in high concentrations in neuronal synapses, and in some regions of the brain it may constitute up to 2% of the total protein content. Activation of CaM kinase II has been linked to memory and learning processes in the vertebrate nervous system. Targets of a CaM kinase II inhibitor include CaM kinase II. Examples of a CaM kinase II inhibitor include, but are not limited to, 5-Isoquinolinesulfonic acid, 4-[(2S)-2-[(5-isoquinolinylsulfonyl)methylamino]-3-oxo-3-(4-phenyl-1-piperazinyl)propyl]phenyl ester (9CI); and benzenesulfonamide, N-[2-[[[3-(4-chlorophenyl)-2-propenyl]methyl]amino]methyl]phenyl]-N-(2-hydroxyethyl)-4-methoxy-(9CI).

[0297] The term "a CD45 tyrosine phosphatase inhibitor", as used herein, relates to a compound which targets, decreases or inhibits dephosphorylating regulatory pTyr residues on Src-family protein-tyrosine kinases, which aids in the treatment of a variety of inflammatory and immune disorders. An example of a CD45 tyrosine phosphatase inhibitor includes, but is not limited to, Phosphonic acid, [[2-(4-bromophenoxy)-5-nitrophenyl]hydroxymethyl]-(9CI).

[0298] The term "a CDC25 phosphatase inhibitor", as used herein, relates to compound which targets, decreases or inhibits overexpressed dephosphorylate cyclin-dependent kinases in tumors. An example of a CDC25 phosphatase inhibitor includes 1,4-naphthalenedione, 2,3-bis[(2-hydroyethyl)thio]-(9Cl).

[0299] The term "a CHK kinase inhibitor", as used herein, relates to a compound which targets, decreases or inhibits overexpression of the antiapoptotic protein Bcl-2. Targets of a CHK kinase inhibitor are CHK1 and/or CHK2. An example of a CHK kinase inhibitor includes, but is not limited to, Debromohymenialdisine.

[0300] The term "compounds targeting/decreasing a protein or lipid kinase activity; or a protein or lipid phosphatase activity; or further anti-angiogenic compounds", as used herein, includes, but is not limited to, protein tyrosine kinase and/or serine and/or theroine kinase inhibitors or lipid kinase inhibitors, for example:

[0301] compounds targeting, decreasing or inhibiting the activity of the vascular endothelial growth factor-receptors (VEGF), such as compounds which target, decrese or inhibit the activity of VEGF, especially compounds which inhibit the VEGF receptor, wuch as, but not limited to, 7H-pyrrolo[2,3-d]pyrimidine derivatives, including {6-[4-(4-ethyl-piperazine-1-ylmethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrinidinpyrimidin-4-yl}-((R)-1-phenyl-ethyl)-amine; BAY 43-9006; isolcholine compounds disclosed in WO 00/09495 such as (4-tert-butyl-phenyl)-94-pyridin-4-ylmethyl-isoquinolin-1-yl)-amine; and

[0302] compounds targeting, decreasing or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as compounds which target, decrease or inhibit the activity of PDGFR, especially compounds which inhibit the PDGF receptor, e.g., a N-phenyl-2-pyrimidine-amine derivative, e.g., imatinib, SU101, SU6668 and GFB-111;

[0303] compounds targeting, decreasing or inhibiting the activity of the fibroblast growth factor-receptors (FGFR);

[0304] compounds targeting, decreasing or inhibiting the activity of the insulin-like growth factor receptor 1 (IGF-1R), such as compounds which target, decrease or inhibit the activity of IGF-IR, especially compounds which inhibit the IGF-1R receptor. Compounds include but are not limited to the compounds disclosed in WO 02/092599 and derivatives thereof of 4-amino-5-phenyl-7-cyclobutyl-pyrrolo[2,3-d]pyrimidine derivatives (AEW541);

[0305] compounds targeting, decreasing or inhibiting the activity of the Trk receptor tyrosine kinase family;

[0306] compounds targeting, decreasing or inhibiting the activity of the Axl receptor tyrosine kinase family;

[0307] compounds targeting, decreasing or inhibiting the activity of the c-Met receptor;

[0308] compounds targeting, decreasing or inhibiting the activity of the Ret receptor tyrosine kinase;

[0309] compounds targeting, decreasing or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase;

[0310] compounds targeting, decreasing or inhibiting the activity of the C-kit receptor tyrosine kinases (part of the PDGFR family), such as compounds which target, decrease or inhibit the activity of the c-Kit receptor tyrosine kinase family, especially compounds which inhibit the c-Kit receptor, e.g., imatinib;

[0311] compounds targeting, decreasing or inhibiting the activity of members of the c-Abl family and their gene-fusion products, e.g., BCR-Abl kinase, such as compounds which target decrease or inhibit the activity of c-Abl family members and their gene fusion products, e.g., a N-phenyl-2-pyrimidine-amine derivative, e.g., imatinib, PD180970, AG957, NSC 680410 or PD173955 from ParkeDavis; BMS354825

[0312] compounds targeting, decreasing or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK, PDK and Ras/MAPK family members, or PI(3) kinase family, or of the PI(3)-kinase-related kinase family, and/or members of the cyclin-dependent kinase family (CDK) and are especially those staurosporine derivatives disclosed in U.S. Patent No. 5,093,330, e.g., midostaurin; examples of further compounds include, e.g., UCN-01; safingol; BAY 43-9006; Bryostatin 1; Perifosine; Ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196; isochinoline compounds, such as those disclosed in WO 00/09495; FTIs; PD184352 or QAN697, a P13K inhibitor;

[0313] compounds targeting, decreasing or inhibiting the activity of protein-tyrosine kinase, such as imatinib mesylate (GLEEVEC); tyrphostin or pyrymidylaminobenzamide and derivatives thereof. A tyrphostin is preferably a low molecular weight (M_r <1500) compound, or a pharmaceutically acceptable salt thereof, especially a compound selected from the benzylidenemalonitrile class or the S-arylbenzenemalonirile or bisubstrate quinoline class of compounds, more especially any compound selected from the group consisting of Tyrphostin A23/RG-50810, AG 99, Tyrphostin AG 213, Tyrphostin AG 1748, Tyrphostin AG 490, Tyrphostin B44, Tyrphostin B44 (+)

enantiomer, Tyrphostin AG 555, AG 494, Tyrphostin AG 556; AG957 and adaphostin (4-{[(2,5-dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester, NSC 680410, adaphostin);

[0314] When referring to antibody, it is to include intact monoclonal antibodies, nanobodies, polyclonal antibodies, multi-specific antibodies formed from at least 2 intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity.

[0315] The phrase "compound which targets, decreases or inhibits the activity of a protein or lipid phosphatase" as used herein includes but is not limited to inhibitors of phosphatase 1, phosphatase 2A, PTEN or CDC25, e.g., okadaic acid or a derivative thereof.

[0316] The phrase "further anti-angiogenic compounds" includes but is not limited to compounds having another mechanism for their activity, e.g., unrelated to protein or lipid kinase inhibition, e.g., thalidomide (THALOMID) and TNP-470.

[0317] The phrase "compounds which induce cell differentiation processes" as used herein, include but is not limited to retinoic acid, □ or □-tocopherol or □ or □-tocotrienol.

[0318] Examples of a "controlling agent for regulating genistein, olomucine and/or tyrphostins" includes, but are not limited to, Daidzein, which is also known as 4H-1-benzopyran-4-one, 7-hydroxy-3-(4-hydroxyphenyl)-(9CI); Iso-Olomoucine, and Tyrphostin 1.

[0319] The term "cyclooxygenase inhibitor" as used herein includes, but is not limited to, e.g., Cox-2 inhibitors. The term "a COX-2 inhibitor", as used herein, relates to a compound which targets, decreases or inhibits the enzyme cox-2 (cyclooxygenase-2). Examples of a COX-2 inhibitor, include but are not limited to, 1H-indole-3-acetamide, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-N-(2-phenylethyl)-(9CI); 5-alkyl substituted 2-arylaminophenylacetic acid and derivatives, such as celecoxib (CELEBREX), rofecoxib (VIOXX), etoricoxib, valdecoxib; or a 5-alkyl-2-arylaminophenylacetic acid, e.g., 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid, lumiracoxib; and celecoxib.

[0320] The term "a cRAF kinase inhibitor", as used herein, relates to a compound which targets, decreases or inhibits the up-regulation of E-selectin and vascular adhesion molecule-1 induced by TNF. Raf kinases play an important role as extracellular signal-regulating kinases in cell differentiation, proliferation, and apoptosis.

A target of a cRAF kinase inhibitor includes, but is not limited, to RAF1. Examples of a cRAF kinase inhibitor include, but are not limited to, 3-(3,5-dibromo-4-hydroxybenzylidene)-5-iodo-1,3-dihydroindol-2-one; and benzamide, 3-(dimethylamino)-N-[3-[(4-hydroxybenzoyl)amino]-4-methylphenyl]-(9Cl).

[0321] The term "a cyclin dependent kinase inhibitor", as used herein, relates to a compound which targets, decreases or inhibits cyclin dependent kinase which play a role in the regulation of the mammalian cell cycle. Cell cycle progression is regulated by a series of sequential events that include the activation and subsequent inactivation of cyclin dependent kinases (Cdks) and cyclins. Cdks are a group of serine/threonine kinases that form active heterodimeric complexes by binding to their regulatory subunits, cyclins. Examples of targets of a cyclin dependent kinase inhibitor include, but are not limited to, CDK, AHR, CDK1, CDK2, CDK5, CDK4/6, GSK3beta, and ERK. Examples of a cyclin dependent kinase inhibitor include, but are not limited to, N9-Isopropyl-Olomoucine; Olomoucine; Purvalanol B, which is also known as Benzoic acid, 2-chloro-4-[[2-[[(1R)-1-(hydroxymethyl)-2-methylpropyl]amino]-9-(1-methylethyl)-9H-purin-6-yl]amino]- (9Cl); Roascovitine; Indirubin, which is also known as 2H-Indol-2-one, 3-(1,3-dihydro-3-oxo-2H-indol-2-ylidene)-1,3-dihydro- (9Cl); Kenpaullone, which is also known as Indolo[3,2-d][1]benzazepin-6(5H)-one, 9-bromo-7,12-dihydro- (9Cl); purvalanol A, which is also known as 1-Butanol, 2-[[6-[(3-chlorophenyl)amino]-9-(1-methylethyl)-9H-purin-2-yl]amino]-3-methyl-, (2R)- (9Cl); and Indirubin-3'-monooxime.

