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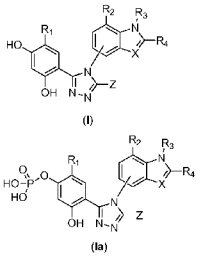
[Continued on next page]

(54) **Title**: COMBINATION THERAPY OF HSP90 INHIBITORY COMPOUNDS WITH PROTEASOME INHIBITORS

(57) **Abstract**: A composition comprising a proteasome inhibitor, and an Hsp90 inhibitor according to the following formuae (I) or (Ia), a tautomer, or a pharmaceutically acceptable salt thereof, wherein the variables in the structural formulae are defined herein. Also provided are methods for treating a proliferative disorder such as cancer in a subject in need thereof, using pharmaceutical combinations described herein.



(I)

(Ia)

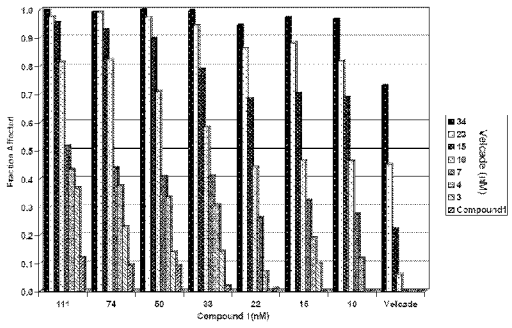


Fig. 1

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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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COMBINATION THERAPY OF HSP90 INHIBITORY COMPOUNDS WITH PROTEASOME INHIBITORS

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Patent Application Nos. 61/431,802, filed on January 11, 2011, and 61/489,020, filed on May 23, 2011. The contents of each of these applications are incorporated herein by reference in their entireties.

BACKGROUND OF THE INVENTION

Although tremendous advances have been made in elucidating the genomic abnormalities that cause malignant cancer cells, currently available chemotherapy remains unsatisfactory, and the prognosis for the majority of patients diagnosed with cancer remains dismal. Most chemotherapeutic agents act on a specific molecular target thought to be involved in the development of the malignant phenotype. However, a complex network of signaling pathways regulate cell proliferation and the majority of malignant cancers are facilitated by multiple genetic abnormalities in these pathways. Therefore, it is less likely that a therapeutic agent that acts on one molecular target will be fully effective in curing a patient who has cancer.

Heat shock proteins (HSPs) are a class of chaperone proteins that are up-regulated in response to elevated temperature and other environmental stresses, such as ultraviolet light, nutrient deprivation and oxygen deprivation. HSPs act as chaperones to other cellular proteins (called client proteins), facilitate their proper folding and repair and aid in the refolding of misfolded client proteins. There are several known families of HSPs, each having its own set of client proteins. The Hsp90 family is one of the most abundant HSP families accounting for about 1-2% of proteins in a cell that is not under stress and increasing to about 4-6% in a cell under stress. Inhibition of Hsp90 results in the degradation of its client proteins via the ubiquitin proteasome pathway. Unlike other chaperone proteins, the client proteins of Hsp90 are mostly protein kinases or transcription factors involved in signal transduction, and a number of its client proteins have been shown to be involved in the progression of cancer.

SUMMARY OF THE INVENTION

It is now found that certain triazolone Hsp90 inhibitors, alone or in combination with proteasome inhibitors, are surprisingly effective at treating subjects with certain cancers without further increasing the side effect profile of the single agents. The particular combination therapies disclosed herein demonstrate surprising biological activity by demonstrating significant anticancer effects.

The present method utilizes Hsp90 inhibitors according to formulae (I) or (Ia) described herein below, or a compound in Tables 1 or 2 for the treatment of proliferative disorders, such as cancer, in combination with a proteasome inhibitor. A method of treating a subject with cancer includes the step of administering to the subject an Hsp90 inhibitor according to formulae (I) or (Ia), or a compound in Tables 1 or 2 and a proteasome inhibitor useful for the treatment of cancer. In one embodiment, the administration of the Hsp90 inhibitor and the proteasome inhibitor are done concurrently. In another embodiment, the administration of the Hsp90 inhibitor and the proteasome inhibitor are done sequentially. In another embodiment, the administration of the Hsp90 inhibitor and the proteasome inhibitor are dosed independently. In any one of these embodiments, the proteasome inhibitor may be disulfiram, epigallocatechin-3-gallate, salinosporamide A, carfilzomib, or bortezomib. In any one of these embodiments, the Hsp90 inhibitor may be a compound represented by formulae (I) or (Ia) or a compound in Tables 1 or 2.

In one embodiment, the method provides a kit for administration of the combination therapy having separate pharmaceutical compositions containing the Hsp90 inhibitor according to formulae (I) or (Ia), or a compound in Tables 1 or 2, and the proteasome inhibitor. In another embodiment, the kit includes one pharmaceutical composition containing both the Hsp90 inhibitor and the proteasome inhibitor in the same composition. In any of these embodiments, each pharmaceutical composition may include one or more pharmaceutically acceptable carrier or diluent. In any one of these embodiments, the proteasome inhibitor may be disulfiram, epigallocatechin-3-gallate, salinosporamide A, carfilzomib, or bortezomib. In any one of these embodiments, the Hsp90 inhibitor may be a compound represented in Tables 1 or 2.

In one embodiment, the method includes use of an Hsp90 inhibitor according to formulae (I) or (Ia) or a compound in Tables 1 or 2 for the manufacture of a medicament for treating cancer in combination with a proteasome inhibitor.

In certain embodiments, the treatments utilize an Hsp90 inhibitory compound according to formulae (I) or (Ia) or a compound in Tables 1 or 2 with a proteasome inhibitor to help to arrest, partially or fully, or reduce the development of multidrug resistant cancerous cells in a subject. In this embodiment, the combinations may allow a reduced efficacious amount of the proteasome inhibitor given to a subject, because the Hsp90 inhibitor should inhibit the development of multidrug-resistant cancerous cells. In one embodiment, the proteasome inhibitor may be disulfiram, epigallocatechin-3-gallate, salinosporamide A, carfilzomib, or bortezomib. In another embodiment, the proteasome inhibitor is bortezomib. In another embodiment, the proteasome inhibitor is carfilzomib.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects, features and advantages of the invention will be apparent from the following more particular description of some embodiments of the invention, as illustrated in the accompanying drawings in which like reference characters refer to the same parts throughout the different views. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating the principles of the invention.

Figure 1 shows the affected fractions of H1703 cells that were killed by compound **1**, bortezomib, or the combination of the two drugs at the indicated concentrations.

Figure 2 shows the fractions affected by the combinations of bortezomib at a concentration of 15 nM with different amounts of compound **1**, which was a breakdown from Figure 1.

Figure 3 shows quantitation of synergy that was determined by CalcuSyn from Figure 1. The isobologram was shown on the left, and algebraic estimate on the right.

Figure 4 shows combination of bortezomib at day 1 and compound **1** at Day 2 in H1703 cells. Top panel showed the changes in apoptosis by Western blot via increased PARP cleavage in combination treatment 24 hr after compound **1** exposure. Bottom panel showed complete cell death by microscopy in the combination arm 72 hours after compound **1** exposure, in contrast to the weak activity displayed by monotherapy.

Figure 5 shows concurrent combination of bortezomib and compound **1** for one hour on both days 1 and 2. Top panel showed the fractions of H1703 cells that were killed by bortezomib, compound **1** or the combination of the two drugs 72 hr after the last exposure. Bottom panel showed that complete cell death by microscopy in the combination arm 72 hours after final drug exposure, in contrast to the weak activity displayed by monotherapy.

Figure 6 shows combination of bortezomib at day 1 and compound **1** at day 2 in H1838 cells. Top panel showed the fraction of H1838 cells killed by bortezomib, compound **1,** or the combination of the two drugs 72 hr after compound **1** exposure. Bottom panel showed that complete cell death by microscopy in the combination arm 72 hours after compound **1** exposure, in contrast to the weak activity displayed by monotherapy.

Figure 7 shows combination of bortezomib at day 1 and compound **1** at day 2 in H1975 cells, with the affected fractions of H1975 cells that were killed by bortezomib, compound **1** or the combination of the two drugs 72 hr after compound **1** exposure.

Figure 8 left panel shows the treatment result of Detroit 562 head and neck cancer cells for 1 hour with bortezomib and compound **1** on 2 consecutive days and viability assessed 72 hr post last dose; right panel shows the treatment result of HCT116 colon cancer cells for 1 hour with bortezomib on 2 consecutive days and with a single dose of compound **1** (200 nM) for 1 hour on Day 2. The measure of viability was done 72 hours after compound **1** exposure.

Figure 9 shows the affected fractions of U266 cells that were killed by compound **1**, bortezomib or the combination of the two drugs at the indicated concentrations (left) and the affected fractions of U266 cells that were killed by compound **1**, carfilzomib or the combination of the two drugs at the indicated concentrations (right).

DETAILED DESCRIPTION OF THE INVENTION

Definitions

Unless otherwise specified, the below terms used herein are defined as follows:

As used herein, the term "alkyl" means a saturated or unsaturated, straight chain or branched, non-cyclic hydrocarbon having from 1 to 10 carbon atoms. Representative straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl and n-decyl; while representative branched alkyls include isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, isopentyl, 2-methylbutyl, 3-methylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylbutyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 2,3-dimethylhexyl, 2,4-dimethylhexyl, 2,5-dimethylhexyl, 2,2-dimethylpentyl, 2,2-dimethylhexyl, 3,3-dimtheylpentyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 2-ethylpentyl, 3-ethylpentyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 2-methyl-2-ethylpentyl, 2-methyl-3-ethylpentyl, 2-methyl-4-ethylpentyl, 2-methyl-2-ethylhexyl, 2-methyl-3-ethylhexyl, 2-methyl-4-ethylhexyl, 2,2-diethylpentyl, 3,3-diethylhexyl, 2,2-diethylhexyl, 3,3-diethylhexyl, and the like. The term "(C_1-C_6)alkyl" means a saturated, straight chain or branched, non-cyclic hydrocarbon having from 1 to 6 carbon atoms. Alkyl groups included in compounds described herein may be optionally substituted with one or more substituents. Examples of unsaturated alkyls include vinyl, allyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 2-decenyl, 3-decenyl, acetylenyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3-methyl-1-butynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 5-hexynyl, 1-heptynyl, 2-heptynyl, 6-heptynyl, 1-octynyl, 2-octynyl, 7-octynyl, 1-nonynyl, 2-nonynyl, 8-nonynyl, 1-decynyl, 2-decynyl, 9-decynyl, and the

like. Alkyl groups included in compounds described herein may be optionally substituted with one or more substituents.

As used herein, the term "cycloalkyl" means a saturated or unsaturated, mono- or polycyclic, non-aromatic hydrocarbon having from 3 to 20 carbon atoms. Representative cycloalkyls include cyclopropyl, 1-methylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, octahydropentalenyl, cyclohexenyl, cyclooctenyl, cyclohexynyl, and the like. Cycloalkyl groups included in the compounds described herein may be optionally substituted with one or more substituents.

As used herein, the term "alkylene" refers to an alkyl group that has two points of attachment. The term "(C_1-C_6)alkylene" refers to an alkylene group that has from one to six carbon atoms. Straight chain (C_1-C_6)alkylene groups are preferred. Non-limiting examples of alkylene groups include methylene (-CH_2-), ethylene (-CH_2CH_2-), n-propylene (-$CH_2CH_2CH_2$-), isopropylene (-$CH_2CH(CH_3)$-), and the like. Alkylene groups may be saturated or unsaturated, and may be optionally substituted with one or more substituents.

As used herein, the term "lower" refers to a group having up to four atoms. For example, a "lower alkyl" refers to an alkyl radical having from 1 to 4 carbon atoms, "lower alkoxy" refers to "–O-(C_1-C_4)alkyl.

As used herein, the term "haloalkyl" means an alkyl group, in which one or more, including all, the hydrogen radicals are replaced by a halo group(s), wherein each halo group is independently selected from –F, -Cl, -Br, and -I. For example, the term "halomethyl" means a methyl in which one to three hydrogen radical(s) have been replaced by a halo group. Representative haloalkyl groups include trifluoromethyl, bromomethyl, 1,2-dichloroethyl, 4-iodobutyl, 2-fluoropentyl, and the like.

As used herein, an "alkoxy" is an alkyl group which is attached to another moiety via an oxygen linker. Alkoxy groups included in compounds described herein may be optionally substituted with one or more substituents.

As used herein, a "haloalkoxy" is a haloalkyl group which is attached to another moiety via an oxygen linker.

As used herein, the term an "aromatic ring" or "aryl" means a mono- or polycyclic hydrocarbon, containing from 6 to 15 carbon atoms, in which at least one ring is aromatic. Examples of suitable aryl groups include phenyl, tolyl, anthracenyl, fluorenyl, indenyl, azulenyl,

and naphthyl, as well as benzo-fused carbocyclic moieties such as 5,6,7,8-tetrahydronaphthyl. Aryl groups included in compounds described herein may be optionally substituted with one or more substituents. In one embodiment, the aryl group is a monocyclic ring, wherein the ring comprises 6 carbon atoms, referred to herein as "(C_6)aryl."

As used herein, the term "aralkyl" means an aryl group that is attached to another group by a (C_1-C_6)alkylene group. Representative aralkyl groups include benzyl, 2-phenyl-ethyl, naphth-3-yl-methyl and the like. Aralkyl groups included in compounds described herein may be optionally substituted with one or more substituents.

As used herein, the term "heterocyclyl" means a monocyclic or a polycyclic, saturated or unsaturated, non-aromatic ring or ring system which typically contains 5- to 20-members and at least one heteroatom. A heterocyclic ring system can contain saturated ring(s) or unsaturated non-aromatic ring(s), or a mixture thereof. A 3- to 10-membered heterocycle can contain up to 5 heteroatoms, and a 7- to 20-membered heterocycle can contain up to 7 heteroatoms. Typically, a heterocycle has at least one carbon atom ring member. Each heteroatom is independently selected from nitrogen, which can be oxidized (*e.g.*, N(O)) or quaternized, oxygen and sulfur, including sulfoxide and sulfone. The heterocycle may be attached via any heteroatom or carbon atom. Representative heterocycles include morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyrindinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like. A heteroatom may be substituted with a protecting group known to those of ordinary skill in the art, for example, a nitrogen atom may be substituted with a tert-butoxycarbonyl group. Furthermore, the heterocyclyl included in compounds described herein may be optionally substituted with one or more substituents. Only stable isomers of such substituted heterocyclic groups are contemplated in this definition.

As used herein, the term "heteroaryl", or like terms, means a monocyclic or a polycyclic, unsaturated radical containing at least one heteroatom, in which at least one ring is aromatic. Polycyclic heteroaryl rings must contain at least one heteroatom, but not all rings of a polycyclic heteroaryl moiety must contain heteroatoms. Each heteroatom is independently selected from nitrogen, which can be oxidized (*e.g.*, N(O)) or quaternized, oxygen and sulfur, including sulfoxide and sulfone. Representative heteroaryl groups include pyridyl, 1-oxo-pyridyl, furanyl, benzo[1,3]dioxolyl, benzo[1,4]dioxinyl, thienyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, an isoxazolyl, quinolinyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, a triazinyl, triazolyl, thiadiazolyl, isoquinolinyl, indazolyl, benzoxazolyl, benzofuryl, indolizinyl, imidazopyridyl, tetrazolyl, benzimidazolyl, benzothiazolyl, benzothiadiazolyl, benzoxadiazolyl,

indolyl, tetrahydroindolyl, azaindolyl, imidazopyridyl, quinazolinyl, purinyl, pyrrolo[2,3]pyrimidinyl, pyrazolo[3,4]pyrimidinyl, imidazo[1,2-a]pyridyl, and benzothienyl. In one embodiment, the heteroaromatic ring is selected from 5-8 membered monocyclic heteroaryl rings. The point of attachment of a heteroaromatic or heteroaryl ring may be at either a carbon atom or a heteroatom. Heteroaryl groups included in compounds described herein may be optionally substituted with one or more substituents. As used herein, the term "(C_5)heteroaryl" means an heteroaromatic ring of 5 members, wherein at least one carbon atom of the ring is replaced with a heteroatom, such as oxygen, sulfur or nitrogen. Representative (C_5)heteroaryls include furanyl, thienyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyrazinyl, triazolyl, thiadiazolyl, and the like. As used herein, the term "(C_6)heteroaryl" means an aromatic heterocyclic ring of 6 members, wherein at least one carbon atom of the ring is replaced with a heteroatom such as, for example, oxygen, nitrogen or sulfur. Representative (C_6)heteroaryls include pyridyl, pyridazinyl, pyrazinyl, triazinyl, tetrazinyl, and the like.

As used herein, the term "heteroaralkyl" means a heteroaryl group that is attached to another group by a (C_1-C_6)alkylene. Representative heteroaralkyls include 2-(pyridin-4-yl)-propyl, 2-(thien-3-yl)-ethyl, imidazol-4-yl-methyl, and the like. Heteroaralkyl groups included in compounds described herein may be optionally substituted with one or more substituents.

As used herein, the term "halogen" or "halo" means -F, -Cl, -Br or -I.