[0322] The term "a cysteine protease inhibitor", as used herein, relates to a compound which targets, decreases or inhibits cystein protease which plays a vital role in mammalian cellular turnover and apotosis. An example of a cystein protease inhibitor includes, but is not limited to, 4-morpholinecarboxamide,N-[(1S)-3-fluoro-2-oxo-1-(2-phenylethyl)propyl]amino]-2-oxo-1-(phenylmethyl)ethyl]-(9Cl).

[0323] The term "a DNA intercalator" as used herein, relates to a compound which binds to DNA and inhibits DNA, RNA, and protein synthesis. Examples of a DNA intercalator include, but are not limited to, Plicamycin and Dactinomycin.

[0324] The term "a DNA strand breaker" as used herein, relates to a compound which causes DNA strand scission and results in inhibition of DNA synthesis, ininhibition of RNA and protein synthesis. An example of a DNA strand breaker includes, but is not limited to, Bleomycin.

[0325] The term "an E3 Ligase inhibitor", as used herein, relates to a compound which targets, decreases or inhibits the E3 ligase which inhibits the transfer of ubiquitin

chains to proteins, marking them for degradation in the proteasome. An example of a E3 ligase inhibitor includes, but is not limited to, N-((3,3,3-trifluoro-2-trifluoromethyl)propionyl)sulfa nilamide.

[0326] The term "EDG binder" as used herein, includes, but is not limited to, a class of immunosuppressants that modulates lymphocyte recirculation, such as FTY720.

[0327] The term "an endocrine hormone", as used herein, relates to a compound which by acting mainly on the pituitary gland causes the suppression of hormones in males, the net effect is a reduction of testosterone to castration levels. In females, both ovarian estrogen and androgen synthesis are inhibited. An example of an endocrine hormone includes, but is not limited to, Leuprolide and megestrol acetate.

[0328] The term "a farnesyltransferase inhibitor", as used herein, relates to a compound which targets, decreases or inhibits the Ras protein, which is commonly abnormally active in cancer. A target of a farnesyltransferase inhibitor includes, but is not limited to RAS. Examples of a farnesyltransferase inhibitor include, but are not limited to, a-hydroxyfarnesylphosphonic acid; butanoic acid, 2-[[(2S)-2-[[(2S,3S)-2-[[(2R)-2-amino-3-mercaptopropyl]amino]-3-methylpentyl]oxy]-1-oxo-3-phenylpropyl]amino]-4-(methylsulfonyl)-,1-methylethyl ester, (2S)-(9ci); and Manumycin A.

[0329] The term "a Flk-1 kinase inhibitor", as used herein, relates to a compound which targets, decreases or inhibits Flk-1 tyrosine kinase activity. A target of a Flk-1 kinase inhibitor includes, but is not limited to, KDR. An example of a Flk-1 kinase inhibitor includes, but is not limited to, 2-propenamide, 2-cyano-3-[4-hydroxy-3,5-bis(1-methylethyl)phenyl]-N-(3-phenylpropyl)-,(2E)-(9CI). The phrase "compounds which target, decrease or inhibit the activity of Flt-3" as used herein, includes, but is not limited to compounds, proteins or antibodies which inhibit Flt-3, e.g., N-benzoyl-staurosporine, midostaurin, a staurosporine derivative, SU11248 and MLN518.

[0330] The term "gonadorelin agonist", as used herein, includes, but is not limited to, abarelix, goserelin and goserelin acetate. Goserelin is disclosed in U.S. Patent No. 4,100,274 and is marketed as ZOLADEX. Abarelix can be formulated, e.g., as disclosed in U.S. Patent No. 5,843,901.

[0331] The term "a Glycogen synthase kinase-3 (GSK3) inhibitor", as used herein, relates to a compound which targets, decreases or inhibits glycogen synthase kinase-3 (GSK3). Glycogen Synthase Kinase-3 (GSK-3; tau protein kinase I), a highly conserved, ubiquitously expressed serine/threonine protein kinase, is involved in the

signal transduction cascades of multiple cellular processes. which is a protein kinase that has been shown to be involved in the regulation of a diverse array of cellular functions, including protein synthesis, cell proliferation, cell differentiation, microtubule assembly/disassembly, and apoptosis. An example of a GSK3 inhibitor includes, but is not limited to, indirubin-3'-monooxime.

[0332] The term "heparanase inhibitor", as used herein, refers to compounds which target, decrease or inhibit heparin sulphate degradation. The term includes, but is not limited to, PI-88.

[0333] The phrase "agent used in the treatment of hematologic malignancies", as used herein, includes, but is not limited to, FMS-like tyrosine kinase inhibitors, e.g., compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R); interferon, 1-b-D-arabinofuransylcytosine (ara-c) and bisulfan; and ALK inhibitors, e.g., compounds which target, decrease or inhibit anaplastic lymphoma kinase.

[0334] The term "a histone deacetylase (HDAC) inhibitor", as used herein, relates to a compound which inhibits the histone deacetylase and which possess anti-proliferative activity. This includes but is not limited to compounds disclosed in WO 02/22577, especially N-hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, and N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2E-2-propenamide and pharmaceutically acceptable salts thereof (LBH589). It further includes Suberoylanilide hydroxamic acid (SAHA); [4-(2-amino-phenylcarbamoyl)-benzyl]-carbamic acid pyridine-3-ylmethyl ester and derivatives thereof; butyric acid, pyroxamide, trichostatin A, Oxamflatin, apicidin, Depsipeptide; depudecin and trapoxin.Other examples include depudecin; HC Toxin, which is also known as Cyclo[L-alanyl-D-alanyl-(2S,3S)-2-amino-8-oxo-9,10-epoxydecanoyl-D-prolyl] (9CI); sodium phenylbutyrate, suberoyl bis-hydroxamic acid; and Trichostatin A.

[0335] The phrase "an implant containing corticosteroids" as used herein, includes, but is not limited to agents, such as, e.g., fluocinolone and dexamethasone.

[0336] The term "a I-kappa B-alpha kinase inhibitor (IKK)", as used herein, relates to a compound which targets, decreases or inhibits NF-kappaB. An example of an IKK inhibitor includes, but is not limited to, 2-propenenitrile, 3-[(4-methylphenyl)sulfonyl]-, (2E)-(9CI).

[0337] The term "an insulin receptor tyrosine kinase inhibitor", as used herein, relates to a compound which modulates the activities of phosphatidylinositol 3-kinase, microtubule-associated protein, and S6 kinases. An example of an insulin receptor tyrosine kinase inhibitor includes, but is not limited to, hydroxyl-2-naphthalenylmethylphosphonic acid.

[0338] The term "a c-Jun N-terminal kinase (JNK) kinase inhibitor", as used herein, relates to a compound which targets, decreases or inhibits Jun N-terminal kinase. Jun N-terminal kinase (JNK), a serine-directed protein kinase, is involved in the phosphorylation and activation of c-Jun and ATF2 and plays a significant role in metabolism, growth, cell differentiation, and apoptosis. A target for a JNK kinase inhibitor includes, but is not limited to, DNMT. Examples of a JNK kinase inhibitor include, but are not limited to, pyrazoleanthrone and/or epigallocatechin gallate.

[0339] The term "a microtubule binding agent", as used herein, refers to a compound which acts by disrupting the microtubular network that is essential for mitotic and interphase cellular function. Examples of a microtubule binding agent include, but are not limited to, Vinblastine Sulfate; Vincristine Sulfate; Vindesine; Vinorelbine; Docetaxel; Paclitaxel; vinorelbine; discodermolides; cochicine and epothilonesand derivatives thereof, e.g., epothilone B or a derivative thereof. Paclitaxel is marketed as TAXOL; docetaxel as TAXOTERE; vinblastine sulfate as VINBLASTIN R.P; and vincristine sulfate as FARMISTIN. Also included are the generic forms of paclitaxel as well as various dosage forms of paclitaxel. Generic forms of paclitaxel include, but are not limited to, betaxolol hydrochloride. Various dosage forms of paclitaxel include, but are not limited to albumin nanoparticle paclitaxel marketed as ABRAXANE; ONXOL, CYTOTAX Discodermolide can be obtained, e.g., as disclosed in U.S. Patent No. 5,010,099. Also included are Epotholine derivatives which are disclosed in U.S. Patent No. 6,194,181, WO 98/10121, WO 98/25929, WO 98/08849, WO 99/43653, WO 98/22461 and WO 00/31247. Especially preferred are Epotholine A and/or B.

[0340] The term "a Mitogen-activated protein (MAP) kinase-inhibitor", as used herein, relates to a compound which targets, decreases or inhibits Mitogen-activated protein. The mitogen-activated protein (MAP) kinases are a group of protein serine/threonine kinases that are activated in response to a variety of extracellular stimuli and mediate signal transduction from the cell surface to the nucleus. They regulate several physiological and pathological cellular phenomena, including inflammation, apoptotic cell death, oncogenic transformation, tumor cell invasion, and

metastasis. An example of a MAP kinase inhibitor includes, but is not limited to, benzenesulfonamide, N-[2-[[[3-(4-chlorophenyl)-2-propenyl]methyl]amino]methyl]phenyl]-N-(2-hydroxyethyl)-4-methoxy-(9Cl).

[0341] The term "a MDM2 inhibitor", as used herein, relates to a compound which targets, decreases or inhibits the interaction of MDM2 and the p53 tumor suppressor. An example of a a MDM2 inhibitor includes, but is not limited to, trans-4-iodo, 4'-boranyl-chalcone.

[0342] The term "a MEK inhibitor", as used herein, relates to a compound which targets, decreases or inhibits the kinase activity of MAP kinase, MEK. A target of a MEK inhibitor includes, but is not limited to, ERK. An indirect target of a MEK inhibitor includes, but is not limited to, cyclin D1. An example of a MEK inhibitor includes, but is not limited to, butanedinitrile, bis[amino[2-aminophenyl)thio]methylene]-(9Cl).

[0343] The term "methionine aminopeptidase inhibitor", as used herein, includes, but is not limited to, compounds which target, decrease or inhibit the activity of methionine aminopeptidase. Compounds which target, decrease or inhibit the activity of methionine aminopeptidase are, e.g., bengamide or a derivative thereof.

[0344] The term "a MMP inhibitor", as used herein, relates to a compound which targets, decreases or inhibits a class of protease enzyme that selectively catalyze the hydrolysis of polypeptide bonds including the enzymes MMP-2 and MMP-9 that are involved in promoting the loss of tissue structure around tumours and facilitating tumour growth, angiogenesis, and metastasis. A target of a MMP inhibitor includes, but is not limited to, polypeptide deformylase. Example of a MMP inhibitor include, but are not limited to, Actinonin, which is also known as Butanediamide, N4-hydroxy-N1-[(1S)-1-[[(2S)-2-(hydroxymethyl)-1-pyrrolidinyl]carbonyl]-2-methylpropyl]-2-pentyl-, (2R)- (9Cl); epigallocatechin gallate; collagen peptidomimetic and non-peptidomimetic inhibitors; tetracycline derivatives, e.g., hydroxamate peptidomimetic inhibitor batimastat; and its orally-bioavailable analogue marimastat, prinomastat,, metastat, Neovastat, Tanomastat, TAA211, MMI270B or AAJ996.

[0345]

[0346] The term "monoclonal antibodies", as used herein, includes, but is not limited to bevacizumab,, Ibritumomab tiuxetan, and tositumomab and iodine I 131. Bevacizumab can be administered in the form as it is marketed, e.g. AVASTIN; Rituximab as MABTHERA; Ibritumomab tiuxetan as ZEVULIN; and tositumomab and iodine I 131 as BEXXAR.

[0347] The term "a NGFR tyrosine-kinase-inhibitor", as used herein, relates to a compound which targets, decreases or inhibits nerve growth factor dependent $p140^{c\text{-}trk}$ tyrosine phosphorylation. Targets of a NGFR tyrosine-kinase-inhibitor include, but are not limited to, FLK1, FAK, TrkA, and/or TrkC. An indirect target inhibits expression of RAF1. An example of a NGFR tyrosine-kinase-inhibitor includes, but is not limited to, Tyrphostin AG 879.

[0348] The term "a p38 MAP kinase inhibitor", as used herein, relates to a compound which targets, decreases or inhibits p38-MAPK, which is a MAPK family member. A MAPK family member is a serine/threonine kinase activated by phosphorylation of tyrosine and threonine residues. This kinase is phosphorylated and activated by many cellular stresses and inflammatory stimuli, thought to be involved in the regulation of important cellular responses such as apoptosis and inflammatory reactions. An example of a a p38 MAP kinase inhibitor includes, but is not limited to, Phenol, 4-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]-(9CI). An example of a a SAPK2/p38 kinase inhibitor includes, but is not limited to, benzamide, 3-(dimethylamino)-N-[3-[(4-hydroxybenzoyl)amino]-4-methylphenyl]-(9CI).

[0349] The term "a p56 tyrosine kinase inhibitor", as used herein, relates to a compound which targets, decreases or inhibits p56 tyrosine kinase, which is an enzyme that is a lymphoid-specific src family tyrosine kinase critical for T-cell development and activation. A target of a p56 tyrosine kinase inhibitor includes, but is not limited to, Lck. Lck is associated with the cytoplasmic domains of CD4, CD8 and the beta-chain of the IL-2 receptor, and is thought to be involved in the earliest steps of TCR-mediated T-cell activation. Examples of a p56 tyrosine kinase inhibitor include, but are not limited to, damnacanthal, which is also known as 2-anthracenecarboxaldehyde,9,10-dihydro-3-hydroxy-1methoxy-9,10-dioxo-(9CI), and/or Tyrphostin 46.

[0350] The term "a PDGFR tyrosine kinase inhibitor", as used herein, relates to compounds targeting, decreasing or inhibiting the activity of the C-kit receptor tyrosine kinases (part of the PDGFR family), such as compounds which target, decrease or inhibit the activity of the c-Kit receptor tyrosine kinase family, especially compounds which inhibit the c-Kit receptor, PDGF plays a central role in regulating cell proliferation, chemotaxis, and survival in normal cells as well as in various disease states such as cancer, atherosclerosis, and fibrotic disease. The PDGF family is composed of dimeric isoforms (PDGF-AA, PDGF-BB, PDGF-AB, PDGF-CC, and PDGF-DD), which exert their cellular effects by differentially binding to two receptor tyrosine kinases. PDGFR-α

and PDGFR-ß have molecular masses of ~170 and 180 kDa, respectively. Examples of targets of a PDGFR tyrosine kinase inhibitor includes, but are not limited to PDGFR, FLT3 and/or c-KIT. Example of a PDGFR tyrosine kinase inhibitor include, but are not limited to, Tyrphostin AG 1296; Tyrphostin 9; 1,3-butadiene-1,1,3-tricarbonitrile,2-amino-4-(1H-indol-5-yl)-(9Cl); Imatinib and IRESSA.

[0351] The term "a phosphatidylinositol 3-kinase inhibitor", as used herein, relates to a compound which targets, decreases or inhibits PI 3-kinase. PI 3-kinase activity has been shown to increase in response to a number of hormonal and growth factor stimuli, including insulin, platelet-derived growth factor, insulin-like growth factor, epidermal growth factor, colony-stimulating factor, and hepatocyte growth factor, and has been implicated in processes related to cellular growth and transformation. An example of a target of a phosphatidylinositol 3-kinase inhibitor includes, but is not limited to, Pi3K. Examples of a phosphatidylinositol 3-kinase inhibitor include, but are not limited to, Wortmannin, which is also known as 3H-Furo[4,3,2-de]indeno[4,5-h]-2-benzopyran-3,6,9-trione, 11-(acetyloxy)-1,6b,7,8,9a,10,11,11b-octahydro-1-(methoxymethyl)-9a,11b-dimethyl-, (1S,6bR,9aS,11R,11bR)- (9CI); 8-phenyl-2-(morpholin-4-yl)-chromen-4-one, 4-(trifluoromethyl)-5-(2,6-dimorpholinopyrimidin-4-yl)pyridin-2-amine, 2-Methyl-2-[4-(3-methyl-2-oxo-8-quinolin-3-yl-2,3-dihydro-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile and/or Quercetin Dihydrate.

[0352] The term "a phosphatase inhibitor", as used herein, relates to a compound which targets, decreases or inhibits phosphatase. Phosphatases remove the phosphoryl group and restore the protein to its original dephosphorylated state. Hence, the phosphorylation- dephosphorylation cycle can be regarded as a molecular "on-off" switch. Examples of a phosphatase inhibitor include, but are not limited to, cantharidic acid; cantharidin; and L-leucinamide, N-[4-(2-carboxyethenyl)benzoyl]glycyl-L-α-glutamyl-,(E)-(9Cl).

[0353] The term "photodynamic therapy", as used herein, refers to therapy which uses certain chemicals known as photosensitizing agents to treat or prevent cancers. Examples of photodynamic therapy include, but are not limited to, treatment with agents, such as, e.g., VISUDYNE and porfimer sodium.

[0354] The term "a platinum agent", as used herein, relates to a compound which contains Platinum and inhibit DNA synthesis by forming interstrand and intrastrand cross-linking of DNA molecules. Examples of a a platinum agent include, but are not limited to, Carboplatin; Cisplatin; Oxaliplatin; cisplatinum; Satraplatin and platinum

agents such as ZD0473. Carboplatin can be administered, e.g., in the form as it is marketed, e.g., CARBOPLAT; and oxaliplatin as ELOXATIN.

[0355] The term "a protein phosphatase inhibitor", as used herein, relate to a compound which targets, decreases or inhibits protein phosphatase. The term "a PP1 or PP2 inhibitor", as used herein, relates to a compound which targets, decreases or inhibits Ser/Thr protein phosphatases. Type I phosphatases, which include PP1, can be inhibited by two heat-stable proteins known as Inhibitor-1 (I-1) and Inhibitor-2 (I-2). They preferentially -subunit of phosphorylase kinase. Type II phosphatases are dephosphorylate the subdivided into spontaneously active (PP2A), CA^{2+}-dependent (PP2B), and Mg^{2+}-dependent (PP2C) classes of phosphatases. Examples of a PP1 and PP2A inhibitor include, but are not limited to, cantharidic acid and/or cantharidin. The term "tyrosine phosphatase inhibitor", as used here, relates to a compouns which targets, decreases or inhibits tyrosine phosphatase. Protein tyrosine phosphatases (PTPs) are relatively recent additions to the phosphatase family. They remove phosphate groups from phosphorylated tyrosine residues of proteins. PTPs display diverse structural features and play important roles in the regulation of cell proliferation, differentiation, cell adhesion and motility, and cytoskeletal function. Examples of targets of a tyrosine phosphatase inhibitor include, but are not limited to, alkaline phosphatase (ALP), heparanase, PTPase, and/or prostatic acid phosphatase. Examples of a tyrosine phosphatase inhibitor include, but are not limited to, L-P-bromotetramisole oxalate; 2(5H)-furanone,4-hydroxy-5-(hydroxymethyl)-3-(1-oxohexadecyl)-, (5R)-(9CI); and benzylphosphonic acid.

[0356] The term "a PKC inhibitor", as used herein, relates to a compound which targets, decreases or inhibits protein kinase C as well as its isozymes. Protein kinase C (PKC), a ubiquitous, phospholipid-dependent enzyme, is involved in signal transduction associated with cell proliferation, differentiation, and apoptosis. Examples of a target of a PKC inhibitor include, but are not limited to, MAPK and/or NF-kappaB. Examples of a PKC inhibitor include, but are not limited to, 1-H-pyrrolo-2,5-dione,3-[1-[3-(dimethylamino)propyl]-1H-indol-3-yl]-4-(1H-indol-3-yl)-(9CI); Bisindolylmaleimide IX; Sphingosine, which is known as 4-Octadecene-1,3-diol, 2-amino-, (2S,3R,4E)- (9CI); staurosporine, which is known as 9,13-Epoxy-1H,9H-diindolo[1,2,3-gh:3',2',1'-lm]pyrrolo[3,4-j][1,7]benzodiazonin-1-one, 2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-11-(methylamino)-, (9S,10R,11R,13R)- (9CI); tyrphostin 51; and Hypericin,

which is also known as Phenanthro[1,10,9,8-opqra]perylene-7,14-dione, 1,3,4,6,8,13-hexahydroxy-10,11-dimethyl-, stereoisomer (6Cl,7Cl,8Cl,9Cl).