Suitable substituents for an alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, aralkyl, heteroaryl, and heteroaralkyl groups include are those substituents which form a stable compound described herein without significantly adversely affecting the reactivity or biological activity of the compound described herein. Examples of substituents for an alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, aralkyl, heteroaryl, and heteroaralkyl include an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteraralkyl, heteroalkyl, alkoxy, (each of which can be optionally and independently substituted), $-C(O)NR^{28}R^{29}$, $-C(S)NR^{28}R^{29}$, $-C(NR^{32})NR^{28}R^{29}$, $-NR^{33}C(O)R^{31}$, $-NR^{33}C(S)R^{31}$, $-NR^{33}C(NR^{32})R^{31}$, halo, $-OR^{33}$, cyano, nitro, $-C(O)R^{33}$, $-C(S)R^{33}$, $-C(NR^{32})R^{33}$, $-NR^{28}R^{29}$, $-C(O)OR^{33}$, $-C(S)OR^{33}$, $-C(NR^{32})OR^{33}$, $-OC(O)R^{33}$, $-OC(S)R^{33}$, $-OC(NR^{32})R^{33}$, $-NR^{30}C(O)NR^{28}R^{29}$, $-NR^{33}C(S)NR^{28}R^{29}$, $-NR^{33}C(NR^{32})NR^{28}R^{29}$, $-OC(O)NR^{28}R^{29}$, $-OC(S)NR^{28}R^{29}$, $-OC(NR^{32})NR^{28}R^{29}$, $-NR^{33}C(O)OR^{31}$, $-NR^{33}C(S)OR^{31}$, $-NR^{33}C(NR^{32})OR^{31}$, $-S(O)_kR^{33}$, $-OS(O)_kR^{33}$, $-NR^{33}S(O)_kR^{33}$, $-S(O)_kNR^{28}R^{29}$, $-OS(O)_kNR^{28}R^{29}$, $-NR^{33}S(O)_kNR^{28}R^{29}$, guanidino, $-C(O)SR^{31}$, $-C(S)SR^{31}$, $-C(NR^{32})SR^{31}$, $-OC(O)OR^{31}$, $-OC(S)OR^{31}$, $-OC(NR^{32})OR^{31}$, $-SC(O)R^{33}$, $-SC(O)OR^{31}$, $-SC(NR^{32})OR^{31}$, $-SC(S)R^{33}$,

$-SC(S)OR^{31}$, $-SC(O)NR^{28}R^{29}$, $-SC(NR^{32})NR^{28}R^{29}$, $-SC(S)NR^{28}R^{29}$, $-SC(NR^{32})R^{33}$, $-OS(O)_kOR^{31}$, $-S(O)_kOR^{31}$, $-NR^{30}S(O)_kOR^{31}$, $-SS(O)_kR^{33}$, $-SS(O)_kOR^{31}$, $-SS(O)_kNR^{28}R^{29}$, $-OP(O)(OR^{31})_2$, or $-SP(O)(OR^{31})_2$. In addition, any saturated portion of an alkyl, cycloalkyl, alkylene, heterocyclyl, alkenyl, cycloalkenyl, alkynyl, aralkyl and heteroaralkyl groups, may also be substituted with =O, =S, or $=N-R^{32}$. Each R^{28} and R^{29} is independently H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, aralkyl, or heteraralkyl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, aralkyl, or heteroalkyl represented by R^{28} or R^{29} is optionally and independently substituted. Each R^{30}, R^{31} and R^{33} is independently H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, aralkyl, or heteraralkyl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, aralkyl, and heteraralkyl represented by R^{30} or R^{31} or R^{33} is optionally and independently unsubstituted. Each R^{32} is independently H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteraralkyl, $-C(O)R^{33}$, $-C(O)NR^{28}R^{29}$, $-S(O)_kR^{33}$, or $-S(O)_kNR^{28}R^{29}$, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, aralkyl and heteraralkyl represented by R^{32} is optionally and independently substituted. The variable k is 0, 1 or 2. In some embodiments, suitable substituents include C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 haloalkoxy, C1-C4 hydroxyalkyl, halo, or hydroxyl.

When a heterocyclyl, heteroaryl or heteroaralkyl group contains a nitrogen atom, it may be substituted or unsubstituted. When a nitrogen atom in the aromatic ring of a heteroaryl group has a substituent, the nitrogen may be oxidized or a quaternary nitrogen.

As used herein, the terms “subject”, “patient” and “mammal” are used interchangeably. The terms “subject” and “patient” refer to an animal (*e.g.*, a bird such as a chicken, quail or turkey, or a mammal), preferably a mammal including a non-primate (*e.g.*, a cow, pig, horse, sheep, rabbit, guinea pig, rat, cat, dog, and mouse) and a primate (*e.g.*, a monkey, chimpanzee and a human), and more preferably a human. In one embodiment, the subject is a non-human animal such as a farm animal (*e.g.*, a horse, cow, pig or sheep), or a pet (*e.g.*, a dog, cat, guinea pig or rabbit). In another embodiment, the subject is a human.

Unless indicated otherwise, the compounds described herein containing reactive functional groups, such as, for example, carboxy, hydroxy, thiol and amino moieties, also include corresponding protected derivatives thereof. “Protected derivatives” are those compounds in which a reactive site or sites are blocked with one ore more protecting groups. Examples of suitable protecting groups for hydroxyl groups include benzyl, methoxymethyl, allyl, trimethylsilyl, tert-butyldimethylsilyl, acetate, and the like. Examples of suitable amine

protecting groups include benzyloxycarbonyl, tert-butoxycarbonyl, tert-butyl, benzyl and fluorenylmethyloxy-carbonyl (Fmoc). Examples of suitable thiol protecting groups include benzyl, tert-butyl, acetyl, methoxymethyl and the like. Other suitable protecting groups are well known to those of ordinary skill in the art and include those found in T. W. GREENE, PROTECTING GROUPS IN ORGANIC SYNTHESIS, (John Wiley & Sons, Inc., 1981).

As used herein, the term "compound(s) described herein" or similar terms refers to a compound of formulae (I), or (Ia) or a compound in Tables 1 or 2 or a tautomer or pharmaceutically acceptable salt thereof. Also included in the scope of the embodiments are a solvate, clathrate, hydrate, polymorph, prodrug, or protected derivative of a compound of formulae (I), or (Ia), or a compound in Tables 1 or 2.

The compounds described herein may contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (*i.e.*, geometric isomers), enantiomers or diastereomers. Each chemical structure shown herein, including the compounds described herein, encompass all of the corresponding compound's enantiomers, diastereomers and geometric isomers, that is, both the stereochemically pure form (*e.g.*, geometrically pure, enantiomerically pure, or diastereomerically pure) and isomeric mixtures (*e.g.*, enantiomeric, diastereomeric and geometric isomeric mixtures). In some cases, one enantiomer, diastereomer or geometric isomer will possess superior activity or an improved toxicity or kinetic profile compared to other isomers. In those cases, such enantiomers, diastereomers and geometric isomers of compounds described herein are preferred.

When a disclosed compound is named or depicted by structure, it is to be understood that solvates (*e.g.*, hydrates) of the compound or a pharmaceutically acceptable salt thereof is also included. "Solvates" refer to crystalline forms wherein solvent molecules are incorporated into the crystal lattice during crystallization. Solvates may include water or nonaqueous solvents such as ethanol, isopropanol, DMSO, acetic acid, ethanolamine and ethyl acetate. When water is the solvent molecule incorporated into the crystal lattice of a solvate, it is typically referred to as a "hydrate". Hydrates include stoichiometric hydrates as well as compositions containing variable amounts of water.

When a disclosed compound is named or depicted by structure, it is to be understood that the compound, including solvates thereof, may exist in crystalline forms, non-crystalline forms or a mixture thereof. The compounds or solvates may also exhibit polymorphism (*i.e.*, the capacity to occur in different crystalline forms). These different crystalline forms are typically known as "polymorphs." It is to be understood that when named or depicted by structure, the disclosed compounds and solvates (*e.g.*, hydrates) also include all polymorphs thereof.

Polymorphs have the same chemical composition but differ in packing, geometrical arrangement and other descriptive properties of the crystalline solid state. Polymorphs, therefore, may have different physical properties such as shape, density, hardness, deformability, stability and dissolution properties. Polymorphs typically exhibit different melting points, IR spectra and X-ray powder diffraction patterns, which may be used for identification. One of ordinary skill in the art will appreciate that different polymorphs may be produced, for example, by changing or adjusting the conditions used in crystallizing the compound. For example, changes in temperature, pressure or solvent may result in different polymorphs. In addition, one polymorph may spontaneously convert to another polymorph under certain conditions.

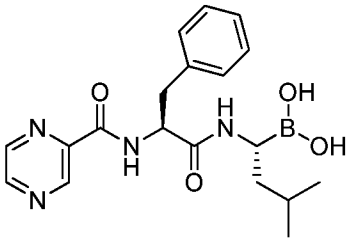
When a disclosed compound is named or depicted by structure, it is to be understood that clathrates ("inclusion compounds") of the compound or its pharmaceutically acceptable salt, solvate or polymorph, are also included. "Clathrate" means a compound described herein, or a salt thereof, in the form of a crystal lattice that contains spaces (*e.g.*, channels) that have a guest molecule trapped within (*e.g.*, a solvent or water).

As used herein, and unless otherwise indicated, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (*in vitro* or *in vivo*) to provide a compound described herein. Prodrugs may become active upon such reaction under biological conditions, or they may have activity in their unreacted forms. Examples of prodrugs contemplated herein include analogs or derivatives of compounds of formulae (I) or (Ia) or a compound in Tables 1 or 2 that comprise biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides and phosphate analogues. Prodrugs can typically be prepared using well-known methods, such as those described by BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY, (Manfred E. Wolff Ed., 5th ed. (1995)) 172-178, 949-982.

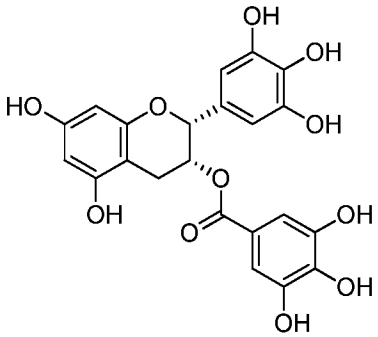
As used herein, "Hsp90" includes each member of the family of heat shock proteins having a mass of about 90-kiloDaltons. For example, in humans the highly conserved Hsp90 family includes the cytosolic Hsp90α and Hsp90β isoforms, as well as GRP94, which is found in the endoplasmic reticulum, and HSP75/TRAP1, which is found in the mitochondrial matrix.

As used herein, the term "proteasome inhibitors" refers to a class of compounds that act on proteasome. These compounds prevent degradation of pro-apoptotic factors, permitting activation of programmed cell death in neoplastic cells dependent upon suppression of pro-apoptotic pathways. In normal cells, the proteasome regulates protein expression and function by degradation of ubiquitinylated proteins, and also cleanses the cell of abnormal or misfolded

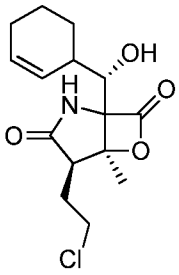
proteins. Proteasome inhibitors include disulfiram (CAS No. 97-77-8), epigallocatechin-3-gallate (CAS No. 989-51-5), salinosporamide A, carfilzomib (CAS No. 868540-17-4) and bortezomib (CAS No. 179324-69-7). Bortezomib is one of the proteasome inhibitors used to treat relapsed multiple myeloma and mantle cell lymphoma in humans. The chemical structures of bortezomib, epigallocatechin-3-gallate, and salinosporamide A are shown below.



bortezomib



epigallocatechin gallate



salinosporamide A

As used herein, a "proliferative disorder" or a "hyperproliferative disorder," and other equivalent terms, means a disease or medical condition involving pathological growth of cells. Proliferative disorders include cancer, smooth muscle cell proliferation, systemic sclerosis, cirrhosis of the liver, adult respiratory distress syndrome, idiopathic cardiomyopathy, lupus erythematosus, retinopathy, (*e.g.*, diabetic retinopathy or other retinopathies), cardiac hyperplasia, reproductive system associated disorders such as benign prostatic hyperplasia and ovarian cysts, pulmonary fibrosis, endometriosis, fibromatosis, harmatomas, lymphangiomatosis, sarcoidosis and desmoid tumors. Non-cancerous proliferative disorders also include hyperproliferation of cells in the skin such as psoriasis and its varied clinical forms, Reiter's syndrome, pityriasis rubra pilaris, hyperproliferative variants of disorders of keratinization (*e.g.*, actinic keratosis, senile keratosis), scleroderma, and the like. In one embodiment, the proliferative disorder is a myeloproliferative disorder. In one aspect, the myeloproliferative disorder is polycythemia vera, idiopathic myelofibrosis, myelodysplastic syndrome, psoriasis or essential thrombocythemia. In one embodiment, the proliferative disorder expresses JAK2V617F mutation of JAK2. In an aspect of this embodiment, the proliferative disorder is polycythemia vera, idiopathic myelofibrosis, or essential thrombocythemia. In one aspect, the proliferative disorder is polycythemia vera.

As used herein, the term "pharmaceutically acceptable salt" refers to a salt prepared from a compound of formulae (I) or (Ia) or a compound in Tables 1 or 2 having an acidic functional group, such as a carboxylic acid functional group, and a pharmaceutically acceptable

inorganic or organic base. Suitable bases include hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; N-methyl,N-ethylamine; diethylamine; triethylamine; mono-, *bis*-, or *tris*-(2-hydroxy-lower alkyl amines), such as *mono*-, *bis*-, or *tris*-(2-hydroxyethyl)amine, 2-hydroxy-*tert*-butylamine, or *tris*-(hydroxymethyl)methylamine, N, N,-di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl)amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and the like. The term "pharmaceutically acceptable salt" also refers to a salt prepared from a compound of formulae (I) or (Ia) or a compound in Tables 1 or 2 having a basic functional group, such as an amine functional group, and a pharmaceutically acceptable inorganic or organic acid. Suitable acids include hydrogen sulfate, citric acid, acetic acid, oxalic acid, hydrochloric acid (HCl), hydrogen bromide (HBr), hydrogen iodide (HI), nitric acid, hydrogen bisulfide, phosphoric acid, isonicotinic acid, oleic acid, tannic acid, pantothenic acid, saccharic acid, lactic acid, salicylic acid, tartaric acid, bitartratic acid, ascorbic acid, succinic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucaronic acid, formic acid, benzoic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, pamoic acid and *p*-toluenesulfonic acid.

As used herein, the term "pharmaceutically acceptable solvate," is a solvate formed from the association of one or more pharmaceutically acceptable solvent molecules to one of the compounds of formulae (I) or (Ia) or a compound in Tables 1 or 2. The term "solvate" includes hydrates, *e.g.*, hemihydrate, monohydrate, dihydrate, trihydrate, tetrahydrate, and the like.

A pharmaceutically acceptable carrier may contain inert ingredients which do not unduly inhibit the biological activity of the compound(s) described herein. The pharmaceutically acceptable carriers should be biocompatible, *i.e.*, non-toxic, non-inflammatory, non-immunogenic and devoid of other undesired reactions upon the administration to a subject. Standard pharmaceutical formulation techniques can be employed, such as those described in REMINGTON, J. P., REMINGTON'S PHARMACEUTICAL SCIENCES (Mack Pub. Co., 17th ed., 1985). Suitable pharmaceutical carriers for parenteral administration include, for example, sterile water, physiological saline, bacteriostatic saline (saline containing about 0.9% mg/ml benzyl alcohol), phosphate-buffered saline, Hank's solution, Ringer's-lactate, and the like. Methods for encapsulating compositions, such as in a coating of hard gelatin or cyclodextran, are known in the art. *See* BAKER, *ET AL.*, CONTROLLED RELEASE OF BIOLOGICAL ACTIVE AGENTS, (John Wiley and Sons, 1986).

As used herein, the term "effective amount" refers to an amount of a compound described herein which is sufficient to reduce or ameliorate the severity, duration, progression, or onset of a disease or disorder, delay onset of a disease or disorder, retard or halt the advancement of a disease or disorder, cause the regression of a disease or disorder, prevent or delay the recurrence, development, onset or progression of a symptom associated with a disease or disorder, or enhance or improve the therapeutic effect(s) of another therapy. In one embodiment of the invention, the disease or disorder is a proliferative disorder. The precise amount of compound administered to a subject will depend on the mode of administration, the type and severity of the disease or condition and on the characteristics of the subject, such as general health, age, sex, body weight and tolerance to drugs. For example, for a proliferative disease or disorder, determination of an effective amount will also depend on the degree, severity and type of cell proliferation. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. When co-administered with other therapeutic agents, *e.g.*, when co-administered with an anti-cancer agent, an "effective amount" of any additional therapeutic agent(s) will depend on the type of drug used. Suitable dosages are known for approved therapeutic agents and can be adjusted by the skilled artisan according to the condition of the subject, the type of condition(s) being treated and the amount of a compound being used. In cases where no amount is expressly noted, an effective amount should be assumed. Non-limiting examples of an effective amount of a compound described herein are provided herein below. In a specific embodiment, the invention provides a method of treating, managing, or ameliorating a disease or disorder, *e.g.* a proliferative disorder, or one or more symptoms thereof, the method comprising administering to a subject in need thereof a dose of the Hsp90 inhibitor at least 150 μg/kg, at least 250 μg/kg, at least 500 μg/kg, at least 1 mg/kg, at least 5 mg/kg, at least 10 mg/kg, at least 25 mg/kg, at least 50 mg/kg, at least 75 mg/kg, at least 100 mg/kg, at least 125 mg/kg, at least 150 mg/kg, or at least 200 mg/kg or more of one or more compounds described herein once every day, once every 2 days, once every 3 days, once every 4 days, once every 5 days, once every 6 days, once every 7 days, once every 8 days, once every 10 days, once every two weeks, once every three weeks, or once a month.