[0357] The term "a PKC delta kinase inhibitor", as used herein, relates to a compound which targets, decreases or inhibits the delta isozymes of PKC. The delta isozyme is a conventional PKC isozymes and is Ca^{2+}-dependent. An example of a PKC delta kinase inhibitor includes, but is not limited to, Rottlerin, which is also known as 2-Propen-1-one, 1-[6-[(3-acetyl-2,4,6-trihydroxy-5-methylphenyl)methyl]-5,7-dihydroxy-2,2-dimethyl-2H-1-benzopyran-8-yl]-3-phenyl-, (2E)- (9Cl).

[0358] The term "a polyamine synthesis inhibitor", as used herein, relates to a compound which targets, decreases or inhibits polyamines spermidine. The polyamines spermidine and spermine are of vital importance for cell proliferation, although their precise mechanism of action is unclear. Tumor cells have an altered polyamine homeostasis reflected by increased activity of biosynthetic enzymes and elevated polyamine pools. Examples of a a polyamine synthesis inhibitor include, but are not limited to, DMFO, which is also known as (-)-2-difluoromethylornithin; N1, N12-diethylspermine 4HCl.

[0359] The term "a proteosome inhibitor", as used herein, relates to a compound which targets, decreases or inhibits proteosome. Examples of targets of a proteosome inhibitor include, but are not limited to, O(2)(-)-generating NADPH oxidase, NF-kappaB, and/or farnesyltransferase, geranylgeranyltransferase I. Examples of a proteosome inhibitor include, but are not limited to, aclacinomycin A; gliotoxin; PS-341; MLN 341; bortezomib; or Velcade.

[0360] The term "a PTP1B inhibitor", as used herein, relates to a compound which targets, decreases or inhibits PTP1B, a protein tyrosine kinase inhibitor. An example of a PTP1B inhibitor includes, but is not limited to, L-leucinamide, N-[4-(2-carboxyethenyl)benzoyl]glycyl-L-α-glutamyl-,(E)-(9Cl).

[0361] The term "a protein tyrosine kinase inhibitor", as used herein, relates to a compound which which targets, decreases or inhibits protein tyrosine kinases. Protein tyrosine kinases (PTKs) play a key role in the regulation of cell proliferation, differentiation, metabolism, migration, and survival. They are classified as receptor PTKs and non-receptor PTKs. Receptor PTKs contain a single polypeptide chain with a transmembrane segment. The extracellular end of this segment contains a high affinity ligand-binding domain, while the cytoplasmic end comprises the catalytic core and the regulatory sequences. Examples of targets of a tyrosine kinase inhibitor include, but are

not limited to, ERK1, ERK2, Bruton's tyrosine kinase (Btk), JAK2, ERK ½, PDGFR, and/or FLT3. Examples of indirect targets include, but are not limited to, TNFalpha, NO, PGE2, IRAK, iNOS, ICAM-1, and/or E-selectin. Examples of a tyrosine kinase inhibitor include, but are not limited to, Tyrphostin AG 126; Tyrphostin Ag 1288; Tyrphostin Ag 1295; Geldanamycin; and Genistein.

[0362] Non-receptor tyrosine kinases include members of the Src, Tec, JAK, Fes, Abl, FAK, Csk, and Syk families. They are located in the cytoplasm as well as in the nucleus. They exhibit distinct kinase regulation, substrate phosphorylation, and function. Deregulation of these kinases has also been linked to several human diseases.

[0363] The term "a SRC family tyrosine kinase inhibitor", as used herein, relates to a compound which which targets, decreases or inhibits SRC. Examples of a SRC family tyrosine kinase inhibitor include, but are not limited to, PP1, which is also known as 1H-Pyrazolo[3,4-d]pyrimidin-4-amine, 1-(1,1-dimethylethyl)-3-(1-naphthalenyl)- (9CI); and PP2, which is also known as 1H-Pyrazolo[3,4-d]pyrimidin-4-amine, 3-(4-chlorophenyl)-1-(1,1-dimethylethyl)- (9CI).

[0364] The term "a Syk tyrosine kinase inhibitor", as used herein, relates to a compound which targets, decreases or inhibits Syk. Examples of targets for a Syk tyrosine kinase inhibitor include, but are not limited to, Syk, STAT3, and/or STAT5. An example of a Syk tyrosine kinase inhibitor includes, but is not limited to, Piceatannol, which is also known as 1,2-Benzenediol, 4-[(1E)-2-(3,5-dihydroxyphenyl)ethenyl]- (9CI).

[0365] The term "a Janus (JAK-2 and/or JAK-3) tyrosine kinase inhibitor", as used herein, relates to a compound which targets, decreases or inhibits janus tyrosine kinase. Janus tyrosine kinase inhibitor are shown anti-leukemic agents with anti-thrombotic, anti-allergic and immunosuppressive properties. Targets of a JAK-2 and/or JAK-3 tyrosine kinase inhibitor include, but are not limited to, JAK2, JAK3, STAT3. An indirect target of an JAK-2 and/or JAK-3 tyrosine kinase inhibitor includes, but is not limited to CDK2. Examples of a JAK-2 and/or JAK-3 tyrosine kinase inhibitor include, but are not limited to, Tyrphostin AG 490; and 2-naphthyl vinyl ketone.

[0366] The term "inhibitor of Ras oncogenic isoforms", as used herein, includes, but is not limited to H-Ras, K-Ras or N-Ras, as used herein, refers to compounds which target, decrease or inhibit the oncogenic activity of Ras, e.g., a farnesyl transferase inhibitor (FTI), e.g., L-744832, DK8G557 or R115777 (ZARNESTRA).

[0367] The term "a retinoid", as used herein, refers to compounds that target, decrease or inhibit retinoid dependent receptors. Examples include, but are not limited to Isotretinoin and Tretinoin.

[0368] The term "ribonucleotide reductase inhibitor" as used herein, includes, but is not limited to, pyrimidine or purine nucleoside analogs including, but not limited to, fludarabine and/or ara-C; 6-thioguanine; 5-FU; cladribine; 6-mercaptopurine, especially in combination with ara-C against ALL; and/or pentostatin. Ribonucleotide reductase inhibitors are especially hydroxyurea or 2-hydroxy-1H-isoindole-1,3-dione derivatives, such as PL-1, PL-2, PL-3, PL-4, PL-5, PL-6, PL-7 or PL-8. See Nandy et al., Acta Oncologica, Vol. 33, No. 8, pp. 953-961 (1994).

[0369] The term "a RNA polymerase II elongation inhibitor", as used herein, relates to a compound which targets, decreases or inhibits insulin-stimulated nuclear and cytosolic p70S6 kinase in CHO cells; targets, decreases or inhibits RNA polymerase II transcription, which may be dependent on casein kinase II; and targets, decreases or inhibits germinal vesicle breakdown in bovine oocytes An example of a RNA polymerase II elongation inhibitor includes, but is not limited to, 5,6-dichloro-1-beta-D-ribofuranosylbenzimidazole.

[0370] The term "S-adenosylmethionine decarboxylase inhibitors", as used herein, includes, but is not limited to, the compounds disclosed in U.S. Patent No. 5,461,076.

[0371] The term "a serine/threonine kinase inhibitor", as used herein, relates to a compound which inhibits serine/threonine kinases. An example of a target of a serine/threonine kinase inhibitor includes, but is not limited to, dsRNA-dependent protein kinase (PKR). Examples of indirect targets of a serine/threonine kinase inhibitor include, but are not limited to, MCP-1, NF-kappaB, eIF2alpha, COX2, RANTES, IL8,CYP2A5, IGF-1, CYP2B1, CYP2B2, CYP2H1, ALAS-1, HIF-1, erythropoietin, and/or CYP1A1. An example of a serine/theronin kinase inhibitor includes, but is not limited to, 2-aminopurine, also known as 1H-purin-2-amine(9CI).

[0372] The term "somatostatin receptor antagonist", as used herein, includes, but is not limited to, agents which target, treat or inhibit the somatostatin receptor, such as octreoride and SOM230.

[0373] The term "a sterol biosynthesis inhibitor", as used herein, relates to a compound which inhibits the biosynthesis of sterols such as cholesterol Examples of targets for a sterol biosynthesis inhibitor include, but are not limited to squalene

epoxidase, and CYP2D6. An example of a sterol biosynthesis inhibitor includes, but is not limited to, terbinadine.

[0374] The term "telomerase inhibitor", as used herein, includes, but is not limited to compounds which target, decrease or inhibit the activity of telomerase. Compounds which target, decrease or inhibit the activity of telomerase are especially compounds which inhibit the telomerase receptor, e.g., telomestatin.

[0375] The term "a topoisomerase inhibitor", includes a topoisomerase I inhibitor and a topoisomerase II inhibitor. Examples of a topoisomerase I inhibitor include, but are not limited to, topotecan, gimatecan, irinotecan, camptothecian and its analogues, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148 (compound A1 in WO 99/17804); 10-hydroxycamptothecin acetate salt; etoposide; idarubicin hydrochloride; irinotecan hydrochloride; teniposide; topotecan hydrochloride; doxorubicin; epirubicin hydrochloride; mitoxantrone hydrochloride; and daunorubicin hydrochloride. Irinotecan can be administered, e.g., in the form as it is marketed, e.g., under the trademark CAMPTOSAR. Topotecan can be administered, e.g., in the form as it is marketed, e.g., under the trademark HYCAMTIN. The term "topoisomerase II inhibitor", as used herein, includes, but is not limited to, the anthracyclines, such as doxorubicin, including liposomal formulation, e.g., CAELYX, daunorubicin, including liposomal formulation, e.g., DAUNOSOME, epirubicin, idarubicin and nemorubicin; the anthraquinones mitoxantrone and losoxantrone; and the podophillotoxines etoposide and teniposide. Etoposide is marketed as ETOPOPHOS; teniposide as VM 26-BRISTOL; doxorubicin as ADRIBLASTIN or ADRIAMYCIN; epirubicin as FARMORUBICIN; idarubicin as ZAVEDOS; and mitoxantrone as NOVANTRON.

[0376] The phrase "tumor cell damaging approaches" refers to approaches, such as ionizing radiation. The term "ionizing radiation", referred to above and hereinafter, means ionizing radiation that occurs as either electromagnetic rays, such as X-rays and gamma rays; or particles, such as alpha, beta and gamma particles. Ionizing radiation is provided in, but not limited to, radiation therapy and is known in the art. See Hellman, Cancer, 4th Edition, Vol. 1, Devita et al., Eds., pp. 248-275 (1993).