The dosage of an individual proteasome inhibitor used herein may be equal to or lower than the dose of an individual therapeutic agent when given independently to treat, manage, or ameliorate a disease or disorder, or one or more symptoms thereof. In one embodiment, the disease or disorder being treated with a combination therapy is a proliferative disorder. In another embodiment, the proliferative disorder is cancer. The recommended dosages of therapeutic agents currently used for the treatment, management, or amelioration of a disease or disorder, or one or more symptoms thereof, can obtained from any reference in the art. *See, e.g.*, GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF BASIS OF THERAPEUTICS 9TH ED,

(Hardman, *et al.*, Eds., NY:Mc-Graw-Hill (1996)); PHYSICIAN'S DESK REFERENCE 57TH ED. (Medical Economics Co., Inc., Montvale, NJ (2003)).

As used herein, the terms "treat", "treatment" and "treating" refer to the reduction or amelioration of the progression, severity and/or duration of a disease or disorder, delay of the onset of a disease or disorder, or the amelioration of one or more symptoms (preferably, one or more discernible symptoms) of a disease or disorder, resulting from the administration of one or more therapies (*e.g.*, one or more therapeutic agents such as a compound of the invention). The terms "treat", "treatment" and "treating" also encompass the reduction of the risk of developing a disease or disorder, and the delay or inhibition of the recurrence of a disease or disorder. In one embodiment, the disease or disorder being treated is a proliferative disorder such as cancer. In specific embodiments, the terms "treat", "treatment" and "treating" refer to the amelioration of at least one measurable physical parameter of a disease or disorder, such as growth of a tumor, not necessarily discernible by the patient. In other embodiments the terms "treat", "treatment" and "treating" refer to the inhibition of the progression of a disease or disorder, *e.g.*, a proliferative disorder, either physically by the stabilization of a discernible symptom, physiologically by the stabilization of a physical parameter, or both. In another embodiment, the terms "treat", "treatment" and "treating" of a proliferative disease or disorder refers to the reduction or stabilization of tumor size or cancerous cell count, and/or delay of tumor formation. In another embodiment, the terms "treat", "treating" and "treatment" also encompass the administration of a compound described herein as a prophylactic measure to patients with a predisposition (genetic or environmental) to any disease or disorder described herein.

As used herein, the terms "therapeutic agent" and "therapeutic agents" refer to any agent(s) that can be used in the treatment of a disease or disorder, *e.g.* a proliferative disorder, or one or more symptoms thereof. In certain embodiments, the term "therapeutic agent" refers to a compound described herein. In certain other embodiments, the term "therapeutic agent" does not refer to a compound described herein. Preferably, a therapeutic agent is an agent that is known to be useful for, or has been or is currently being used for the treatment of a disease or disorder, *e.g.*, a proliferative disorder, or one or more symptoms thereof.

As used herein, the term "synergistic" refers to a combination of a compound described herein and another therapeutic agent, which, when taken together, is more effective than the additive effects of the individual therapies. A synergistic effect of a combination of therapies (*e.g.*, a combination of therapeutic agents) permits the use of lower dosages of one or more of the therapeutic agent(s) and/or less frequent administration of the agent(s) to a subject with a disease or disorder, *e.g.*, a proliferative disorder. The ability to utilize lower the dosage of one or

more therapeutic agent and/or to administer the therapeutic agent less frequently reduces the toxicity associated with the administration of the agent to a subject without reducing the efficacy of the therapy in the treatment of a disease or disorder. In addition, a synergistic effect can result in improved efficacy of agents in the prevention, management or treatment of a disease or disorder, *e.g.* a proliferative disorder. Finally, a synergistic effect of a combination of therapies may avoid or reduce adverse or unwanted side effects associated with the use of either therapeutic agent alone.

As used herein, the phrase "side effects" encompasses unwanted and adverse effects of a therapeutic agent. Side effects are always unwanted, but unwanted effects are not necessarily adverse. An adverse effect from a therapeutic agent might be harmful or uncomfortable or risky to a subject. Side effects include fever, chills, lethargy, gastrointestinal toxicities (including gastric and intestinal ulcerations and erosions), nausea, vomiting, neurotoxicities, nephrotoxicities, renal toxicities (including such conditions as papillary necrosis and chronic interstitial nephritis), hepatic toxicities (including elevated serum liver enzyme levels), myelotoxicities (including leukopenia, myelosuppression, thrombocytopenia and anemia), dry mouth, metallic taste, prolongation of gestation, weakness, somnolence, pain (including muscle pain, bone pain and headache), hair loss, asthenia, dizziness, extra-pyramidal symptoms, akathisia, cardiovascular disturbances and sexual dysfunction.

As used herein, the term "in combination" refers to the use of more than one therapeutic agent. The use of the term "in combination" does not restrict the order in which the therapeutic agents are administered to a subject with a disease or disorder, *e.g.*, a proliferative disorder. A first therapeutic agent, such as a compound described herein, can be administered prior to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapeutic agent, such as an anti-cancer agent, to a subject with a disease or disorder, *e.g.* a proliferative disorder, such as cancer. In one embodiment, the Hsp90 inhibitor and the proteasome inhibitor are dosed on independent schedules. In another embodiment, the Hsp90 inhibitor and the proteasome inhibitor are dosed on approximately the same schedule. In another embodiment, the Hsp90 inhibitor and the proteasome inhibitor are dosed concurrently or sequentially on the same day.

As used herein, the terms "therapies" and "therapy" can refer to any protocol(s), method(s), and/or agent(s) that can be used in the prevention, treatment, management, or amelioration of a disease or disorder, *e.g.*, a proliferative disorder, or one or more symptoms thereof.

As used herein, a "protocol" includes dosing schedules and dosing regimens. The protocols herein are methods of use and include therapeutic protocols.

As used herein, a composition that "substantially" comprises a compound means that the composition contains more than about 80% by weight, more preferably more than about 90% by weight, even more preferably more than about 95% by weight, and most preferably more than about 97% by weight of the compound.

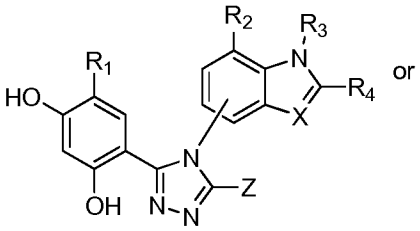
The compounds described herein are defined by their chemical structures and/or chemical names. Where a compound is referred to by both a chemical structure and a chemical name, and the chemical structure and the chemical name conflict, the chemical structure is determinative of the compound's identity.

When administered to a subject (*e.g.*, a non-human animal for veterinary use or for improvement of livestock or to a human for clinical use), the compounds described herein are administered in an isolated form, or as the isolated form in a pharmaceutical composition. As used herein, "isolated" means that the compounds described herein are separated from other components of either: (a) a natural source, such as a plant or cell, preferably bacterial culture, or (b) a synthetic organic chemical reaction mixture. Preferably, the compounds described herein are purified via conventional techniques. As used herein, "purified" means that when isolated, the isolate contains at least 95%, preferably at least 98%, of a compound described herein by weight of the isolate either as a mixture of stereoisomers, or as a diastereomeric or enantiomeric pure isolate.

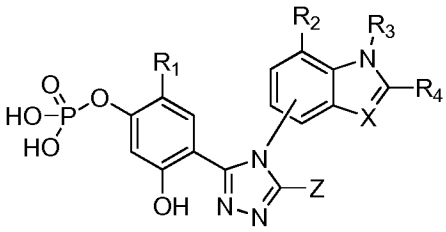
Only those choices and combinations of substituents that result in a stable structure are contemplated. Such choices and combinations will be apparent to those of ordinary skill in the art and may be determined without undue experimentation.

The invention can be understood more fully by reference to the following detailed description and illustrative examples, which are intended to exemplify non-limiting embodiments of the invention.

The methods described herein utilize triazolone compounds listed in Tables 1 or 2, or a compound represented by Formulae (I) or (Ia):



(I)



(Ia)

or a tautomer, or a pharmaceutically acceptable salt thereof, wherein:

Z is OH, SH, or NH_2;

X is CR_4 or N;

R_1 is -H, -OH, -SH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, halo, cyano, nitro, guanidino, a haloalkyl, a heteroalkyl, an alkoxy or cycloalkoxy, a haloalkoxy, $-NR_{10}R_{11}$, $-OR_7$, $-C(O)R_7$, $-C(O)OR_7$, $-C(S)R_7$, $-C(O)SR_7$, $-C(S)SR_7$, $-C(S)OR_7$, $-C(S)NR_{10}R_{11}$, $-C(NR_8)OR_7$, $-C(NR_8)R_7$, $-C(NR_8)NR_{10}R_{11}$, $-C(NR_8)SR_7$, $-OC(O)R_7$, $-OC(O)OR_7$, $-OC(S)OR_7$, $-OC(NR_8)OR_7$, $-SC(O)R_7$, $-SC(O)OR_7$, $-SC(NR_8)OR_7$, $-OC(S)R_7$, $-SC(S)R_7$, $-SC(S)OR_7$, $-OC(O)NR_{10}R_{11}$, $-OC(S)NR_{10}R_{11}$, $-OC(NR_8)NR_{10}R_{11}$, $-SC(O)NR_{10}R_{11}$, $-SC(NR_8)NR_{10}R_{11}$, $-SC(S)NR_{10}R_{11}$, $-OC(NR_8)R_7$, $-SC(NR_8)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-NR_7C(S)R_7$, $-NR_7C(S)OR_7$, $-NR_7C(NR_8)R_7$, $-NR_7C(O)OR_7$, $-NR_7C(NR_8)OR_7$, $-NR_7C(O)NR_{10}R_{11}$, $-NR_7C(S)NR_{10}R_{11}$, $-NR_7C(NR_8)NR_{10}R_{11}$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-OS(O)_pOR_7$, $-OS(O)_pNR_{10}R_{11}$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, $-NR_7S(O)_pNR_{10}R_{11}$, $-NR_7S(O)_pOR_7$, $-S(O)_pNR_{10}R_{11}$, $-SS(O)_pR_7$, $-SS(O)_pOR_7$, $-SS(O)_pNR_{10}R_{11}$, $-OP(O)(OR_7)_2$, or $-SP(O)(OR_7)_2$;

R_2 is -H, -OH, -SH, $-NR_7H$, $-OR_{15}$, $-SR_{15}$, $-NHR_{15}$, $-O(CH_2)_mOH$, $-O(CH_2)_mSH$, $-O(CH_2)_mNR_7H$, $-S(CH_2)_mOH$, $-S(CH_2)_mSH$, $-S(CH_2)_mNR_7H$, $-OC(O)NR_{10}R_{11}$, $-SC(O)NR_{10}R_{11}$, $-NR_7C(O)NR_{10}R_{11}$, $-OC(O)R_7$, $-SC(O)R_7$, $-NR_7C(O)R_7$, $-OC(O)OR_7$, $-SC(O)OR_7$, $-NR_7C(O)OR_7$, $-OCH_2C(O)R_7$, $-SCH_2C(O)R_7$, $-NR_7CH_2C(O)R_7$, $-OCH_2C(O)OR_7$, $-SCH_2C(O)OR_7$, $-NR_7CH_2C(O)OR_7$, $-OCH_2C(O)NR_{10}R_{11}$, $-SCH_2C(O)NR_{10}R_{11}$, $-NR_7CH_2C(O)NR_{10}R_{11}$, $-OS(O)_pR_7$, $-SS(O)_pR_7$, $-NR_7S(O)_pR_7$, $-OS(O)_pNR_{10}R_{11}$, $-SS(O)_pNR_{10}R_{11}$, $-NR_7S(O)_pNR_{10}R_{11}$, $-OS(O)_pOR_7$, $-SS(O)_pOR_7$, $-NR_7S(O)_pOR_7$, $-OC(S)R_7$, $-SC(S)R_7$, $-NR_7C(S)R_7$, $-OC(S)OR_7$, $-SC(S)OR_7$, $-NR_7C(S)OR_7$, $-OC(S)NR_{10}R_{11}$, $-SC(S)NR_{10}R_{11}$, $-NR_7C(S)NR_{10}R_{11}$, $-OC(NR_8)R_7$, $-SC(NR_8)R_7$, $-NR_7C(NR_8)R_7$, $-OC(NR_8)OR_7$, $-SC(NR_8)OR_7$, $-NR_7C(NR_8)OR_7$, $-OC(NR_8)NR_{10}R_{11}$, $-SC(NR_8)NR_{10}R_{11}$, or $-NR_7C(NR_8)NR_{10}R_{11}$;

R_3 is -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, hydroxyalkyl, alkoxyalkyl, a haloalkyl, a heteroalkyl, $-C(O)R_7$, $-(CH_2)_mC(O)OR_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-S(O)_pR_7$, $-S(O)_pOR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_4 is -H, -OH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, hydroxyalkyl, alkoxyalkyl, halo, cyano, nitro, guanidino, a haloalkyl, a heteroalkyl, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, $-S(O)_pNR_{10}R_{11}$, or R_3 and R_4 taken together with the carbon atoms to which they are attached form an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heterocyclyl, or an optionally substituted heteroaryl;

R_7 and R_8, for each occurrence, are, independently, -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally

substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

R_{10} and R_{11}, for each occurrence, are independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R_{10} and R_{11}, taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

R_{15}, for each occurrence, is independently, a lower alkyl;

p, for each occurrence, is, independently, 1 or 2; and

m, for each occurrence, is independently, 1, 2, 3, or 4.

In one embodiment, in formula (I) or (Ia), X is CR_4.

In another embodiment, in formula (I) or (Ia), X is N.

In another embodiment, in formula (I) or (Ia), R_1 is selected from the group consisting of -H, lower alkyl, lower alkoxy, lower cycloalkyl, and lower cycloalkoxy.

In another embodiment, in formula (I) or (Ia), R_1 is selected from the group consisting of -H, methyl, ethyl, propyl, isopropyl, cyclopropyl, methoxy, ethoxy, propoxy, and cyclopropoxy.

In another embodiment, in formula (I) or (Ia), R_3 is selected from the group consisting of –H, a lower alkyl, a lower cycloalkyl, $-C(O)N(R_{27})_2$, and -C(O)OH, wherein R_{27} is -H or a lower alkyl.

In another embodiment, in formula (I) or (Ia), R_3 is selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, *sec*-butyl, *tert*-butyl, n-pentyl, n-hexyl, -C(O)OH, $-(CH_2)_mC(O)OH$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, and $-C(O)N(CH_3)_2$.

In one embodiment, R_4 is H or a lower alkyl.

In another embodiment, in formula (I) or (Ia), R_4 is selected from the group consisting of -H, methyl, ethyl, propyl, isopropyl or cyclopropyl.

In another embodiment, in formula (I) or (Ia), R_1 is selected from the group consisting of -H, -OH, -SH, $-NH_2$, a lower alkoxy and a lower alkyl amino.

In another embodiment, in formula (I) or (Ia), R_1 is selected from the group consisting of -H, -OH, methoxy and ethoxy.

In another embodiment, in formula (I) or (Ia), Z is -OH.

In another embodiment, in formula (I) or (Ia), Z is –SH.

In another embodiment, in formula (I) or (Ia), R_2 is selected from the group consisting of -H, -OH, -SH, -NH_2, a lower alkoxy and a lower alkyl amino.

In another embodiment, in formula (I) or (Ia), R_2 is selected from the group consisting of -H, -OH, methoxy, and ethoxy.

In another embodiment, in formula (I) or (Ia), R_1 is selected from the group consisting of -H, methyl, ethyl, propyl, isopropyl, cyclopropyl, methoxy, ethoxy, propoxy, and cyclopropoxy; R_3 is selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, *sec*-butyl, *tert*-butyl, n-pentyl, n-hexyl, -C(O)OH, -$(CH_2)_m$C(O)OH, -CH_2OCH_3, -$CH_2CH_2OCH_3$, and -C(O)N$(CH_3)_2$; R_4 is selected from the group consisting of -H, methyl, ethyl, propyl, isopropyl or cyclopropyl; R_2 is selected from the group consisting of -H, -OH, -SH, -NH_2, a lower alkoxy and a lower alkyl amino; and Z is OH.

In another embodiment, in formula (I) or (Ia), R_1 is selected from the group consisting of -H, methyl, ethyl, propyl, isopropyl, cyclopropyl, methoxy, ethoxy, propoxy, and cyclopropoxy; R_3 is selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, *sec*-butyl, *tert*-butyl, n-pentyl, n-hexyl, -C(O)OH, -$(CH_2)_m$C(O)OH, -CH_2OCH_3, -$CH_2CH_2OCH_3$, and -C(O)N$(CH_3)_2$; R_4 is selected from the group consisting of -H, methyl, ethyl, propyl, isopropyl or cyclopropyl; R_2 is selected from the group consisting of -H, -OH, -SH, -NH_2, a lower alkoxy and a lower alkyl amino; and Z is SH.

In another embodiment, the compound is selected from the group consisting of:

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole,

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole,

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole,

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-isopropyl-indol-4-yl)-5-hydroxy-[1,2,4]triazole,

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indazol-5-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indazol-6-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxyphenyl)-4-(1-ethyl-indol-4-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxyphenyl)-4-(1-isopropyl-indol-4-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxyphenyl)-4-(indol-4-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxyphenyl)-4-(1-methoxyethyl-indol-4-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-isopropyl-indol-4-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxyphenyl)-4-(1-dimethylcarbamoyl-indol-4-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-propyl-indol-4-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1,2,3-trimethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(2,3-dimethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-acetyl-2,3-dimethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-propyl-2,3-dimethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-n-butyl-indol-4-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-n-pentyl-indol-4-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-n-hexyl-indol-4-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-cyclopropyl-phenyl)-4-(1-(1-methylcyclopropyl)-indol-4-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-cyclopropyl-phenyl)-4-(1,2,3-trimethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-methyl-3-ethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-methyl-3-isopropyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1,2-dimethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(N-methyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-cyclopropyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-cyclopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1H-indol-5-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1,2-dimethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-ethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-propyl-indol-5-yl)-5-mercapto-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof.