[0377] The phrase "a monoclonal antibody of VEGF or VEGFR", as used herein, includes but is not limited to, compounds disclosed in WO 98/35958, e.g., 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, e.g., the succinate, or in WO 00/09495, WO 00/27820, WO 00/59509, WO 98/11223, WO 00/27819 and EP 0 769 947; those as described by Prewett et al.,

Cancer Res, Vol. 59, pp. 5209-5218 (1999); Yuan et al., Proc Natl Acad Sci USA, Vol. 93, pp. 14765-14770 (1996); Zhu et al., Cancer Res, Vol. 58, pp. 3209-3214 (1998); and Mordenti et al., Toxicol Pathol, Vol. 27, No. 1, pp. 14-21 (1999) in WO 00/37502 and WO 94/10202; ANGIOSTATIN, described by O'Reilly et al., Cell, Vol. 79, pp. 315-328 (1994); ENDOSTATIN, described by O'Reilly et al., Cell, Vol. 88, pp. 277-285 (1997); anthranilic acid amides; ZD4190; ZD6474; SU5416; SU6668; bevacizumab; or anti-VEGF antibodies or anti-VEGF receptor antibodies, e.g., rhuMAb and RHUFab; VEGF aptamer, e.g., Macugon; FLT-4 inhibitors; FLT-3 inhibitors; VEGFR-2 IgG1 antibody; Angiozyme (RPI 4610); and Avastan.

[0378] The term "VEGFR tyrosine kinase inhibitor", as used herein, relates to a compound which targets, decreases and/or inhibits the known angiogenic growth factors and cytokines implicated in the modulation of normal and pathological angiogenesis. The VEGF family (VEGF-A, VEGF-B, VEGF-C, VEGF-D) and their corresponding receptor tyrosine kinases [VEGFR-1 (Flt-1), VEGFR-2 (Flk-1, KDR), and VEGFR-3 (Flt-4)] play a paramount and indispensable role in regulating the multiple facets of the angiogenic and lymphangiogenic processes. An example of a VEGFR tyrosine kinase inhibitor includes, but is not limited to, 3-(4-dimethylaminobenzylidenyl)-2-indolinone.

[0379] The term "RANKL inhibitor", as used herein, relates to a compound that targets, decreases or inhibits RANK/RANKL pathway. RANK inhibitors prevent osteoclast-mediated bone loss in a range of conditions including osteoporosis, treatment-induced bone loss (bone loss due to glucocorticoid treatment and immunosuppression), rheumatoid arthritis, bone metastases and multiple myeloma. An example of a RANKL inhibitor includes, but is not limited to, denosumab.

[0380]

[0381] The following is a description by way of example only.

Example 1

[0382] Two cancer derived cell lines are used (BT474 and MDA-MB-231). These are human breast carcinoma cell lines. The cell lines are commercially available from American Type Culture Collection (ATCC). BT474 cells are maintained in Hybri-Care medium (ATCC) supplemented with 10% v/v fetal calf serum and 2 mM L-glutamine. MDB-MB-231 cells are grown in RPMI 1640 medium (Animed, Allschwil, Switzerland) supplemented with 10% v/v fetal calf serum and 2 mM L-glutamine. The media are

supplemented with 100 microgramm/ml penicillin/streptomycin and cells are maintained at 37° C in 5% CO_2.

[0383] After division and medium change, cells from stock culture are seeded at a density of 3.3 x 10^4 cells/cm^2 (BT474) and 1.2 x 10^4 cells/cm^2 (MDB-MB-231) on cell plates and incubated for 48 hours at 37° C and 5% CO_2 prior to the treatment with DMSO vehicle, 20 nM everolimus (RAD001) and/or various concentrations of AUY922 (compound 1) for 24 hours. To prepare cell lysates culture plates are washed once with ice-cold phosphor buffered saline (PBS) containing 1 mM phenylmethylsulfonyl fluoride (PMSF) and once with ice-cold extraction buffer (50 mM Hepes pH 7.4, 150 mM NaCl, 25 mM beta-glycerophosphate, 25 mM NaF, 5 mM EGTA, 1 mM EDTA, 15 mM PPi, 2 mM sodium orthovanadate, 10 mM sodium molybdate, leupeptin (10 microgramm/ml), aprotinin (10 microgramm/ml), 1 mM DTT and 1 mM PMSF. Cells are extracted in the same buffer, containing 1% NP-40. The extracts are homogenized, cleared by centrifugation, aliquoted and frozen at -80° C. Protein concentration is determined with the BCA Protein Assay (Pierce, Rockford, IL, USA).

[0384] Twenty micrograms of cell extracts are resolved electrophoretically on 12% denaturing sodium dodecyl sulfate polyacrylamide gels (SDS-PAGE) and transferred to polyvinylidene difluoride filters by wet-blotting (1 hour at 250 mA) and probed overnight at 4°C with the following primary antibodies :

[0385] anti-phospho-Akt (Ser473) (clone 14-05; 1:2000) obtained from DAKO (Glostrup, Denmark) and diluted in PBS, 0.5 % v/v Tween.

[0386] anti-phospho-Akt (T308) (cat # 9275; 1:1000) obtained from Cell Signaling Technology (Beverly, MA, USA) and diluted in PBS, 0.1 % v/v Tween.

[0387] anti-Akt (cat # 1085-1; 1:5000) obtained from Epitomics (Burlingame, CA, USA) and diluted in PBS, 0.5 % v/v Tween.

[0388] Anti-Actin (cat # MAB1501; 1:20,000) obtained from Chemicon (Billerica, MA, USA) and diluted in PBS, 0.1 % v/v Tween.

[0389] After incubation with the appropriate primary antibody (above), decorated proteins are revealed using horseradish peroxidase-conjugated anti-mouse or anti-rabbit immunoglobulins followed by enhanced chemiluminescence (ECL Plus kit) and quantified using Quantity One Software (Bio-Rad, Munich, Germany).

Example 2

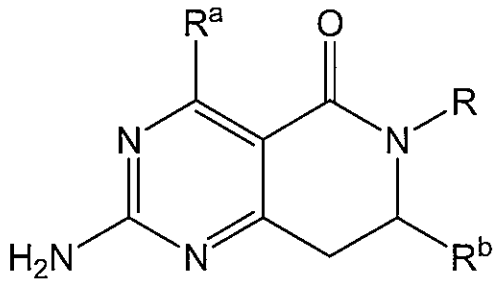
[0390] Figure 1 shows AKT phosphorylation levels in presence of everolimus (RAD001) and everolimus (RAD001) in combination with compound I ((R)-2-amino-7-[2-(6-methoxy-pyridin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one) in BT474 breast tumor cells. The mTOR inhibition with RAD001 activates Akt in tumor cells (O'Reilly et al., 2006). The Western blot analysis demonstrates that in BT-474 cells treated with 20 nM RAD001 increased levels of phosphorylated AKT (P-AKT(S_{473}) and P-AKT(T_{308})) compared to an untreated control are observed. When the cells were treated with 50-100 nM compound I ((R)-2-amino-7-[2-(6-methoxy-pyridin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one), AKT phosporylation ((P-AKT(S_{473}) and P-AKT(T_{308})) was diminished. In the presence of 50-100 nM compound I, the addition of 20 nM RAD001 did not cause increase in AKT phosphorylation (P-AKT(S_{473}) and P-AKT(T_{308})). AKT levels were not significantly affected by any of the treatments. Actin is used to demonstrate equal protein loading on each lane on the Western blot.

Example 3

[0391] Figure 2 shows the AKT phosphorylation levels in presence of everolimus (RAD001) and everolimus (RAD001) in combination with compound I ((R)-2-amino-7-[2-(6-methoxy-pyridin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one) in MDA-MB-231 breast tumor cells. It has been demonstrated that mTOR inhibition with RAD001 activates Akt in tumor cells (O'Reilly et al., 2006). The Western blot analysis demonstrates that in MDA-MB-231 cells treated with 20 nM RAD001 increased levels of phosphorylated AKT (P-AKT(S_{473})) compared to an untreated control are observed. When the cells were treated with 50-100 nM compound I, AKT phosporylation (P-AKT(S_{473})) was diminished. In the presence of 50-100 nM compound I ((R)-2-amino-7-[2-(6-methoxy-pyridin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one), addition of 20 nM RAD001 did not cause increased phosphorylation of AKT at amino acid residue T_{308}. AKT levels were slightly decreased in the presence of 100 nM Compound I ((R)-2-amino-7-[2-(6-methoxy-pyridin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one) consistent with the fact that AKT is a client protein for Hsp90. Actin was used to demonstrate equal protein loading on each lane on the Western blot.

WHAT IS CLAIMED IS:

1. A pharmaceutical combination comprising (a) a Hsp90 inhibitor compound according to Formula (I)



(I)

or a pharmaceutically acceptable salt or prodrug thereof, wherein

R^a is selected from the group consisting of

(1) hydrogen,

(2) halogen,

(3) hydroxyl,

(4) C_1-C_6 alkoxy,

(5) thiol,

(6) C_1-C_6 alkylthiol,

(7) substituted or unsubstituted C_1-C_6 alkyl,

(8) amino or substituted amino,

(9) substituted or unsubstituted aryl,

(10) substituted or unsubstituted heteroaryl, and

(11) substituted or unsubstituted heterocyclyl;

R is selected from the group consisting of

(1) hydrogen,

(2) substituted or unsubstituted C_1-C_6 alkyl,

(3) substituted or unsubstituted C_2-C_6 alkenyl,

(4) substituted or unsubstituted C_2-C_6 alkynyl,

(5) substituted or unsubstituted C_3-C_7 cycloalkyl,

(6) substituted or unsubstituted C_5-C_7 cycloalkenyl,

(7) substituted or unsubstituted aryl,

(8) substituted or unsubstituted heteroaryl, and

(9) substituted or unsubstituted heterocyclyl;

R^b is selected from the group consisting of

(1) substituted or unsubstituted C_3-C_7 cycloalkyl,

(2) substituted or unsubstituted C_5-C_7 cycloalkenyl,

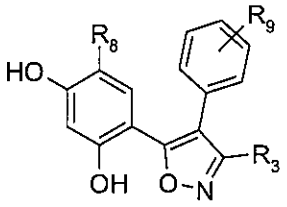
(3) substituted or unsubstituted aryl,

(4) substituted or unsubstituted heteroaryl, and

(5) substituted or unsubstituted heterocyclyl; and

with the proviso that when R^a is amino, then R^b is not phenyl, 4-alkyl-phenyl, 4-alkoxy-phenyl, or 4-halo-phenyl, or

a compound of formula (E)



(E)

wherein

R_3 is selected from methylaminocarbonyl $CH_3CH_2NHC(=O)$- , ethylaminocarbonyl $CH_3CH_2NHC(=O)$-, propylaminocarbonyl $CH_3CH_2CH_2NHC(=O)$-, or isopropylaminocarbonyl $(CH_3)_2CHNHC(=O)$-),

R_8 is selected from methyl, ethyl, isopropyl, bromo, or chloro; and

R_9 is $–CH_2NR^{10}R^{11}$ or $–NR^{10}R^{11}$ wherein the substituted amino group $–NR^{10}R^{11}$ is a morpholinyl, piperidinyl, piperazinyl, pyrroliidinyl, ethylamino, isopropylamino, diethylamino, cyclohexylamino, cyclopentylamino, methoxyethylamino, piperidin-4-yl, N-acetylpiperazinyl, N-methylpiperazinyl, methylsulfonylamino, thiomorpholinyl, thiomorpholinyl-dioxide, 4-hydroxyethylpiperidinyl or 4-hydroxypiperidinyl

a $–CH_2–$ that links with a morpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, ethylamino, isopropylamino, diethylamino, cyclohexylamino, cyclopentylamino, methoxyethylamino, piperidin-4-yl, N-acetylpiperazinyl, N-methylpiperazinyl, methylsulfonylamino, thiomorpholinyl, thiomorpholinyl-dioxide, 4-hydroxyethylpiperidinyl or 4-hydroxypiperidinyl,

or a pharmaceutically acceptable salt or prodrug thereof,

and (b) a PI3Kinase inhibitor.