In another embodiment, the compound is selected from the group consisting of

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-ethyl-benzimidazol-4-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-ethyl-benzimidazol -4-yl)-5-mercapto-[1,2,4]triazole HCL salt,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(2-methyl-3-ethyl-benzimidazol-5-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-ethyl-2-methyl-benzimidazol-5-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-2-trifluoromethyl-benzimidazol-5-yl)-5-mercapto-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof.

In another embodiment, the compound is selected from the group consisting of

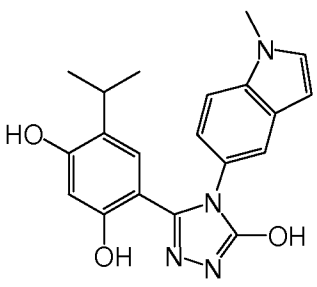
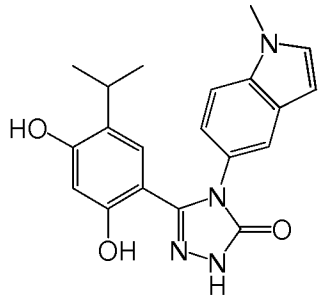
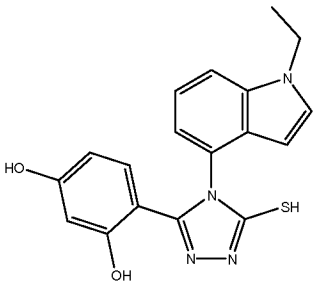
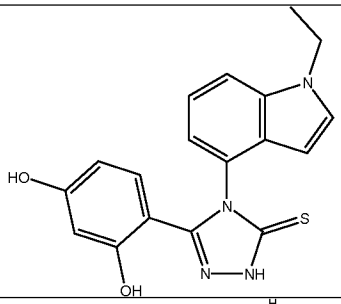
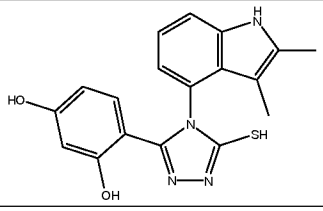
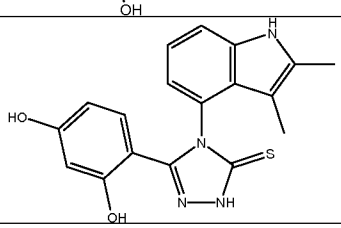
5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate,

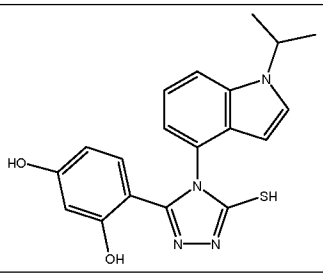
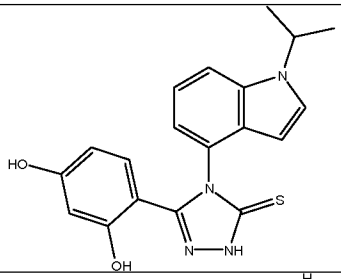
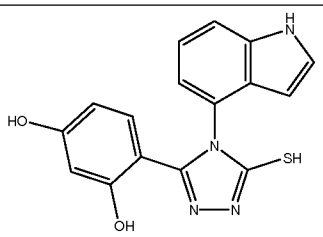
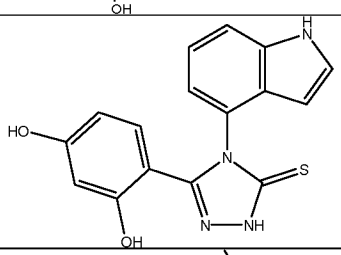
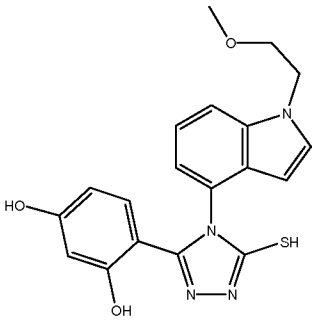
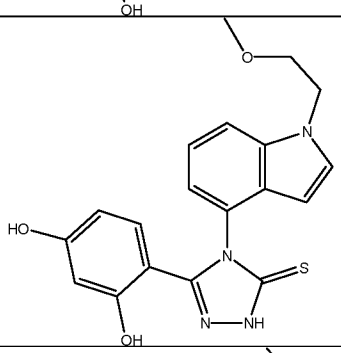
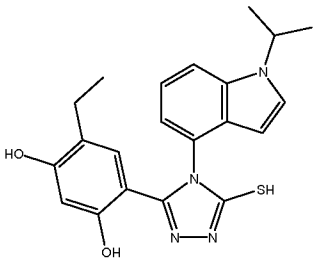
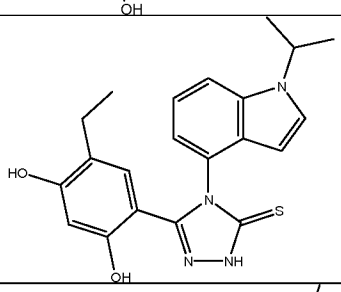
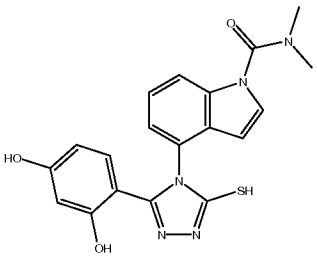
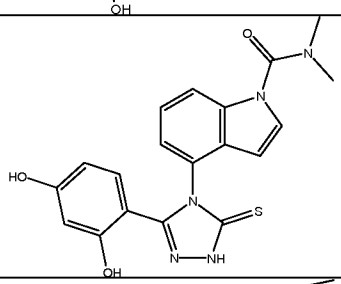
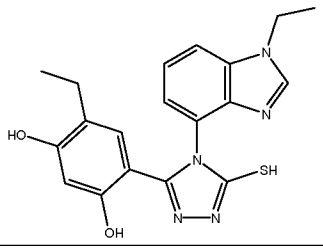
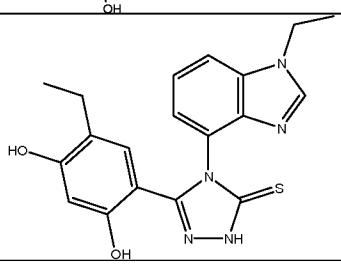
sodium 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl phosphate,

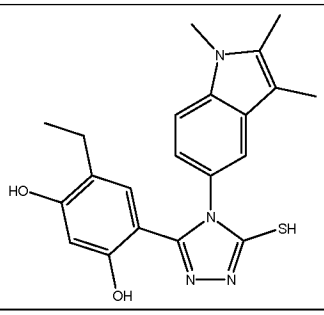
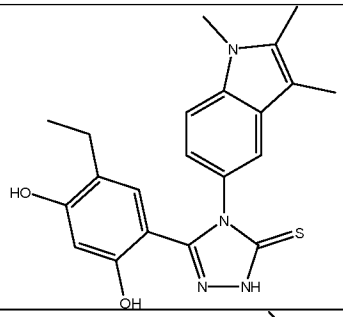
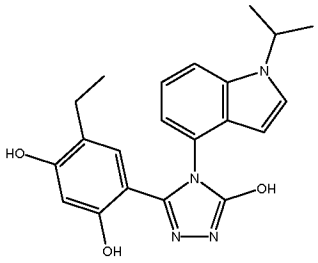
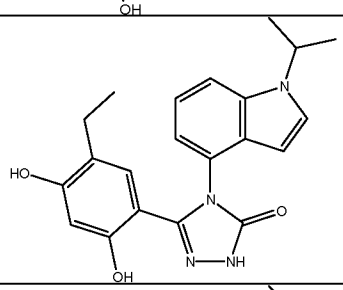
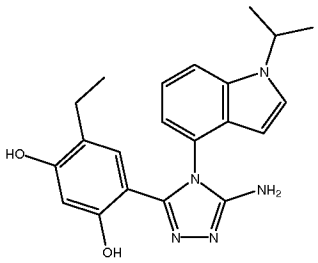
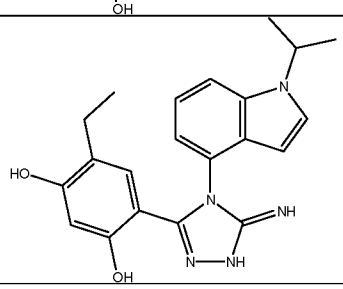
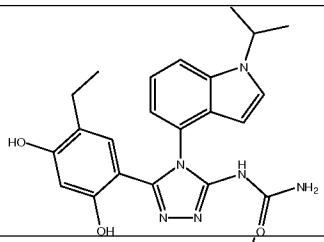
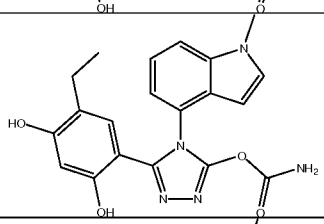
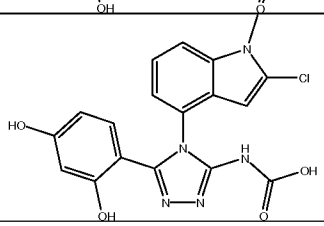
2-(3,4-dimethoxyphenethyl)-5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)phenyl dihydrogen phosphate,
5-hydroxy-2-isopropyl-4-(5-mercapto-4-(4-methoxybenzyl)-4H-1,2,4-triazol-3-yl)phenyl dihydrogen phosphate,
5-hydroxy-4-(5-hydroxy-4-(4-methoxybenzyl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate,
4-(4-(1,3-dimethyl-1H-indol-5-yl)-5-hydroxy-4H-1,2,4-triazol-3-yl)-2-ethyl-5-hydroxyphenyl dihydrogen phosphate, or a tautomer, or a pharmaceutically acceptable salt thereof.

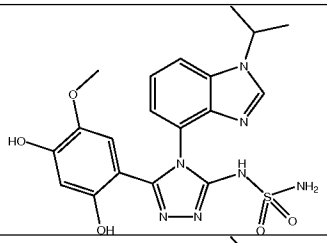
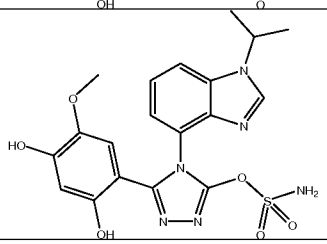
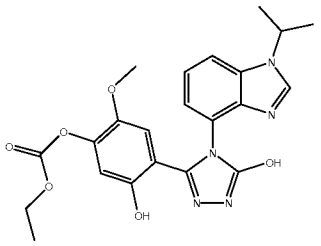
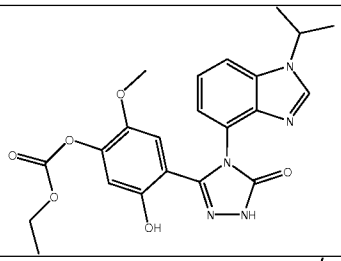
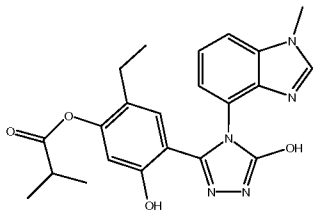
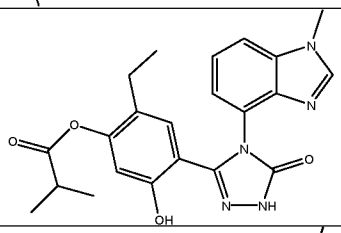
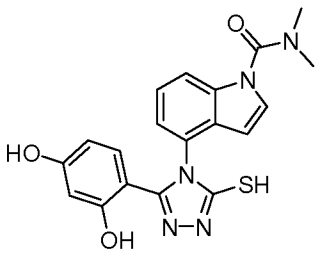
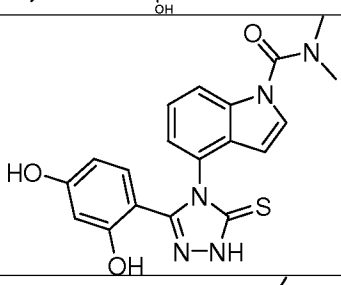
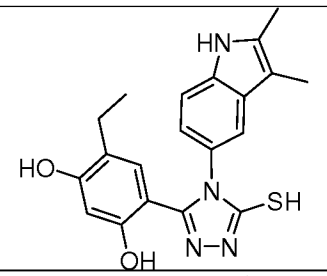
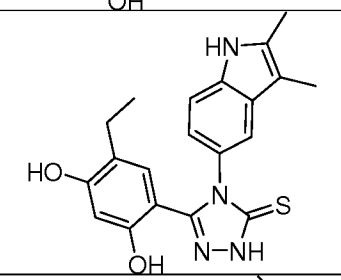
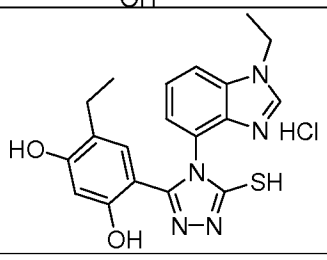
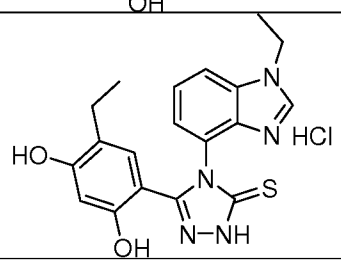
Hsp90 inhibitory compounds, as well as tautomers or pharmaceutically acceptable salts thereof, that may be used in the methods described herein are depicted in Tables 1 or 2.

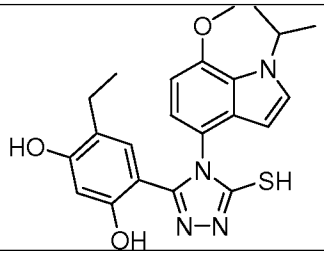
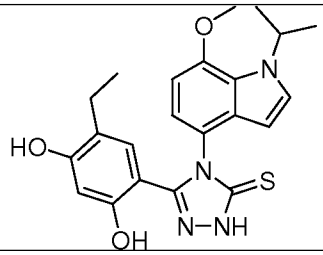
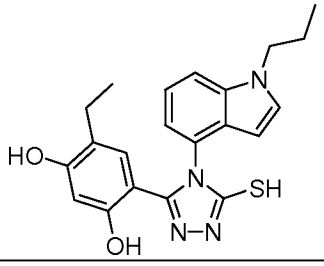
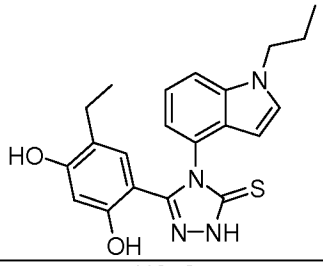
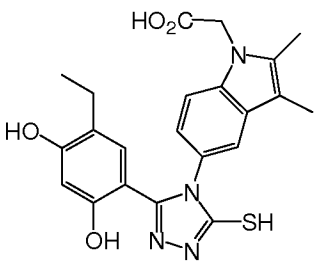
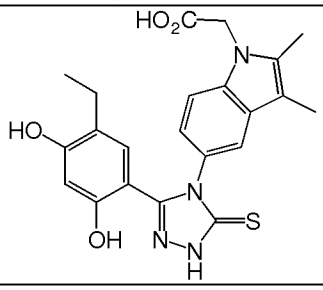
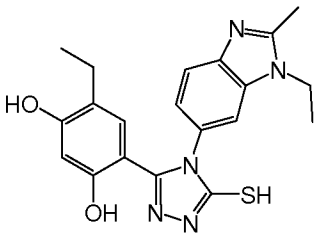
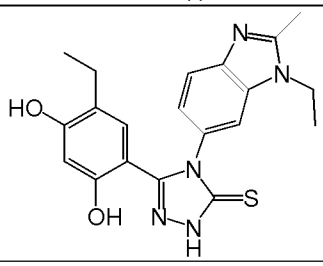
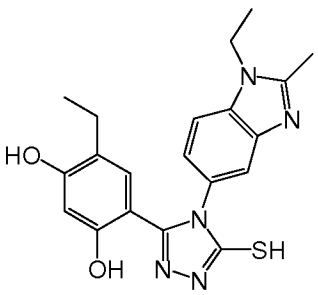
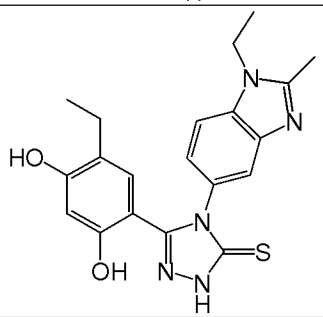
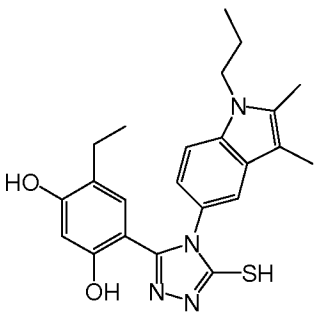
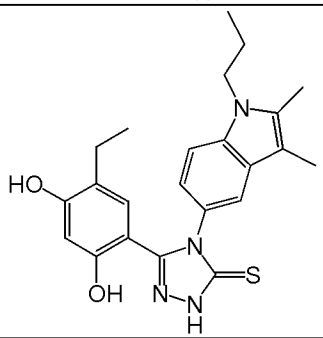
Table 1

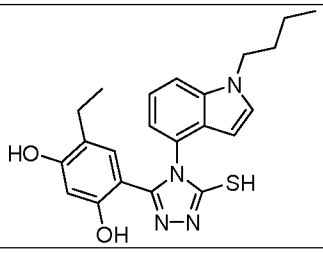
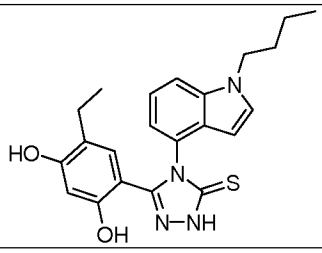
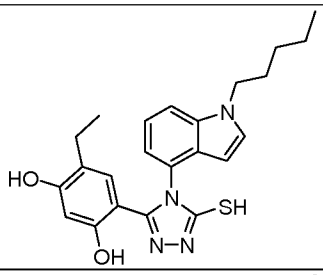
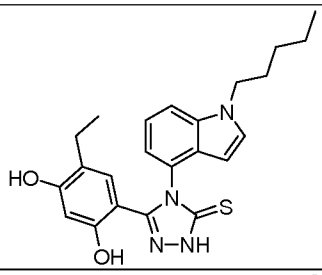
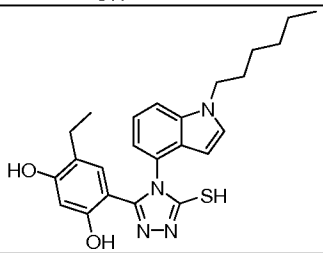
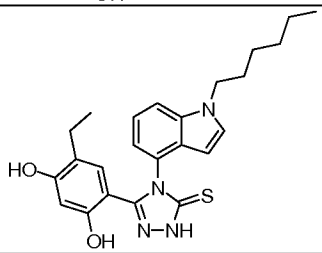
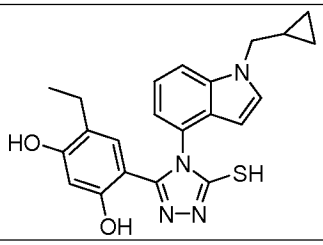
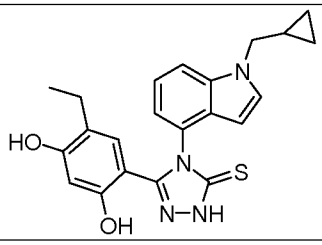
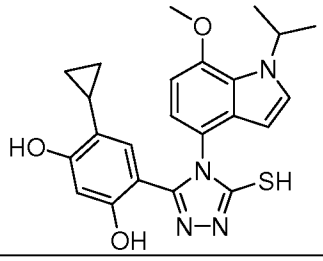
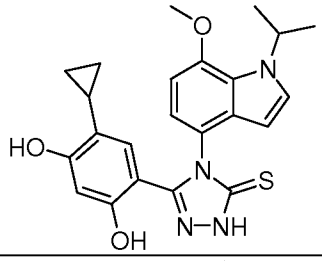
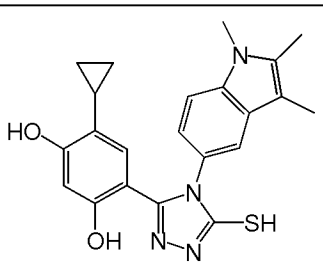
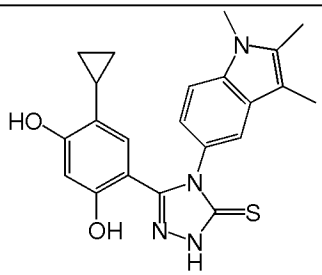
	STRUCTURE	TAUTOMERIC STRUCTURE	NAME
1			3-(2,4-DIHYDROXY-5-ISOPROPYL-PHENYL)-4-(1-METHYL-INDOL-5-YL)-5-HYDROXY-[1,2,4] TRIAZOLE
2			3-(2,4-DIHYDROXYPHENYL)-4-(1-ETHYL-INDOL-4-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
3			3-(2,4-DIHYDROXY-PHENYL)-4-(2,3-DIMETHYL-1*H*-INDOL-4-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE

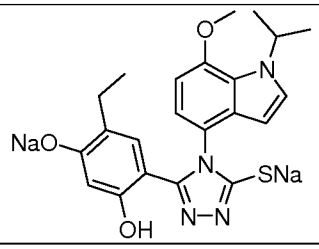
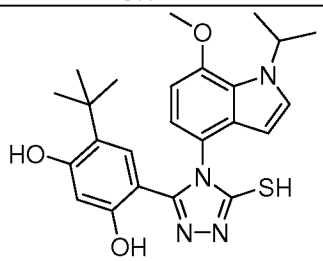
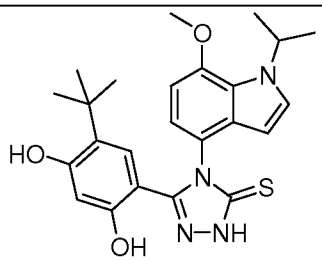
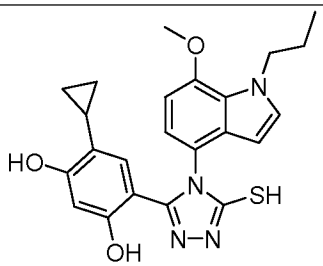
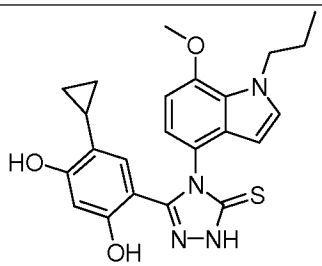
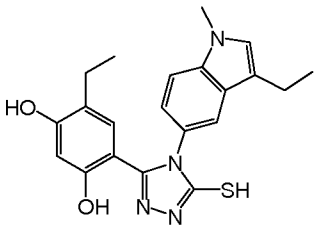
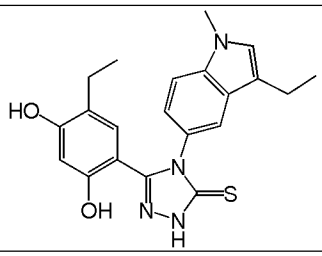
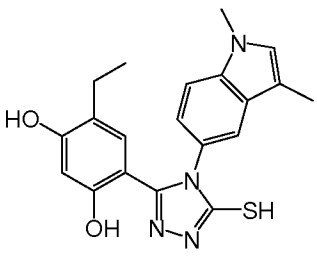
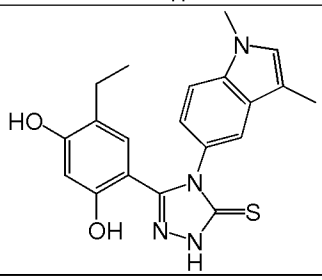
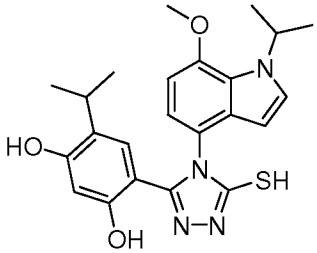
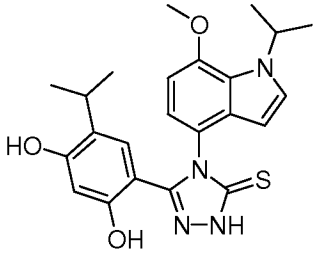
	STRUCTURE	TAUTOMERIC STRUCTURE	NAME
4			3-(2,4-DIHYDROXYPHENYL)-4-(1-ISOPROPYL-INDOL-4-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
5			3-(2,4-DIHYDROXY-PHENYL)-4-(INDOL-4-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
6			3-(2,4-DIHYDROXY-PHENYL)-4-[1-(2-METHOXYETHOXY)-INDOL-4-YL]-5-MERCAPTO-[1,2,4] TRIAZOLE
7			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1-ISOPROPYL-INDOL-4-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
8			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-[1-(DIMETHYL-CARBAMOYL)-INDOL-4-YL]-5-MERCAPTO-[1,2,4] TRIAZOLE
9			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1-ETHYL-BENZOIMIDAZOL-4-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE

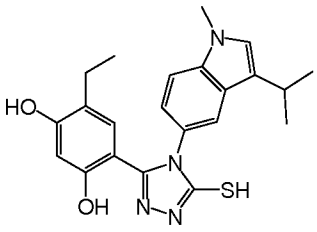
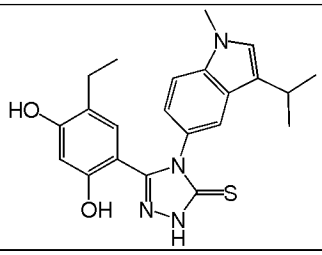
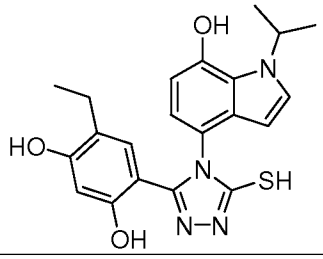
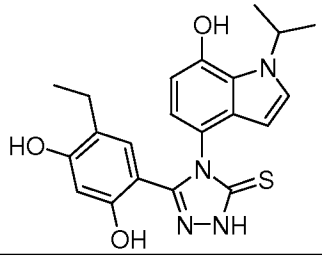
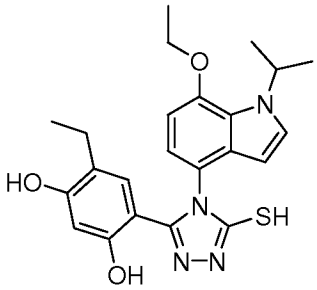
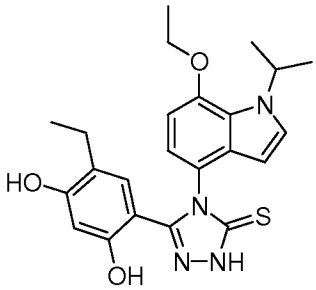
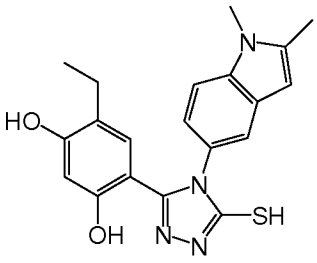
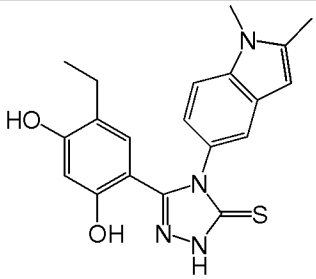
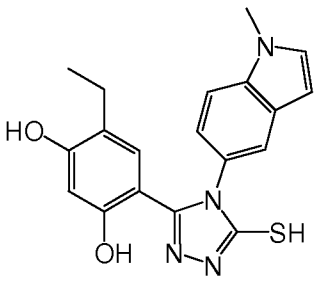
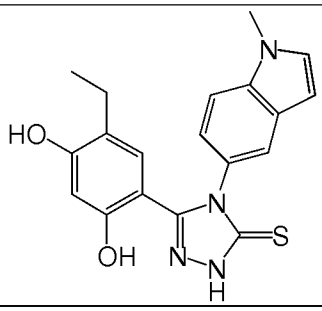
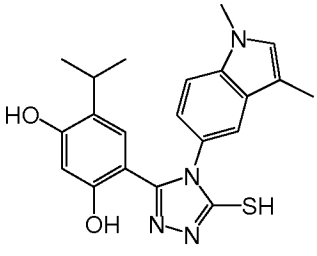
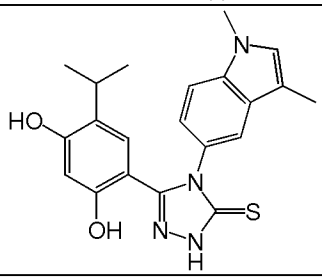
	STRUCTURE	TAUTOMERIC STRUCTURE	NAME
10			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1,2,3-TRIMETHYL-INDOL-5-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
11			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1-ISOPROPYL-INDOL-3-YL)-5-HYDROXY-[1,2,4] TRIAZOLE
12			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1-ISOPROPYL-INDOL-4-YL)-5-AMINO-[1,2,4] TRIAZOLE
15			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1-ISOPROPYL-INDOL-4-YL)-5-UREIDO-[1,2,4] TRIAZOLE
16			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1-METHYL-INDOL-4-YL)-5-CARBAMOYLOXY-[1,2,4] TRIAZOLE
17			3-(2,4-DIHYDROXY-PHENYL)-4-(1-METHYL-2-CHLORO-INDOL-4-YL)-5-CARBAMOYLOXY-[1,2,4] TRIAZOLE

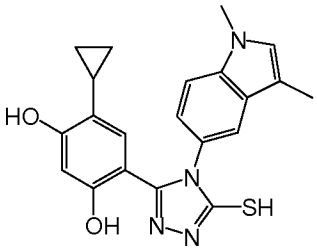
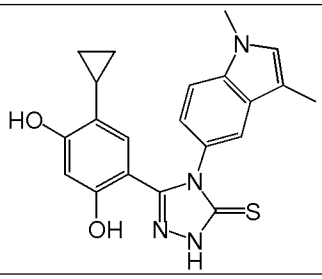
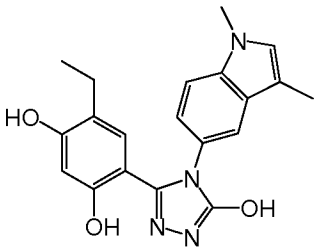
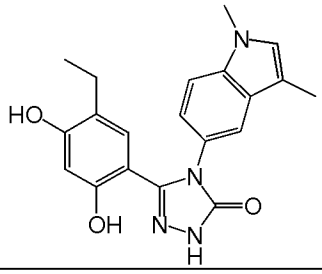
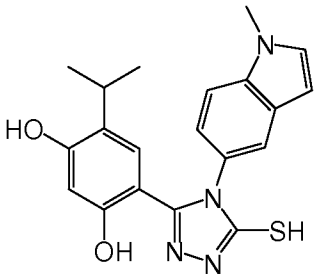
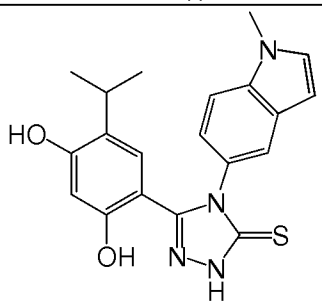
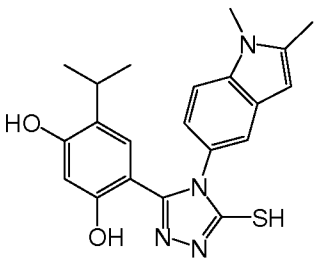
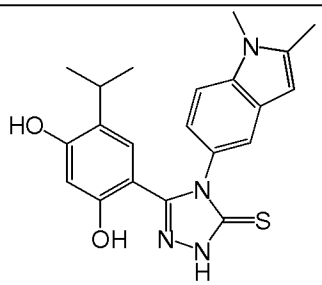
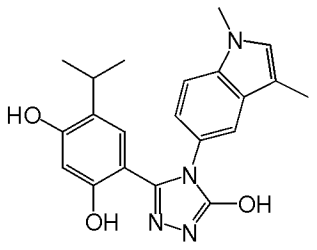
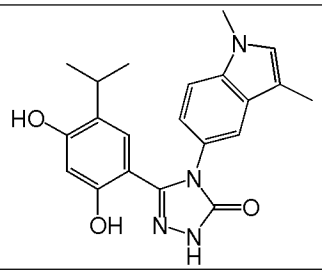
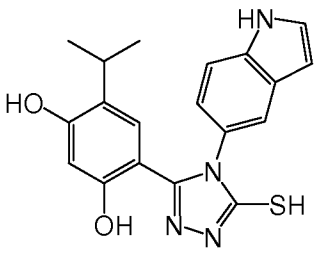
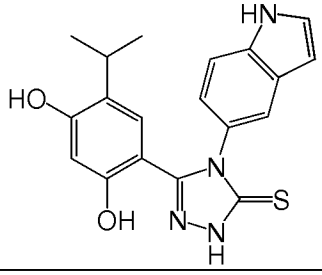
	STRUCTURE	TAUTOMERIC STRUCTURE	NAME
18			3-(2,4-DIHYDROXY-5-METHOXY-PHENYL)-4-(1-ISOPROPYL-BENZOIMIDAZOL-4-YL)-5-(SULFAMOYLAMINO)- [1,2,4] TRIAZOLE
20			3-(2,4-DIHYDROXY-5-METHOXY-PHENYL)-4-(1-ISOPROPYL-BENZOIMIDAZOL-4-YL)-5-(SULFAMOYLOXY)- [1,2,4] TRIAZOLE
21			3-(2-HYDROXY-4-ETHOXYCARBONYOXY-5-METHOXY-PHENYL)-4-(1-ISOPROPYL-BENZOIMIDAZOL-4-YL)-5-HYDROXY-[1,2,4] TRIAZOLE
22			3-[2-HYDROXY-4-ISOBUTYRYLOXY-5-ETHYL-PHENYL]-4-(1-METHYL-BENZO-IMIDAZOL-4-YL)-5-HYDROXY-[1,2,4] TRIAZOLE
23			3-(2,4-DIHYDROXY-PHENYL)-4-(1-DIMETHYLCARBAMOYL-INDOL-4-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
24			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(2,3-DIMETHYL-INDOL-5-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
25			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1-ETHYL-1H-BENZOIMIDAZOL-4-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE, HCL SALT

	STRUCTURE	TAUTOMERIC STRUCTURE	NAME
26			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1-ISOPROPYL-7-METHOXY-INDOL-4-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
27			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1-PROPYL-INDOL-4-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
28			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1-ACETYL-2,3-DIMETHYL-INDOL-5-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
29			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(2-METHYL-3-ETHYL- BENZIMIDAZOL-5-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
30			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1-ETHYL-2-METHYL- BENZIMIDAZOL-5-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
31			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1-PROPYL-2,3-DIMETHYL-INDOL-5-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE

	STRUCTURE	TAUTOMERIC STRUCTURE	NAME
34			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1-N-BUTYL-INDOL-4-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
35			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1-N-PENTYL-INDOL-4-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
36			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1-N-HEXYL-INDOL-4-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
37			3-(2,4-DIHYDROXY-5-CYCLOPROPYL-PHENYL)-4-(1-(1-METHYLCYCLOPROPYL)-INDOL-4-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
38			3-(2,4-DIHYDROXY-5-CYCLOPROPYL-PHENYL)-4-(1-ISOPROPYL-7-METHOXY-INDOL-4-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
39			3-(2,4-DIHYDROXY-5-CYCLOPROPYL-PHENYL)-4-(1,2,3-TRIMETHYL-INDOL-5-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE

	STRUCTURE	TAUTOMERIC STRUCTURE	NAME
40			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1-ISOPROPYL-7-METHOXY-INDOL-4-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE DISODIUM SALT
41			3-(2,4-DIHYDROXY-5-*TERT*-BUTYL-PHENYL)-4-(1-ISOPROPYL-7-METHOXY-INDOL-4-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
42			3-(2,4-DIHYDROXY-5-CYCLOPROPYL-PHENYL)-4-(1-PROPYL-7-METHOXY-INDOL-4-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
43			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1-METHYL-3-ETHYL-INDOL-5-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
44			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1,3-DIMETHYL-INDOL-5-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
45			3-(2,4-DIHYDROXY-5-ISOPROPYL-PHENYL)-4-(1-ISOPROPYL-7-METHOXY-INDOL-4-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE

	STRUCTURE	TAUTOMERIC STRUCTURE	NAME
46			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1-METHYL-3-ISOPROPYL-INDOL-5-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
48			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1-ISOPROPYL-7-HYDROXY-INDOL-4-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
49			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1-ISOPROPYL-7-ETHOXY-INDOL-4-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
50			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1,2-DIMETHYL-INDOL-5-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
51			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(N-METHYL-INDOL-5-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
55			3-(2,4-DIHYDROXY-5-ISOPROPYL-PHENYL)-4-(1,3-DIMETHYL-INDOL-5-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE

	STRUCTURE	TAUTOMERIC STRUCTURE	NAME
56			3-(2,4-DIHYDROXY-5-CYCLOPROPYL-PHENYL)-4-(1,3-DIMETHYL-INDOL-5-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
57			3-(2,4-DIHYDROXY-5-ETHYL-PHENYL)-4-(1,3-DIMETHYL-INDOL-5-YL)-5-HYDROXY-[1,2,4] TRIAZOLE
58			3-(2,4-DIHYDROXY-5-ISOPROPYL-PHENYL)-4-(N-METHYL-INDOL-5-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
59			3-(2,4-DIHYDROXY-5-ISOPROPYL-PHENYL)-4-(1,2-DIMETHYL-INDOL-5-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
60			3-(2,4-DIHYDROXY-5-ISOPROPYL-PHENYL)-4-(1,3-DIMETHYL-INDOL-5-YL)-5-HYDROXY-[1,2,4] TRIAZOLE
62			3-(2,4-DIHYDROXY-5-ISOPROPYL-PHENYL)-4-(1H-INDOL-5-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE

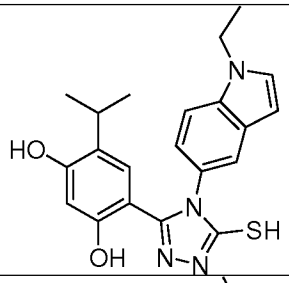
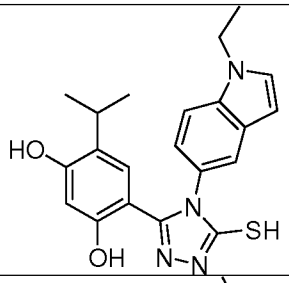
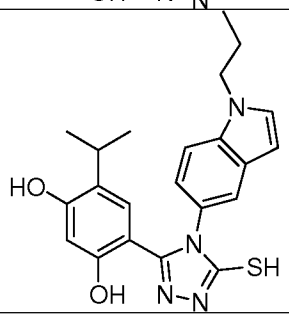
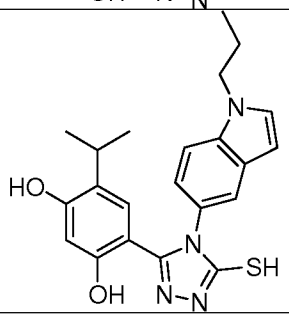
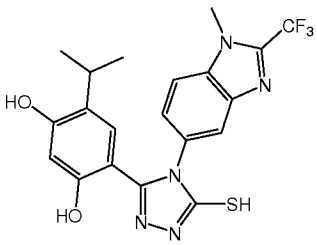
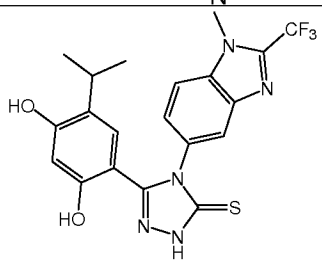
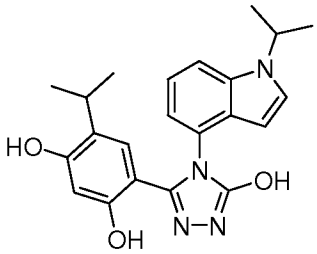
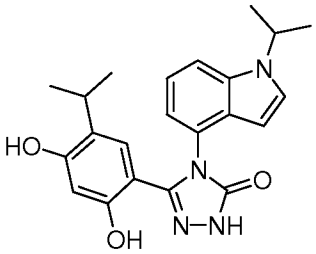
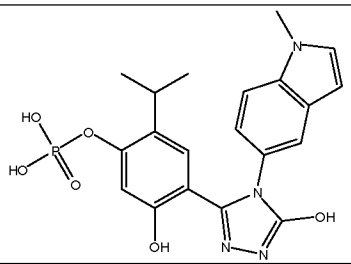
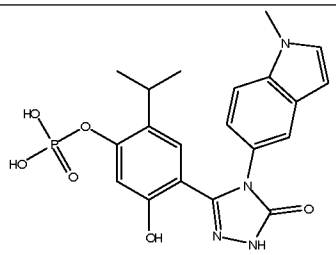
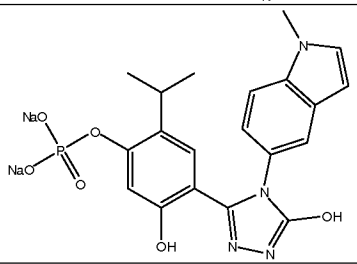
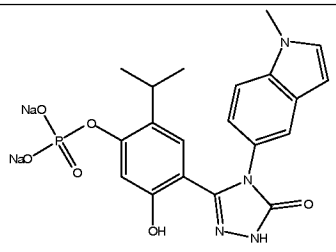
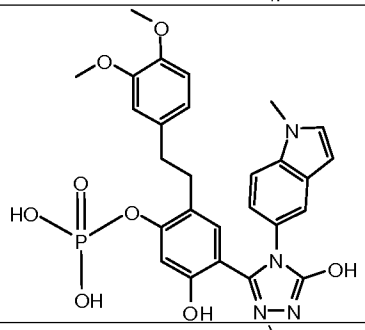
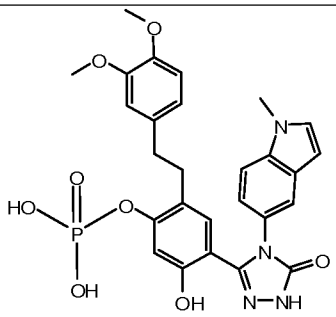
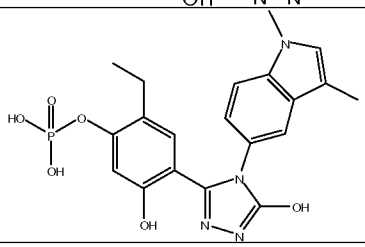
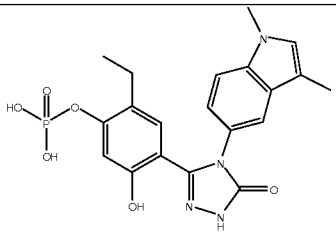
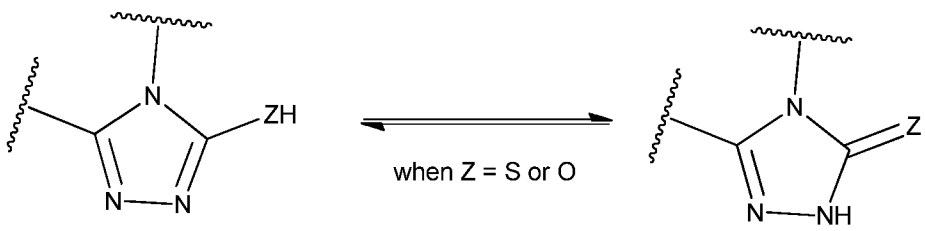
	STRUCTURE	TAUTOMERIC STRUCTURE	NAME
63			3-(2,4-DIHYDROXY-5-ISOPROPYL-PHENYL)-4-(1-ETHYL-INDOL-5-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
64			3-(2,4-DIHYDROXY-5-ISOPROPYL-PHENYL)-4-(1-PROPYL-INDOL-5-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
65			3-(2,4-DIHYDROXY-5-ISOPROPYL-PHENYL)-4-(1-METHYL-2-TRIFLUOROMETHYL-BENZIMIDAZOL-5-YL)-5-MERCAPTO-[1,2,4] TRIAZOLE
66			3-(2,4-DIHYDROXY-5-ISOPROPYL-PHENYL)-4-(1-ISOPROPYL-INDOL-4-YL)-5-HYDROXY-[1,2,4] TRIAZOLE

Table 2: Compounds according to Formula (Ia)

NO.	STRUCTURE	TAUTOMERIC STRUCTURE	NAME
1A			5-HYDROXY-4-(5-HYDROXY-4-(1-METHYL-1H-INDOL-5-YL)-4H-1,2,4-TRIAZOL-3-YL)-2-ISOPROPYLPHENYL DIHYDROGEN PHOSPHATE
2A			SODIUM 5-HYDROXY-4-(5-HYDROXY-4-(1-METHYL-1H-INDOL-5-YL)-4H-1,2,4-TRIAZOL-3-YL)-2-ISOPROPYLPHENYL PHOSPHATE
3A			2-(3,4-DIMETHOXYPHENETHYL)-5-HYDROXY-4-(5-HYDROXY-4-(1-METHYL-1H-INDOL-5-YL)-4H-1,2,4-TRIAZOL-3-YL)PHENYL DIHYDROGEN PHOSPHATE
4A			4-(4-(1,3-DIMETHYL-1H-INDOL-5-YL)-5-HYDROXY-4H-1,2,4-TRIAZOL-3-YL)-2-ETHYL-5-HYDROXYPHENYL DIHYDROGEN PHOSPHATE

The Hsp90 inhibitory compounds used in the disclosed combination methods can be prepared according to the disclosed procedures such as in U.S. Patent Publication No. 2006/0167070, and PCT publication No. WO2009/023211.

These triazolone compounds typically can form a tautomeric structure as shown below and as exemplified by the tautomeric structures shown in Tables 1 and 2:



The present invention provides pharmaceutical combinations for the treatment, prophylaxis, and amelioration of proliferative disorders, such as cancer. In a specific embodiment, the combination comprises one or more Hsp90 inhibitors according to formulae (I) or (Ia), or a compound in Tables 1 or 2, or a tautomer or a pharmaceutically acceptable salt thereof in addition to a proteasome inhibitor.

In one embodiment, the combination includes a pharmaceutical composition or a single unit dosage form containing both an Hsp90 inhibitor and a proteasome inhibitor. Pharmaceutical combinations and dosage forms described herein comprise the two active ingredients in relative amounts and formulated in such a way that a given pharmaceutical combination or dosage form can be used to treat proliferative disorders, such as cancer. Preferred pharmaceutical combinations and dosage forms comprise a compound of formulae (I) or (Ia), or a compound in Tables 1 or 2, or a tautomer or pharmaceutically acceptable salt thereof, in combination with a proteasome inhibitor. In other embodiments, the Hsp90 inhibitor and the proteasome inhibitor may be in individual or separate pharmaceutical compositions, depending on the dosing schedules, preferred routes of administration, and available formulations of the two inhibitors. Optionally, these embodiments can also contain one or more additional therapeutic agents.

The pharmaceutical combinations described herein are formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral, intranasal (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. In a specific embodiment, the combination is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous, subcutaneous, intramuscular, oral, intranasal or topical administration to human beings. In one embodiment, the combination is formulated in accordance with routine procedures for subcutaneous administration to human beings.

In a specific embodiment, the combination therapies described herein comprise one or more compounds and at least one other therapy which has the same mechanism of action as the compounds. In another specific embodiment, the combination therapies described herein comprise one or more compounds described herein and at least one other therapy which has a different mechanism of action than the compounds. In certain embodiments, the combination therapies described herein improve the therapeutic effect of one or more triazolone compounds described herein by functioning together with the proteasome inhibitor to have an additive or synergistic effect. In certain embodiments, the combination therapies described herein reduce the side effects associated with the therapies. In certain embodiments, the combination therapies described herein reduce the effective dosage of one or more of the therapies.

In a specific embodiment, the combination comprising one or more triazolone compounds described herein is administered to a subject, preferably a human, to prevent, treat, manage, or ameliorate cancer, or one or more symptom thereof. In accordance with the invention, the pharmaceutical combinations described herein may also comprise one or more other agents being used, have been used, or are known to be useful in the treatment or amelioration of cancer, particularly colorectal cancer, colon cancer, head and neck cancer, breast cancer, non-small cell lung cancer, prostate cancer, renal cell carcinoma, pancreatic cancer, ovarian cancer, peritoneal cancer, rectal cancer, kidney cancer, Hodgkin's lymphoma, bladder cancer, hepatocellular cancer, gastric cancer, squamous cell carcinoma, cervical cancer, uterine cancer, chronic lymphocytic leukemia, lymphoma, myeloma, gastrointestinal stromal tumor (GIST), solid tumor, hematological tumor, or multiple myeloma. The pharmaceutical combinations described herein utilize pharmaceutical compositions and dosage forms which comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy.

The triazolone compounds described herein can be also formulated into or administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566.

The present invention also provides a method of treating a proliferative disorder in a subject, comprising administering to the subject an effective amount of the combination of an Hsp90 inhibitor and a proteasome inhibitor as described herein. In one embodiment, the proliferative disorder is cancer. In one aspect of this embodiment, the cancer is colorectal cancer, colon cancer, head and neck cancer, breast cancer, non-small cell lung cancer, prostate cancer, renal cell carcinoma, pancreatic cancer, ovarian cancer, peritoneal cancer, rectal cancer, kidney cancer, Hodgkin's lymphoma, bladder cancer, hepatocellular cancer, gastric cancer, squamous cell carcinoma, cervical cancer, uterine cancer, chronic lymphocytic leukemia, lymphoma, myeloma, gastrointestinal stromal tumor (GIST), or multiple myeloma. In another aspect of this embodiment, the cancer is non-small cell lung cancer, colon cancer, head and neck cancer, solid tumor, hematological tumor, or multiple myeloma.

Smooth muscle cell proliferation includes hyperproliferation of cells in the vasculature, for example, intimal smooth muscle cell hyperplasia, restenosis and vascular occlusion, particularly stenosis following biologically- or mechanically-mediated vascular injury, *e.g.*, vascular injury associated with angioplasty. Moreover, intimal smooth muscle cell hyperplasia can include hyperplasia in smooth muscle other than the vasculature, *e.g.*, bile duct blockage,

bronchial airways of the lung in patients with asthma, in the kidneys of patients with renal interstitial fibrosis, and the like.

In one embodiment, the disclosed method is believed to be effective in treating a subject with non-solid tumors such as multiple myeloma. In another embodiment, the disclosed method is believed to be effective against T-cell leukemia, *e.g.*, as exemplified by Jurkat and CEM cell lines; B-cell leukemia, *e.g.*, as exemplified by the SB cell line; promyelocytes, *e.g.*, as exemplified by the HL-60 cell line; uterine sarcoma, *e.g.*, as exemplified by the MES-SA cell line; monocytic leukemia, *e.g.*, as exemplified by the THP-1(acute) cell line; and lymphoma, *e.g.*, as exemplified by the U937 cell line.

Some of the disclosed methods can be also effective at treating subjects whose cancer has become "drug resistant" or "multi-drug resistant". A cancer which initially responded to an anti-cancer drug becomes resistant to the anti-cancer drug when the anti-cancer drug is no longer effective in treating the subject with the cancer. For example, many tumors will initially respond to treatment with an anti-cancer drug by decreasing in size or even going into remission, only to develop resistance to the drug. "Drug resistant" tumors are characterized by a resumption of their growth and/or reappearance after having seemingly gone into remission, despite the administration of increased dosages of the anti-cancer drug. Cancers that have developed resistance to two or more anti-cancer drugs are said to be "multi-drug resistant". For example, it is common for cancers to become resistant to three or more anti-cancer agents, often five or more anti-cancer agents and at times ten or more anti-cancer agents.

Other anti-proliferative or anti-cancer therapies may be combined with the compounds described herein to treat proliferative diseases and cancer. Other therapies or anti-cancer agents that may be used in combination with the anti-cancer agents described herein include surgery, radiotherapy (including gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes), endocrine therapy, biologic response modifiers (including interferons, interleukins, and tumor necrosis factor (TNF)), hyperthermia and cryotherapy, agents to attenuate any adverse effects (*e.g.*, antiemetics), and other approved chemotherapeutic drugs.