2. The pharmaceutical combination according to claim 1, wherein the PI3Kinase inhibitor is 3H-Furo[4,3,2-de]indeno[4,5-h]-2-benzopyran-3,6,9-trione, 11-(acetyloxy)-1,6b,7,8,9a,10,11,11b-octahydro-1-(methoxymethyl)-9a,11b-dimethyl-, (1S,6bR,9aS,11R,11bR)- (9CI); 8-phenyl-2-(morpholin-4-yl)-chromen-4-one, 4-(trifluoromethyl)-5-(2,6-dimorpholinopyrimidin-4-yl)pyridin-2-amine, 2-Methyl-2-[4-(3-methyl-2-oxo-8-quinolin-3-yl-2,3-dihydro-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile or Quercetin Dihydrate; or a pharmaceutically acceptable salt thereof.

3. The pharmaceutical combination according to claim 2, wherein the PI3Kinase inhibitor is 4-(trifluoromethyl)-5-(2,6-dimorpholinopyrimidin-4-yl)pyridin-2-amine or a pharmaceutically acceptable salt thereof.

4. The pharmaceutical combination according to claim 2, wherein the PI3Kinase inhibitor is 2-Methyl-2-[4-(3-methyl-2-oxo-8-quinolin-3-yl-2,3-dihydro-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile or a pharmaceutically acceptable salt thereof.

5. The pharmaceutical combination according to claim 1, wherein the Hsp90 inhibitor is (R)-2-amino-7-[2-(2-fluoro-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(S)-2-amino-6-benzyl-7-[4-fluoro-2-(2-fluoro-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-[4-fluoro-2-(2-fluoro-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-(2-bromo-4-fluoro-phenyl)-6-[(S)-1-(4-methoxy-phenyl)-ethyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-[2-(6-methoxy-pyridin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-[4-fluoro-2-(6-methoxy-pyridin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(6-methoxy-pyridin-2-yl)-phenyl]-4,6-dimethyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(2-fluoro-pyridin-3-yl)-phenyl]-4,6-dimethyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(6-methoxypyridin-2-yl)phenyl]-4-methyl-7,8-dihydropyrido[4,3-*d*]pyrimidin-5(6*H*)-one;

2-amino-7-[2-(6-methoxy-pyrazin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-[4-fluoro-2-(6-methoxy-pyrazin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

2-amino-7-[4-fluoro-2-(6-methoxy-pyrazin-2-yl)-phenyl]-4,6-dimethyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[2-(2-methoxy-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5,2'-difluoro-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5-fluoro-2'-trifluoromethoxy-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[2-(2-chloro-pyridin-3-yl)-4-fluoro-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(6-fluoro-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(4-fluoro-2-isoquinolin-4-yl-phenyl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5,3'-difluoro-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[2-(4-chloro-pyridin-3-yl)-4-fluoro-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5,2'-difluoro-3'-methoxy-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5,4'-difluoro-2'-methyl-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5-fluoro-2'-methoxy-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(4-fluoro-2-pyrimidin-5-yl-phenyl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(2-methoxy-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5-fluoro-3'-methoxy-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-6-(3-amino-propyl)-7-[4-fluoro-2-(6-methoxy-pyridin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(4-fluoro-2-pyridin-3-yl-phenyl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5,2'-difluoro-4'-methyl-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(1-methyl-1H-pyrazol-4-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(1H-pyrazol-4-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-4-methyl-7-(5,2',3'-trifluoro-biphenyl-2-yl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(2-bromo-4-fluoro-phenyl)-4-methyl-6-(2-methyl-2-morpholin-4-yl-propyl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

2-amino-7-(3'-dimethylamino-5-fluoro-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[2-(2,4-dimethoxy-pyrimidin-5-yl)-4-fluoro-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(5-methoxy-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(4-fluoro-2-pyrimidin-5-yl-phenyl)-4-methyl-6-(2-methyl-2-morpholin-4-yl-propyl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(2-methoxy-pyridin-3-yl)-phenyl]-4-methyl-6-(2-methyl-2-morpholin-4-yl-propyl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5-fluoro-3'-methoxy-biphenyl-2-yl)-4-methyl-6-(2-methyl-2-morpholin-4-yl-propyl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-[4-fluoro-2-(4-methoxy-5-methyl-pyrimidin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

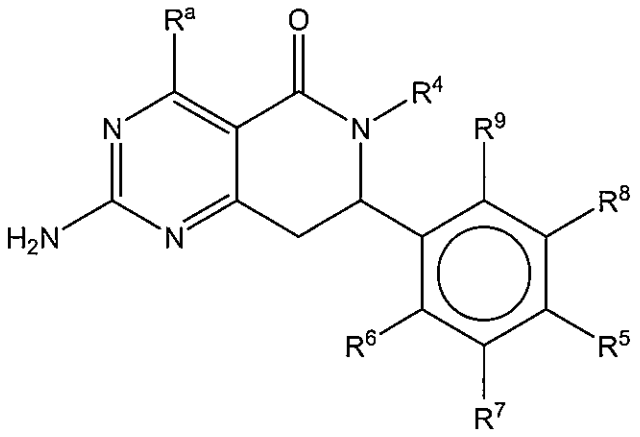
2-amino-7-(4-fluoro-2-furan-3-yl-phenyl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

5-(2,4-Dihydroxy-5-isopropyl-phenyl)-4-(4-morpholin-4-ylmethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide or

a pharmaceutically acceptable salt or prodrug thereof.

6. A pharmaceutical combination comprising

(a) an Hsp 90 inhibitor according to formula (III)



(III)

or a pharmaceutically acceptable salt or prodrug thereof, wherein

wherein R^a is selected from the group consisting of

(1) hydrogen,

(2) halogen,

(3) hydroxyl,

(4) C_1-C_6 alkoxy,

(5) thiol,

(6) C_1-C_6 alkylthiol,

(7) substituted or unsubstituted C_1-C_6 alkyl,

(8) amino or substituted amino,

(9) substituted or unsubstituted aryl,

(10) substituted or unsubstituted heteroaryl, and

(11) substituted or unsubstituted heterocyclyl;

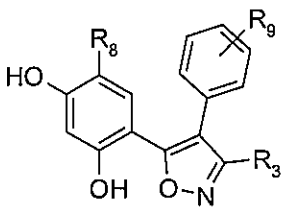
R^4 is hydrogen or substituted or unsubstituted C_1-C_6 alkyl;

R^5 is hydrogen, alkyl, alkoxy, or halo;

each of R^6, R^7, R^8, and R^9 are independently selected from the group consisting of hydrogen, alkyl, alkoxy, halo, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

with the proviso that when R^a is amino and R^6, R^7, R^8, and R^9 are hydrogen, then R^5 is not hydrogen, alkyl, alkoxy, or halo; or

a compound of formula (E)



(E)

wherein

R_3 is selected from methylaminocarbonyl $CH_3CH_2NHC(=O)$- , ethylaminocarbonyl $CH_3CH_2NHC(=O)$-, propylaminocarbonyl $CH_3CH_2CH_2NHC(=O)$-, or isopropylaminocarbonyl $(CH_3)_2CHNHC(=O)$-),

R_8 is selected from methyl, ethyl, isopropyl, bromo, or chloro; and

R_9 is $-CH_2NR^{10}R^{11}$ or $-NR^{10}R^{11}$ wherein the substituted amino group $-NR^{10}R^{11}$ is a morpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, ethylamino, isopropylamino, diethylamino, cyclohexylamino, cyclopentylamino, methoxyethylamino, piperidin-4-yl, N-acetylpiperazinyl, N-methylpiperazinyl, methylsulfonylamino, thiomorpholinyl, thiomorpholinyl-dioxide, 4-hydroxyethylpiperidinyl or 4-hydroxypiperidinyl,

or a pharmaceutically acceptable salt or prodrug thereof,

and (b) a PI3Kinase inhibitor.