The therapeutic agents of the combination therapies described herein can be administered sequentially or concurrently. In one embodiment, the administration of the Hsp90 inhibitor and the proteasome inhibitor are done concurrently. In another embodiment, the administration of the Hsp90 inhibitor and the proteasome inhibitor are done separately. In another embodiment, the administration of the Hsp90 inhibitor and the proteasome inhibitor are

done sequentially. In one embodiment, the administration of the Hsp90 inhibitor and the proteasome inhibitor are done until the cancer is cured or stabilized or improved.

In one specific embodiment, the present method includes treating, managing, or ameliorating cancer, or one or more symptoms thereof, comprising administering to a subject in need thereof one or more compounds represented by the structural formulae (I) or (Ia) or a compound in Table 1 or Table 2, in combination with a proteasome inhibitor such as disulfiram, epigallocatechin-3-gallate, salinosporamide A, carfilzomib, or bortezomib, wherein the cancer is selected from the group consisting of colorectal cancer, colon cancer, head and neck cancer, breast cancer, non-small cell lung cancer, prostate cancer, renal cell carcinoma, pancreatic cancer, ovarian cancer, peritoneal cancer, rectal cancer, kidney cancer, Hodgkin's lymphoma, bladder cancer, hepatocellular cancer, gastric cancer, squamous cell carcinoma, cervical cancer, uterine cancer, chronic lymphocytic leukemia, lymphoma, myeloma, gastrointestinal stromal tumor (GIST), solid tumor, hematological tumor, or multiple myeloma.

In another embodiment, the method of treating a subject with cancer includes administering to the subject an effective amount of a triazolone compound of 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with an effective amount of a proteasome inhibitor. In one embodiment, the cancer is breast cancer, colorectal cancer, colon cancer, non-small cell lung cancer, head and neck cancer, solid cancer, hematological cancer, or multiple myeloma. In one embodiment, the amount of the triazolone compound administered is from about 100 mg/m^2 to about 500 mg/m^2. In one embodiment, the amount of the triazolone compound administered is about 100 mg/m^2, about 110 mg/m^2, about 115 mg/m^2, about 120 mg/m^2, about 125 mg/m2, about 145 mg/m^2, about 150 mg/m^2, about 175 mg/m^2, about 180 mg/m^2, about 200 mg/m^2, about 215 mg/m^2, about 225 mg/m^2, about 250 mg/m^2, or about 260 mg/m^2. In one embodiment, the triazolone compound is administered once weekly. In one embodiment, the triazolone compound is administered twice weekly.

In another embodiment, the method of treating a subject with cancer includes administering to the subject an effective amount of a triazolone compound of 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with an effective amount of bortezomib. In one embodiment, the cancer is breast cancer, colorectal cancer, colon cancer, non-small cell lung cancer, head and neck cancer, solid cancer, hematological cancer, or multiple myeloma. In one embodiment, the amount of the triazolone compound administered is

from about 100 mg/m^2 to about 500 mg/m^2. In one embodiment, the amount of the triazolone compound administered is about 100 mg/m^2, about 110 mg/m^2, about 115 mg/m^2, about 120 mg/m^2, about 125 mg/m2, about 145 mg/m^2, about 150 mg/m^2, about 175 mg/m^2, about 180 mg/m^2, about 200 mg/m^2, about 215 mg/m^2, about 225 mg/m^2, about 250 mg/m^2, or about 260 mg/m^2. In one embodiment, the triazolone compound is administered once weekly. In one embodiment, the triazolone compound is administered twice weekly.

In another embodiment, the method of treating a subject with cancer includes administering to the subject an effective amount of a triazolone compound of 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with an effective amount of carfilzomib. In one embodiment, the cancer is breast cancer, colorectal cancer, colon cancer, non-small cell lung cancer, head and neck cancer, solid cancer, hematological cancer, or multiple myeloma. In one embodiment, the amount of the triazolone compound administered is from about 100 mg/m^2 to about 500 mg/m^2. In one embodiment, the amount of the triazolone compound administered is about 100 mg/m^2, about 110 mg/m^2, about 115 mg/m^2, about 120 mg/m^2, about 125 mg/m2, about 145 mg/m^2, about 150 mg/m^2, about 175 mg/m^2, about 180 mg/m^2, about 200 mg/m^2, about 215 mg/m^2, about 225 mg/m^2, about 250 mg/m^2, or about 260 mg/m^2. In one embodiment, the triazolone compound is administered once weekly. In one embodiment, the triazolone compound is administered twice weekly.

In another embodiment, the method of treating a subject with cancer includes administering to the subject an effective amount of a triazolone compound of 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with an effective amount of a proteasome inhibitor. In one embodiment, the cancer is breast cancer, colorectal cancer, colon cancer, non-small cell lung cancer, head and neck cancer, solid cancer, hematological cancer, or multiple myeloma. In one embodiment, the amount of the triazolone compound administered is from about 100 mg/m^2 to about 500 mg/m^2. In one embodiment, the amount of the triazolone compound administered is about 100 mg/m^2, about 110 mg/m^2, about 115 mg/m^2, about 120 mg/m^2, about 125 mg/m2, about 145 mg/m^2, about 150 mg/m^2, about 175 mg/m^2, about 180 mg/m^2, about 200 mg/m^2, about 215 mg/m^2, about 225 mg/m^2, about 250

mg/m^2, or about 260 mg/m^2. In one embodiment, the triazolone compound is administered once weekly. In one embodiment, the triazolone compound is administered twice weekly.

In another embodiment, the method of treating a subject with cancer includes administering to the subject an effective amount of a triazolone compound of 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with an effective amount of bortezomib. In one embodiment, the cancer is breast cancer, colorectal cancer, colon cancer, non-small cell lung cancer, head and neck cancer, solid cancer, hematological cancer, or multiple myeloma. In one embodiment, the amount of the triazolone compound administered is from about 100 mg/m^2 to about 500 mg/m^2. In one embodiment, the amount of the triazolone compound administered is about 100 mg/m^2, about 110 mg/m^2, about 115 mg/m^2, about 120 mg/m^2, about 125 mg/m2, about 145 mg/m^2, about 150 mg/m^2, about 175 mg/m^2, about 180 mg/m^2, about 200 mg/m^2, about 215 mg/m^2, about 225 mg/m^2, about 250 mg/m^2, or about 260 mg/m^2. In one embodiment, the triazolone compound is administered once weekly. In one embodiment, the triazolone compound is administered twice weekly.

In another embodiment, the method of treating a subject with cancer includes administering to the subject an effective amount of a triazolone compound of 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with an effective amount of carfilzomib. In one embodiment, the cancer is breast cancer, colorectal cancer, colon cancer, non-small cell lung cancer, head and neck cancer, solid cancer, hematological cancer, or multiple myeloma. In one embodiment, the amount of the triazolone compound administered is from about 100 mg/m^2 to about 500 mg/m^2. In one embodiment, the amount of the triazolone compound administered is about 100 mg/m^2, about 110 mg/m^2, about 115 mg/m^2, about 120 mg/m^2, about 125 mg/m2, about 145 mg/m^2, about 150 mg/m^2, about 175 mg/m^2, about 180 mg/m^2, about 200 mg/m^2, about 215 mg/m^2, about 225 mg/m^2, about 250 mg/m^2, or about 260 mg/m^2. In one embodiment, the triazolone compound is administered once weekly. In one embodiment, the triazolone compound is administered twice weekly.

In another embodiment, the method of treating a subject with cancer includes administering to the subject an effective amount of a triazolone compound of 3-(2,4-dihydroxy-

5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with a proteasome inhibitor such as disulfiram, epigallocatechin-3-gallate, salinosporamide A, carfilzomib, or bortezomib, wherein the cancer is selected from the group consisting of colorectal cancer, colon cancer, head and neck cancer, breast cancer, non-small cell lung cancer, prostate cancer, renal cell carcinoma, pancreatic cancer, ovarian cancer, peritoneal cancer, rectal cancer, kidney cancer, Hodgkin's lymphoma, bladder cancer, hepatocellular cancer, gastric cancer, squamous cell carcinoma, cervical cancer, uterine cancer, chronic lymphocytic leukemia, lymphoma, myeloma, gastrointestinal stromal tumor (GIST), solid tumor, hematological tumor or multiple myeloma.

In another embodiment, the method of treating a subject with cancer includes administering to the subject an effective amount of a triazolone compound of 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with a proteasome inhibitor such as disulfiram, epigallocatechin-3-gallate, salinosporamide A, carfilzomib, or bortezomib, wherein the cancer is selected from the group consisting of colorectal cancer, colon cancer, head and neck cancer, breast cancer, non-small cell lung cancer, prostate cancer, renal cell carcinoma, pancreatic cancer, ovarian cancer, peritoneal cancer, rectal cancer, kidney cancer, Hodgkin's lymphoma, bladder cancer, hepatocellular cancer, gastric cancer, squamous cell carcinoma, cervical cancer, uterine cancer, chronic lymphocytic leukemia, lymphoma, myeloma, gastrointestinal stromal tumor (GIST), solid tumor, hematological tumor or multiple myeloma.

In yet another embodiment, the method of treating a subject with cancer, wherein the subject is being or has been treated with a chemotherapeutic agent, includes administering to the subject an effective amount of a triazolone compound represented by the structural formulae (I) or (Ia) or a compound in Table 1 or Table 2, in combination with a proteasome inhibitor such as disulfiram, epigallocatechin-3-gallate, salinosporamide A, carfilzomib, or bortezomib.

In one embodiment, the method of treating a subject with cancer, wherein the subject is being or has been treated with a chemotherapeutic agent, includes administering to the subject an effective amount of a triazolone compound represented by the structural formulae (I) or (Ia) or a compound in Table 1 or Table 2, in combination with a proteasome inhibitor such as disulfiram, epigallocatechin-3-gallate, salinosporamide A, carfilzomib, or bortezomib, wherein the cancer is selected from the group consisting of colorectal cancer, colon cancer, head and neck cancer, breast cancer, non-small cell lung cancer, prostate cancer, renal cell carcinoma, pancreatic cancer, ovarian cancer, peritoneal cancer, rectal cancer, kidney cancer, Hodgkin's lymphoma, bladder cancer, hepatocellular cancer, gastric cancer, squamous cell carcinoma, cervical cancer,

uterine cancer, chronic lymphocytic leukemia, lymphoma, myeloma, gastrointestinal stromal tumor (GIST), solid tumor, hematological tumor or multiple myeloma.

In another embodiment, the method of treating a subject with cancer, wherein the subject is being or has been treated with a chemotherapeutic agent, includes administering to the subject an effective amount of 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with a proteasome inhibitor such as disulfiram, epigallocatechin-3-gallate, salinosporamide A, carfilzomib, or bortezomib.

In another embodiment, the method of treating a subject with cancer, wherein the subject is being or has been treated with a chemotherapeutic agent, includes administering to the subject an effective amount of 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with bortezomib, wherein the cancer is breast cancer, colorectal cancer, colon cancer, non-small cell lung cancer, head and neck cancer, solid cancer, hematological cancer, or multiple myeloma.

In another embodiment, the method of treating a subject with cancer, wherein the subject is being or has been treated with a chemotherapeutic agent, includes administering to the subject an effective amount of 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with carfilzomib, wherein the cancer is breast cancer, colorectal cancer, colon cancer, non-small cell lung cancer, head and neck cancer, solid cancer, hematological cancer, or multiple myeloma.

In another embodiment, the method of treating a subject with cancer, wherein the subject is being or has been treated with a chemotherapeutic agent, includes administering to the subject an effective amount of 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with a proteasome inhibitor such as disulfiram, epigallocatechin-3-gallate, salinosporamide A, carfilzomib, or bortezomib.

In another embodiment, the method of treating a subject with cancer, wherein the subject is being or has been treated with a chemotherapeutic agent, includes administering to the subject an effective amount of 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with bortezomib. In one embodiment, the cancer is breast cancer, colorectal cancer, colon cancer, non-small cell lung cancer, head and neck cancer, solid cancer, hematological cancer, or multiple myeloma.

In another embodiment, the method of treating a subject with cancer, wherein the subject is being or has been treated with a chemotherapeutic agent, includes administering to the subject an effective amount of 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with carfilzomib. In one embodiment, the cancer is breast cancer, colorectal cancer, colon cancer, non-small cell lung cancer, head and neck cancer, solid cancer, hematological cancer, or multiple myeloma.

In one embodiment, the method of treating a subject with cancer, wherein the subject is being or has been treated with a chemotherapeutic agent, includes administering to the subject an effective amount of a triazolone compound of 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with a proteasome inhibitor such as disulfiram, epigallocatechin-3-gallate, salinosporamide A, carfilzomib, or bortezomib, wherein the cancer is selected from the group consisting of colorectal cancer, colon cancer, head and neck cancer, breast cancer, non-small cell lung cancer, prostate cancer, renal cell carcinoma, pancreatic cancer, ovarian cancer, peritoneal cancer, rectal cancer, kidney cancer, Hodgkin's lymphoma, bladder cancer, hepatocellular cancer, gastric cancer, squamous cell carcinoma, cervical cancer, uterine cancer, chronic lymphocytic leukemia, lymphoma, myeloma, gastrointestinal stromal tumor (GIST), solid tumor, hematological tumor or multiple myeloma.

In one embodiment, the method of treating a subject with cancer, wherein the subject is being or has been treated with a chemotherapeutic agent, includes administering to the subject an effective amount of a triazolone compound of 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with a proteasome inhibitor such as disulfiram, epigallocatechin-3-gallate, salinosporamide A, carfilzomib, or bortezomib, wherein the cancer is selected from the group consisting of colorectal cancer, colon cancer, head and neck cancer, breast cancer, non-small cell lung cancer, prostate cancer, renal cell carcinoma, pancreatic cancer, ovarian cancer, peritoneal cancer, rectal cancer, kidney cancer, Hodgkin's lymphoma, bladder cancer, hepatocellular cancer, gastric cancer, squamous cell carcinoma, cervical cancer, uterine cancer, chronic lymphocytic leukemia, lymphoma, myeloma, gastrointestinal stromal tumor (GIST), solid tumor, hematological tumor, or multiple myeloma.

In one embodiment, the method of treating a subject with cancer, wherein the subject has proven refractory to other therapies but is no longer on these therapies, includes administering to the subject an effective amount of a triazolone compound represented by the structural formulae (I) or (Ia) or a compound in Table 1 or Table 2, in combination with a proteasome inhibitor such as disulfiram, epigallocatechin-3-gallate, salinosporamide A,

carfilzomib, or bortezomib, wherein the cancer is selected from the group consisting of colorectal cancer, colon cancer, head and neck cancer, breast cancer, non-small cell lung cancer, prostate cancer, renal cell carcinoma, pancreatic cancer, ovarian cancer, peritoneal cancer, rectal cancer, kidney cancer, Hodgkin's lymphoma, bladder cancer, hepatocellular cancer, gastric cancer, squamous cell carcinoma, cervical cancer, uterine cancer, chronic lymphocytic leukemia, lymphoma, myeloma, gastrointestinal stromal tumor (GIST), solid tumor, hematological tumor or multiple myeloma.

In another embodiment, the method of treating a subject with cancer, wherein the subject has proven refractory to other therapies but is no longer on these therapies, includes administering to the subject an effective amount of 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with a proteasome inhibitor such as disulfiram, epigallocatechin-3-gallate, salinosporamide A, carfilzomib, or bortezomib.

In another embodiment, the method of treating a subject with cancer, wherein the subject has proven refractory to other therapies but is no longer on these therapies, includes administering to the subject an effective amount of 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with bortezomib. In one embodiment, the cancer is breast cancer, colorectal cancer, colon cancer, non-small cell lung cancer, head and neck cancer, solid cancer, hematological cancer, or multiple myeloma.

In another embodiment, the method of treating a subject with cancer, wherein the subject has proven refractory to other therapies but is no longer on these therapies, includes administering to the subject an effective amount of 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with carfilzomib. In one embodiment, the cancer is breast cancer, colorectal cancer, colon cancer, non-small cell lung cancer, head and neck cancer, solid cancer, hematological cancer, or multiple myeloma.

In another embodiment, the method of treating a subject with cancer, wherein the subject has proven refractory to other therapies but is no longer on these therapies, includes administering to the subject an effective amount of 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with a proteasome inhibitor such as disulfiram, epigallocatechin-3-gallate, salinosporamide A, carfilzomib, or bortezomib.

In another embodiment, the method of treating a subject with cancer, wherein the subject has proven refractory to other therapies but is no longer on these therapies, includes

administering to the subject an effective amount of 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with bortezomib. In one embodiment, the cancer is breast cancer, colorectal cancer, colon cancer, non-small cell lung cancer, head and neck cancer, solid cancer, hematological cancer, or multiple myeloma.

In another embodiment, the method of treating a subject with cancer, wherein the subject has proven refractory to other therapies but is no longer on these therapies, includes administering to the subject an effective amount of 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with carfilzomib. In one embodiment, the cancer is breast cancer, colorectal cancer, colon cancer, non-small cell lung cancer, head and neck cancer, solid cancer, hematological cancer, or multiple myeloma.

In one embodiment, the method of treating a subject with cancer, wherein the subject has proven refractory to other therapies but is no longer on these therapies, includes administering to the subject an effective amount of a triazolone compound of 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with a proteasome inhibitor such as disulfiram, epigallocatechin-3-gallate, salinosporamide A, carfilzomib, or bortezomib, wherein the cancer is selected from the group consisting of colorectal cancer, colon cancer, head and neck cancer, breast cancer, non-small cell lung cancer, prostate cancer, renal cell carcinoma, pancreatic cancer, ovarian cancer, peritoneal cancer, rectal cancer, kidney cancer, Hodgkin's lymphoma, bladder cancer, hepatocellular cancer, gastric cancer, squamous cell carcinoma, cervical cancer, uterine cancer, chronic lymphocytic leukemia, lymphoma, myeloma, gastrointestinal stromal tumor (GIST), solid tumor, hematological tumor or multiple myeloma.