7. The pharmaceutical combination according to claim 6, wherein the P13Kinase inhibitor comprises 3H-Furo[4,3,2-de]indeno[4,5-h]-2-benzopyran-3,6,9-trione, 11-(acetyloxy)-1,6b,7,8,9a,10,11,11b-octahydro-1-(methoxymethyl)-9a,11b-dimethyl-, (1S,6bR,9aS,11R,11bR)-(9CI); 8-phenyl-2-(morpholin-4-yl)-chromen-4-one, 4-(trifluoromethyl)-5-(2,6-dimorpholinopyrimidin-4-yl)pyridin-2-amine, 2-Methyl-2-[4-(3-methyl-2-oxo-8-quinolin-3-yl-2,3-dihydro-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile or Quercetin Dihydrate or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical combination comprising (a) an Hsp90 inhibitor that is

(R)-2-amino-7-[2-(2-fluoro-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(S)-2-amino-6-benzyl-7-[4-fluoro-2-(2-fluoro-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-[4-fluoro-2-(2-fluoro-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-(2-bromo-4-fluoro-phenyl)-6-[(S)-1-(4-methoxy-phenyl)-ethyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-[2-(6-methoxy-pyridin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-[4-fluoro-2-(6-methoxy-pyridin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(6-methoxy-pyridin-2-yl)-phenyl]-4,6-dimethyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(2-fluoro-pyridin-3-yl)-phenyl]-4,6-dimethyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(6-methoxypyridin-2-yl)phenyl]-4-methyl-7,8-dihydropyrido[4,3-*d*]pyrimidin-5(6*H*)-one,

2-amino-7-[2-(6-methoxy-pyrazin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-[4-fluoro-2-(6-methoxy-pyrazin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(6-methoxy-pyrazin-2-yl)-phenyl]-4,6-dimethyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[2-(2-methoxy-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5,2'-difluoro-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5-fluoro-2'-trifluoromethoxy-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

2-amino-7-[2-(2-chloro-pyridin-3-yl)-4-fluoro-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(6-fluoro-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(4-fluoro-2-isoquinolin-4-yl-phenyl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5,3'-difluoro-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[2-(4-chloro-pyridin-3-yl)-4-fluoro-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5,2'-difluoro-3'-methoxy-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5,4'-difluoro-2'-methyl-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5-fluoro-2'-methoxy-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(4-fluoro-2-pyrimidin-5-yl-phenyl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(2-methoxy-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5-fluoro-3'-methoxy-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-6-(3-amino-propyl)-7-[4-fluoro-2-(6-methoxy-pyridin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(4-fluoro-2-pyridin-3-yl-phenyl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5,2'-difluoro-4'-methyl-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(1-methyl-1H-pyrazol-4-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(1H-pyrazol-4-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-4-methyl-7-(5,2',3'-trifluoro-biphenyl-2-yl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(2-bromo-4-fluoro-phenyl)-4-methyl-6-(2-methyl-2-morpholin-4-yl-propyl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(3'-dimethylamino-5-fluoro-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[2-(2,4-dimethoxy-pyrimidin-5-yl)-4-fluoro-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(5-methoxy-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(4-fluoro-2-pyrimidin-5-yl-phenyl)-4-methyl-6-(2-methyl-2-morpholin-4-yl-propyl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(2-methoxy-pyridin-3-yl)-phenyl]-4-methyl-6-(2-methyl-2-morpholin-4-yl-propyl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5-fluoro-3'-methoxy-biphenyl-2-yl)-4-methyl-6-(2-methyl-2-morpholin-4-yl-propyl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-[4-fluoro-2-(4-methoxy-5-methyl-pyrimidin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

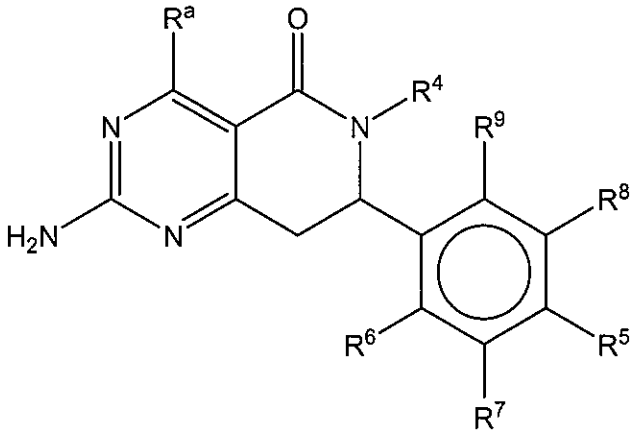
2-amino-7-(4-fluoro-2-furan-3-yl-phenyl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

5-(2,4-Dihydroxy-5-isopropyl-phenyl)-4-(4-morpholin-4-ylmethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide or

a pharmaceutically acceptable salt or prodrug thereof; and

(b) a PI3Kinase inhibitor that is 3H-Furo[4,3,2-de]indeno[4,5-h]-2-benzopyran-3,6,9-trione, 11-(acetyloxy)-1,6b,7,8,9a,10,11,11b-octahydro-1-(methoxymethyl)-9a,11b-dimethyl-, (1S,6bR,9aS,11R,11bR)- (9CI); 8-phenyl-2-(morpholin-4-yl)-chromen-4-one, 4-(trifluoromethyl)-5-(2,6-dimorpholinopyrimidin-4-yl)pyridin-2-amine, 2-Methyl-2-[4-(3-methyl-2-oxo-8-quinolin-3-yl-2,3-dihydro-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile or Quercetin Dihydrate; or a pharmaceutically acceptable salt thereof.

9. A method of treating a proliferative disease comprising administering to a patient in need thereof an effective amount of a first pharmaceutical component and a second pharmaceutical component, wherein the first pharmaceutical component is a Hsp90 inhibitor that is a compound according to formula (III)



(III)

or a pharmaceutically acceptable salt or prodrug thereof, wherein

wherein R^a is selected from the group consisting of

(1) hydrogen,

(2) halogen,

(3) hydroxyl,

(4) C_1-C_6 alkoxy,

(5) thiol,

(6) C_1-C_6 alkylthiol,

(7) substituted or unsubstituted C_1-C_6 alkyl,

(8) amino or substituted amino,

(9) substituted or unsubstituted aryl,

(10) substituted or unsubstituted heteroaryl, and

(11) substituted or unsubstituted heterocyclyl;

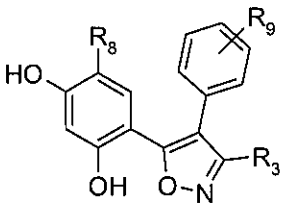
R^4 is hydrogen or substituted or unsubstituted C_1-C_6 alkyl;

R^5 is hydrogen, alkyl, alkoxy, or halo;

each of R^6, R^7, R^8, and R^9 are independently selected from the group consisting of hydrogen, alkyl, alkoxy, halo, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

with the proviso that when R^a is amino and R^6, R^7, R^8, and R^9 are hydrogen, then R^5 is not hydrogen, alkyl, alkoxy, or halo or

a compound of formula (E)



(E)

wherein

R_3 is selected from methylaminocarbonyl $CH_3CH_2NHC(=O)$- , ethylaminocarbonyl $CH_3CH_2NHC(=O)$-, propylaminocarbonyl $CH_3CH_2CH_2NHC(=O)$-, or isopropylaminocarbonyl $(CH_3)_2CHNHC(=O)$-),

R_8 is selected from methyl, ethyl, isopropyl, bromo, or chloro; and

$-R_9$ is $CH_2NR^{10}R^{11}$ or $-NR^{10}R^{11}$ wherein the substituted amino group $-NR^{10}R^{11}$ is a morpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, ethylamino, isopropylamino, diethylamino, cyclohexylamino, cyclopentylamino, methoxyethylamino, piperidin-4-yl, N-acetylpiperazinyl, N-

methylpiperazinyl, methylsulfonylamino, thiomorpholinyl, thiomorpholinyl-dioxide, 4-hydroxyethylpiperidinyl or 4-hydroxypiperidinyl,

or a pharmaceutically acceptable salt or prodrug thereof,

and wherein the second pharmaceutical component is a PI3Kinase inhibitor.

10. The method of claim 9, wherein the PI3Kinase inhibitor is 3H-Furo[4,3,2-de]indeno[4,5-h]-2-benzopyran-3,6,9-trione, 11-(acetyloxy)-1,6b,7,8,9a,10,11,11b-octahydro-1-(methoxymethyl)-9a,11b-dimethyl-, (1S,6bR,9aS,11R,11bR)- (9CI); 8-phenyl-2-(morpholin-4-yl)-chromen-4-one, 4-(trifluoromethyl)-5-(2,6-dimorpholinopyrimidin-4-yl)pyridin-2-amine, 2-Methyl-2-[4-(3-methyl-2-oxo-8-quinolin-3-yl-2,3-dihydro-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile or Quercetin Dihydrate or a pharmaceutically acceptable salt thereof..

11. The method of claim 10, wherein the compound according to Formula (III) is

(R)-2-amino-7-[2-(2-fluoro-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(S)-2-amino-6-benzyl-7-[4-fluoro-2-(2-fluoro-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-[4-fluoro-2-(2-fluoro-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-(2-bromo-4-fluoro-phenyl)-6-[(S)-1-(4-methoxy-phenyl)-ethyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-[2-(6-methoxy-pyridin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one

(R)-2-amino-7-[4-fluoro-2-(6-methoxy-pyridin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(6-methoxy-pyridin-2-yl)-phenyl]-4,6-dimethyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(2-fluoro-pyridin-3-yl)-phenyl]-4,6-dimethyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(6-methoxypyridin-2-yl)phenyl]-4-methyl-7,8-dihydropyrido[4,3-*d*]pyrimidin-5(6*H*)-one,

2-amino-7-[2-(6-methoxy-pyrazin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-[4-fluoro-2-(6-methoxy-pyrazin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(6-methoxy-pyrazin-2-yl)-phenyl]-4,6-dimethyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[2-(2-methoxy-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5,2'-difluoro-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5-fluoro-2'-trifluoromethoxy-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[2-(2-chloro-pyridin-3-yl)-4-fluoro-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(6-fluoro-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(4-fluoro-2-isoquinolin-4-yl-phenyl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5,3'-difluoro-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[2-(4-chloro-pyridin-3-yl)-4-fluoro-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5,2'-difluoro-3'-methoxy-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5,4'-difluoro-2'-methyl-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5-fluoro-2'-methoxy-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(4-fluoro-2-pyrimidin-5-yl-phenyl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(2-methoxy-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5-fluoro-3'-methoxy-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-6-(3-amino-propyl)-7-[4-fluoro-2-(6-methoxy-pyridin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one;

2-amino-7-(4-fluoro-2-pyridin-3-yl-phenyl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5,2'-difluoro-4'-methyl-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(1-methyl-1H-pyrazol-4-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(1H-pyrazol-4-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-4-methyl-7-(5,2',3'-trifluoro-biphenyl-2-yl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(2-bromo-4-fluoro-phenyl)-4-methyl-6-(2-methyl-2-morpholin-4-yl-propyl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(3'-dimethylamino-5-fluoro-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[2-(2,4-dimethoxy-pyrimidin-5-yl)-4-fluoro-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(5-methoxy-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(4-fluoro-2-pyrimidin-5-yl-phenyl)-4-methyl-6-(2-methyl-2-morpholin-4-yl-propyl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(2-methoxy-pyridin-3-yl)-phenyl]-4-methyl-6-(2-methyl-2-morpholin-4-yl-propyl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5-fluoro-3'-methoxy-biphenyl-2-yl)-4-methyl-6-(2-methyl-2-morpholin-4-yl-propyl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-[4-fluoro-2-(4-methoxy-5-methyl-pyrimidin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(4-fluoro-2-furan-3-yl-phenyl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

5-(2,4-Dihydroxy-5-isopropyl-phenyl)-4-(4-morpholin-4-ylmethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide, or

a pharmaceutically acceptable salt or prodrug thereof.

12. The method of claim 9, wherein the PI3Kinase inhibitor is

3H-Furo[4,3,2-de]indeno[4,5-h]-2-benzopyran-3,6,9-trione, 11-(acetyloxy)-1,6b,7,8,9a,10,11,11b-octahydro-1-(methoxymethyl)-9a,11b-dimethyl-, (1S,6bR,9aS,11R,11bR)- (9CI); 8-phenyl-2-(morpholin-4-yl)-chromen-4-one, 4-(trifluoromethyl)-5-(2,6-dimorpholinopyrimidin-4-yl)pyridin-2-amine, 2-Methyl-2-[4-(3-methyl-2-oxo-8-quinolin-3-yl-2,3-dihydro-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile or Quercetin Dihydrate; or a pharmaceutically acceptable salt thereof.

13. The method of claim 12, comprising administering 4-(trifluoromethyl)-5-(2,6-dimorpholinopyrimidin-4-yl)pyridin-2-amine or a pharmaceutically acceptable salt thereof.

14. The method of claim 12, comprising administering 2-Methyl-2-[4-(3-methyl-2-oxo-8-quinolin-3-yl-2,3-dihydro-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile or a pharmaceutically acceptable salt thereof.

15. The method according to claim 9, wherein treating said proliferative disorder is treatment of tumors, myelomas, leukemias, angiogenesis, psoriasis, restenosis, sclerodermitis or fibrosis, carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina or thyroid, sarcoma, glioblastomas, multiple myeloma or gastrointestinal cancer, colon carcinoma, colorectal adenoma, a tumor of the neck and head, an epidermal hyperproliferation, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, lymphomas, a mammary carcinoma, Cowden syndrome, Lhermitte-Dudos disease or Bannayan-Zonana syndrome.

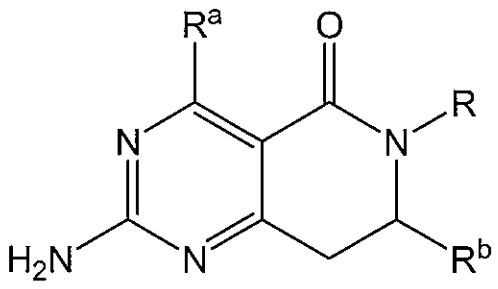
16. The method according to claim 9, wherein the compound according to Formula (III) and the PI3Kinase inhibitor are administered together as a single pharmaceutical composition.

17. The method according to claim 9, wherein the compound according to Formula (III) and the PI3Kinase inhibitor are administered as separate compositions.

18. The method according to claim 9, wherein the compound according to Formula (III) and the PI3Kinase inhibitor are administered sequentially.

19. A method of treating a proliferative disease comprising administering to a patient in need thereof an effective amount of an Hsp 90 inhibitor and a PI3Kinase inhibitor for therapeutic treatment of the proliferative disease.

20. A kit, comprising: (a) a first pharmaceutical composition comprising an Hsp90 inhibitor a compound according to Formula (I)



(I)

or a pharmaceutically acceptable salt or prodrug thereof, in a first pharmaceutically acceptable carrier, wherein

R^a is selected from the group consisting of

(1) hydrogen,

(2) halogen,

(3) hydroxyl,

(4) C_1-C_6 alkoxy,

(5) thiol,

(6) C_1-C_6 alkylthiol,

(7) substituted or unsubstituted C_1-C_6 alkyl,

(8) amino or substituted amino,

(9) substituted or unsubstituted aryl,

(10) substituted or unsubstituted heteroaryl, and

(11) substituted or unsubstituted heterocyclyl;

R is selected from the group consisting of

(1) hydrogen,

(2) substituted or unsubstituted C_1-C_6 alkyl,

(3) substituted or unsubstituted C_2-C_6 alkenyl,

(4) substituted or unsubstituted C_2-C_6 alkynyl,

(5) substituted or unsubstituted C_3-C_7 cycloalkyl,

(6) substituted or unsubstituted C_5-C_7 cycloalkenyl,

(7) substituted or unsubstituted aryl,

(8) substituted or unsubstituted heteroaryl, and

(9) substituted or unsubstituted heterocyclyl;

R^b is selected from the group consisting of

(1) substituted or unsubstituted C_3-C_7 cycloalkyl,

(2) substituted or unsubstituted C_5-C_7 cycloalkenyl,

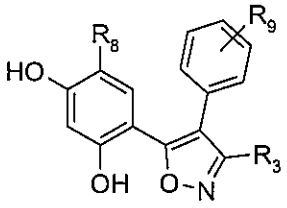
(3) substituted or unsubstituted aryl,

(4) substituted or unsubstituted heteroaryl, and

(5) substituted or unsubstituted heterocyclyl; and

with the proviso that when R^a is amino, then R^b is not phenyl, 4-alkyl-phenyl, 4-alkoxy-phenyl, or 4-halo-phenyl, or

a compound of formula (E)



(E)

wherein

R_3 is selected from methylaminocarbonyl $CH_3CH_2NHC(=O)$- , ethylaminocarbonyl $CH_3CH_2NHC(=O)$-, propylaminocarbonyl $CH_3CH_2CH_2NHC(=O)$-, or isopropylaminocarbonyl $(CH_3)_2CHNHC(=O)$-),

R_8 is selected from methyl, ethyl, isopropyl, bromo, or chloro; and

R_9 is $-CH_2NR^{10}R^{11}$ or $-NR^{10}R^{11}$ wherein the substituted amino group $-NR^{10}R^{11}$ is a morpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, ethylamino, isopropylamino, diethylamino, cyclohexylamino, cyclopentylamino, methoxyethylamino, piperidin-4-yl, N-acetylpiperazinyl, N-methylpiperazinyl, methylsulfonylamino, thiomorpholinyl, thiomorpholinyl-dioxide, 4-hydroxyethylpiperidinyl or 4-hydroxypiperidinyl,

or a pharmaceutically acceptable salt or prodrug thereof,

and (b) a PI3Kinase inhibitor, in a second pharmaceutically acceptable carrier.

wherein

the Hsp90 inhibitor is

(R)-2-amino-7-[2-(2-fluoro-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(S)-2-amino-6-benzyl-7-[4-fluoro-2-(2-fluoro-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-[4-fluoro-2-(2-fluoro-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-(2-bromo-4-fluoro-phenyl)-6-[(S)-1-(4-methoxy-phenyl)-ethyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-[2-(6-methoxy-pyridin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-[4-fluoro-2-(6-methoxy-pyridin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(6-methoxy-pyridin-2-yl)-phenyl]-4,6-dimethyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(2-fluoro-pyridin-3-yl)-phenyl]-4,6-dimethyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(6-methoxypyridin-2-yl)phenyl]-4-methyl-7,8-dihydropyrido[4,3-*d*]pyrimidin-5(6*H*)-one,

2-amino-7-[2-(6-methoxy-pyrazin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-[4-fluoro-2-(6-methoxy-pyrazin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(6-methoxy-pyrazin-2-yl)-phenyl]-4,6-dimethyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[2-(2-methoxy-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5,2'-difluoro-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5-fluoro-2'-trifluoromethoxy-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[2-(2-chloro-pyridin-3-yl)-4-fluoro-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(6-fluoro-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(4-fluoro-2-isoquinolin-4-yl-phenyl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5,3'-difluoro-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[2-(4-chloro-pyridin-3-yl)-4-fluoro-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5,2'-difluoro-3'-methoxy-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5,4'-difluoro-2'-methyl-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5-fluoro-2'-methoxy-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(4-fluoro-2-pyrimidin-5-yl-phenyl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(2-methoxy-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5-fluoro-3'-methoxy-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-6-(3-amino-propyl)-7-[4-fluoro-2-(6-methoxy-pyridin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(4-fluoro-2-pyridin-3-yl-phenyl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5,2'-difluoro-4'-methyl-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(1-methyl-1H-pyrazol-4-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(1H-pyrazol-4-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-4-methyl-7-(5,2',3'-trifluoro-biphenyl-2-yl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(2-bromo-4-fluoro-phenyl)-4-methyl-6-(2-methyl-2-morpholin-4-yl-propyl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(3'-dimethylamino-5-fluoro-biphenyl-2-yl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[2-(2,4-dimethoxy-pyrimidin-5-yl)-4-fluoro-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(5-methoxy-pyridin-3-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(4-fluoro-2-pyrimidin-5-yl-phenyl)-4-methyl-6-(2-methyl-2-morpholin-4-yl-propyl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-[4-fluoro-2-(2-methoxy-pyridin-3-yl)-phenyl]-4-methyl-6-(2-methyl-2-morpholin-4-yl-propyl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(5-fluoro-3'-methoxy-biphenyl-2-yl)-4-methyl-6-(2-methyl-2-morpholin-4-yl-propyl)-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

(R)-2-amino-7-[4-fluoro-2-(4-methoxy-5-methyl-pyrimidin-2-yl)-phenyl]-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

2-amino-7-(4-fluoro-2-furan-3-yl-phenyl)-4-methyl-7,8-dihydro-6H-pyrido[4,3-d]pyrimidin-5-one,

5-(2,4-Dihydroxy-5-isopropyl-phenyl)-4-(4-morpholin-4-ylmethyl-phenyl)-isoxazole-3-carboxylic acid ethylamide or

a pharmaceutically acceptable salt or prodrug thereof; and

the PI3Kinase inhibitor is 3H-Furo[4,3,2-de]indeno[4,5-h]-2-benzopyran-3,6,9-trione, 11-(acetyloxy)-1,6b,7,8,9a,10,11,11b-octahydro-1-(methoxymethyl)-9a,11b-dimethyl-, (1S,6bR,9aS,11R,11bR)- (9CI); 8-phenyl-2-(morpholin-4-yl)-chromen-4-one, 4-(trifluoromethyl)-5-(2,6-dimorpholinopyrimidin-4-yl)pyridin-2-amine, 2-Methyl-2-[4-(3-methyl-2-oxo-8-quinolin-3-yl-2,3-dihydro-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile or Quercetin Dihydrate; or a pharmaceutically acceptable salt thereof.