In one embodiment, the method of treating a subject with cancer, wherein the subject has proven refractory to other therapies but is no longer on these therapies, includes administering to the subject an effective amount of a triazolone compound of 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate, or a tautomer, or a pharmaceutically acceptable salt thereof, in combination with a proteasome inhibitor such as disulfiram, epigallocatechin-3-gallate, salinosporamide A, carfilzomib, or bortezomib, wherein the cancer is selected from the group consisting of colorectal cancer, colon cancer, head and neck cancer, breast cancer, non-small cell lung cancer, prostate cancer, renal cell carcinoma, pancreatic cancer, ovarian cancer, peritoneal cancer, rectal cancer, kidney cancer, Hodgkin's lymphoma, bladder cancer, hepatocellular cancer, gastric cancer, squamous cell carcinoma, cervical cancer, uterine cancer, chronic lymphocytic leukemia,

lymphoma, myeloma, gastrointestinal stromal tumor (GIST), solid tumor, hematological tumor or multiple myeloma.

In one embodiment, the method includes treating a subject with multiple myeloma, comprising administering to the subject an effective amount of a proteasome inhibitor and an effective amount of 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof. In one embodiment, the proteasome inhibitor is bortezomib. In one embodiment, the proteasome inhibitor is carfilzomib.

In one embodiment, the method includes treating a subject with multiple myeloma, comprising administering to the subject an effective amount of a proteasome inhibitor and an effective amount of 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate dihydrogen phosphate, or a tautomer, or a pharmaceutically acceptable salt thereof. In one embodiment, the proteasome inhibitor is bortezomib. In one embodiment, the proteasome inhibitor is carfilzomib.

In one embodiment, the method includes treating a subject with relapsed or refractory multiple myeloma, comprising administering to the subject an effective amount of a proteasome inhibitor and an effective amount of 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof. In one embodiment, the proteasome inhibitor is bortezomib. In one embodiment, the proteasome inhibitor is carfilzomib.

In one embodiment, the method includes treating a subject with relapsed or refractory multiple myeloma, comprising administering to the subject an effective amount of a proteasome inhibitor and an effective amount of 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate dihydrogen phosphate, or a tautomer, or a pharmaceutically acceptable salt thereof. In one embodiment, the proteasome inhibitor is bortezomib. In one embodiment, the proteasome inhibitor is carfilzomib.

In one embodiment, the method also includes treating a subject with multiple myeloma, or relapsed or refractory multiple myeloma, comprising administering to the subject an effective amount of 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof.

In one embodiment, the method also includes treating a subject with multiple myeloma, or relapsed or refractory multiple myeloma, comprising administering to the subject an effective amount of 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate dihydrogen phosphate, or a tautomer, or a pharmaceutically acceptable salt thereof.

In one further embodiment, the method includes inhibiting the growth of a cancer or tumor cell comprising the steps of: (a) contacting the cell with an effective amount of a compound of formulae (I) or (Ia) or a compound in Table (1) or Table (2), or tautomer or a pharmaceutically acceptable salt thereof; and (b) exposing the cell to an effective amount of a proteasome inhibitor such as disulfiram, epigallocatechin-3-gallate, salinosporamide A, carfilzomib, or bortezomib.

In one further embodiment, the method includes inhibiting the growth of a cancer or tumor cell comprising the steps of: (a) contacting the cell with an effective amount of a compound of -(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof; and (b) exposing the cell to an effective amount of a proteasome inhibitor such as disulfiram, epigallocatechin-3-gallate, salinosporamide A, carfilzomib, or bortezomib.

In one further embodiment, the method includes inhibiting the growth of a cancer or tumor cell comprising the steps of: (a) contacting the cell with an effective amount of a compound of -(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof; and (b) exposing the cell to an effective amount of bortezomib.

In one further embodiment, the method includes inhibiting the growth of a cancer or tumor cell comprising the steps of: (a) contacting the cell with an effective amount of a compound of -(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof; and (b) exposing the cell to an effective amount of carfilzomib.

In one further embodiment, the method includes inhibiting the growth of a cancer or tumor cell comprising the steps of: (a) contacting the cell with an effective amount of a compound of -(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof; and (b) exposing the cell to an effective amount of carfilzomib.

In one further embodiment, the method includes inhibiting the growth of a cancer or tumor cell comprising the steps of: (a) contacting the cell with an effective amount of a compound of 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate, or tautomer or a pharmaceutically acceptable salt thereof; and (b) exposing the cell to an effective amount of a proteasome inhibitor such as disulfiram, epigallocatechin-3-gallate, salinosporamide A, carfilzomib, or bortezomib.

In one further embodiment, the method includes inhibiting the growth of a cancer or tumor cell comprising the steps of: (a) contacting the cell with an effective amount of a

compound of 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate, or tautomer or a pharmaceutically acceptable salt thereof; and (b) exposing the cell to an effective amount of bortezomib.

In one further embodiment, the method includes inhibiting the growth of a cancer or tumor cell comprising the steps of: (a) contacting the cell with an effective amount of a compound of 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate, or tautomer or a pharmaceutically acceptable salt thereof; and (b) exposing the cell to an effective amount of carfilzomib.

In general, the recommended daily dose range of a triazolone compound for the conditions described herein lie within the range of from about 0.01 mg to about 1000 mg per day, given as a single once-a-day dose preferably as divided doses throughout a day. In one embodiment, the daily dose is administered twice daily in equally divided doses. Specifically, a daily dose range should be from about 5 mg to about 500 mg per day, more specifically, between about 10 mg and about 200 mg per day. In managing the patient, the therapy should be initiated at a lower dose, perhaps about 1 mg to about 25 mg, and increased if necessary up to about 200 mg to about 1000 mg per day as either a single dose or divided doses, depending on the patient's global response. It may be necessary to use dosages of the active ingredient outside the ranges disclosed herein in some cases, as will be apparent to those of ordinary skill in the art. Furthermore, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response.

Different therapeutically effective amounts may be applicable for different cancers, as will be readily known by those of ordinary skill in the art. Similarly, amounts sufficient to prevent, manage, treat or ameliorate such cancers, but insufficient to cause, or sufficient to reduce, adverse effects associated with the triazolone compounds described herein are also encompassed by the above described dosage amounts and dose frequency schedules. Further, when a patient is administered multiple dosages of a triazolone compound described herein, not all of the dosages need be the same. For example, the dosage administered to the patient may be increased to improve the prophylactic or therapeutic effect of the compound or it may be decreased to reduce one or more side effects that a particular patient is experiencing.

In a specific embodiment, the dosage of the composition comprising a triazolone compound described herein administered to prevent, treat, manage, or ameliorate cancer, or one or more symptoms thereof in a patient is 150 μg/kg, preferably 250 μg/kg, 500 μg/kg, 1 mg/kg, 5 mg/kg, 10 mg/kg, 25 mg/kg, 50 mg/kg, 75 mg/kg, 100 mg/kg, 125 mg/kg, 150 mg/kg, or 200 mg/kg or more of a patient's body weight. In another embodiment, the dosage of the composition comprising a compound described herein administered to prevent, treat, manage, or

ameliorate cancer, or one or more symptoms thereof in a patient is a unit dose of 0.1 mg to 20 mg, 0.1 mg to 15 mg, 0.1 mg to 12 mg, 0.1 mg to 10 mg, 0.1 mg to 8 mg, 0.1 mg to 7 mg, 0.1 mg to 5 mg, 0.1 to 2.5 mg, 0.25 mg to 20 mg, 0.25 to 15 mg, 0.25 to 12 mg, 0.25 to 10 mg, 0.25 to 8 mg, 0.25 mg to 7m g, 0.25 mg to 5 mg, 0.5 mg to 2.5 mg, 1 mg to 20 mg, 1 mg to 15 mg, 1 mg to 12 mg, 1 mg to 10 mg, 1 mg to 8 mg, 1 mg to 7 mg, 1 mg to 5 mg, or 1 mg to 2.5 mg. The unit dose can be administered 1, 2, 3, 4 or more times daily, or once every 2, 3, 4, 5, 6 or 7 days, or once weekly, once every two weeks, once every three weeks or once monthly.

In certain embodiments, when the triazolone compounds described herein are administered in combination with a proteasome inhibitor, the therapies are administered less than 5 minutes apart, less than 30 minutes apart, 1 hour apart, at about 1 hour apart, at about 1 to about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, at about 12 hours to 18 hours apart, 18 hours to 24 hours apart, 24 hours to 36 hours apart, 36 hours to 48 hours apart, 48 hours to 52 hours apart, 52 hours to 60 hours apart, 60 hours to 72 hours apart, 72 hours to 84 hours apart, 84 hours to 96 hours apart, or 96 hours to 120 hours part. In one embodiment, two or more therapies are administered within the same patient visit.

In certain embodiments, one or more compounds described herein and one or more other the therapies (*e.g.*, therapeutic agents) are cyclically administered. Cycling therapy involves the administration of a first therapy (*e.g.*, a first prophylactic or therapeutic agents) for a period of time, followed by the administration of a second therapy (*e.g.*, a second prophylactic or therapeutic agents) for a period of time, followed by the administration of a third therapy (*e.g.*, a third prophylactic or therapeutic agents) for a period of time and so forth, and repeating this sequential administration, *i.e.*, the cycle in order to reduce the development of resistance to one of the agents, to avoid or reduce the side effects of one of the agents, and/or to improve the efficacy of the treatment.

In certain embodiments, administration of the same compound described herein may be repeated and the administrations may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months. In other embodiments, administration of the same prophylactic or therapeutic agent may be repeated and the administration may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months.

In a specific embodiment, a method of preventing, treating, managing, or ameliorating a proliferative disorders, such as cancer, or one or more symptoms thereof, the methods comprising administering to a subject in need thereof a dose of at least 150 μg/kg, preferably at least 250 μg/kg, at least 500 μg/kg, at least 1 mg/kg, at least 5 mg/kg, at least 10 mg/kg, at least 25 mg/kg, at least 50 mg/kg, at least 75 mg/kg, at least 100 mg/kg, at least 125 mg/kg, at least 150 mg/kg, or at least 200 mg/kg or more of one or more compounds described herein once every day, preferably, once every 2 days, once every 3 days, once every 4 days, once every 5 days, once every 6 days, once every 7 days, once every 8 days, once every 10 days, once every two weeks, once every three weeks, or once a month. Alternatively, the dose can be divided into portions (typically equal portions) administered two, three, four or more times a day.

In one embodiment, the amount of compound **1** administered is from about 2 mg/m^2 to about 500 mg/m^2, for example, from about 100 mg/m^2 to about 500 mg/m^2, from about 125 mg/m^2 to about 500 mg/m^2, from about 150 mg/m^2 to about 500 mg/m^2 or from about 175 mg/m^2 to about 500 mg/m^2. In one embodiment, the amount of compound **1** administered is about 100 mg/m^2 to about 300 mg/m^2, from about 125 mg/m^2 to about 300 mg/m^2, from about 150 mg/m^2 to about 300 mg/m^2 or from about 175 mg/m^2 to about 300 mg/m^2. In some embodiments, the amount of compound **1** administered is about 2 mg/m^2, 4 mg/m^2, about 7 mg/m^2, about 10 mg/m^2, about 15 mg/m^2, about 19 mg/m^2, about 23 mg/m^2, about 25 mg/m^2, about 33 mg/m^2, about 35 mg/m^2, about 40 mg/m^2, about 48 mg/m^2, about 49 mg/m^2, about 50 mg/m^2, about 65 mg/m^2, about 75 mg/m^2, about 85 mg/m^2, about 100 mg/m^2, about 110 mg/m^2, about 115 mg/m^2, about 120 mg/m^2, about 145 mg/m^2, about 150 mg/m^2, about 175 mg/m^2, about 180 mg/m^2, about 200 mg/m^2, about 215 mg/m^2 or about 260 mg/m^2.

The language "twice weekly" includes administration of compound **1** two times in about 7 days. For example, the first dose of compound **1** is administered on day 1, and the second dose of compound **1** may be administered on day 2, day 3, day 4, day 5, day 6 or day 7. In some embodiments, the twice weekly administration occurs on days 1 and 3 or days 1 and 4.

In some embodiments, compound **1** is cyclically administered twice weekly. For example, compound **1** is administered for a first period of time, followed by a "dose-free" period, then administered for a second period of time. The language "dose free" includes the period of time in between the first dosing period and the second dosing period in which no compound **1** is administered to the subject. A preferred cycle is administering compound **1** at a dose described above two times during the week for three consecutive weeks followed by one dose-free week. This cycle is then repeated, as described below.

The language "one cycle" includes the first period of time during which compound **1** is administered, followed by a dose-free period of time. The dosing cycle can be repeated and one of skill in the art will be able to determine the appropriate length of time for such a cyclical dosing regimen. In one embodiment, the cycle is repeated at least once. In one embodiment, the cycle is repeated two or more times. In one embodiment, the cycle is repeated 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more times, or as many times as medically necessary as determined by one of skill in the art. In one embodiment, the cycle is repeated until the patient has been determined to be in partial remission (*e.g.*, 50% or greater reduction in the measurable parameters of tumor growth or complete remission (*e.g.*, absence of cancer). One of skill in the art would be able to determine a patient's remission status using routine methods well known in the art.

EXAMPLES

Example 1

A. Materials and Methods

Cell Lines

Human H1703, H1975, H1838 NSCLC cells, U266 multiple myeloma cells, HCT116 colon cancer cells and Detroit562 head and neck cancer cells were purchased from the American Type Culture Collection (Manassas, VA). H1975, H1703, H1838 and U266 cells were grow in RPMI media, HCT116 cells were grown in McCoy's media and Detroit562 cells were grown in MEM. Fetal bovine serum (10%) was added to all media, along with 2 mM L-glutamine and antibiotics (100 IU/ml penicillin and 100 µg/ml streptomycin) purchased from Sigma Aldrich. Cells were maintained at 37°C, 5% CO_2 atmosphere.

Cell Viability Assays

Cell viability was measured using the Cell Titer-Glo assay (Promega). In brief, cells were plated in 96-well plates in triplicate at optimal seeding density (determined empirically for each cell line) and incubated at 37°C, 5% CO_2 atmosphere for 24 hr prior to the addition of drug or vehicle (0.3% DMSO) to the culture medium. At the end of the assay, Cell Titer-Glow was added to the wells per manufactures recommendation, shaken for two minutes and incubated for 10 minutes at room temperature. Luminescence (0.1 sec) was measured with a Victor II

microplate reader (Perkin Elmer) and the resulting data were used to calculate cell viability, normalized to vehicle control.

B. Combination Studies with bortezomib (Velcade®) and compound **1**

Matrix style combinations between bortezomib (LC Laboratories, Woburn, MA) and compound **1** (synthesized by Synta Pharmaceuticals) were performed in H1703 cells. Cells were exposed to a pulse of bortezomib (8 hr on Day 1) followed by washout with media. The next day, cells were pulsed with compound **1** for 8 hr followed by a washout with media. Viability was assessed 72 hr later. Shown in Figure 1, the combination of compound **1** and bortezomib resulted in a tremendous enhancement of cell death. Shown in Figure 2 for greater clarity, a single dose of bortezomib from Figure 1 was re-plotted with the titration of compound **1**. From these results it was clear that weak, but effective, doses of compound **1** markedly increased cell death. For example, bortezomib on its own (15 nM) killed 25% of the cells, compound **1** (50 nM) killed 10 % of the cells, and in combination ~90% of the cells were killed. Similar results were observed if compound **1** was given first, if both drugs were given concurrently for 8 hr on two consecutive days or for 72 hr straight.

Combination Index (CI) was then determined using the median effect analysis software CalcuSyn 2.0 (CalcuSyn, Inc.). A Combination Index greater than 1, equal to 1 or less than 1 indicates antagonism, additivity and synergism, respectively. Shown in Figure 3, all of the combination points in the analysis of 7 and 10 nM bortezomib with a titration of compound **1** displayed CI values of 0.5 or less indicating that this combination is highly synergistic.

To further illustrate these findings, bright field images were taken of the cells treated with single agent or combination therapy and clearly show complete loss of viability in the combination arm as opposed to the weak action of either agent alone (Figure 4). Mechanistically, increased apoptosis (PARP cleavage) was seen in the combination arm in comparison to monotherapy.

Given the strong synergistic relationship between compound **1** and bortezomib with 8 hr exposures of each drug, additional experiments were performed using only a 1 hr exposure of both drugs on Day 1 and Day 2, followed by viability analysis 72 hr later. Shown in Figure 5, bortezomib (22 nM) or compound **1** (74 nM) on their own only kill 15% of the H1703 cells whereas the combination kills >90% of the cells.

Two additional NSCLC cell lines (H1975 and H1838) were utilized, as well as a colon cancer cell line (HCT116) and a head and neck cancer cell line (Detroit562). Shown in Figures

6-8, the combination of compound **1** with bortezomib was highly synergistic in all of the solid tumor cell lines analyzed. Lastly, the combination was assayed in a hematological cell line (multiple myeloma) and the results show enhanced anticancer activity when compound **1** was combined with bortezomib versus monotherapy. Similar results were observed with the second generation proteasome inhibitor carfilzomib (Chemie-TEK, Indianapolis, IN) (Figure 9). In conclusion, these results showed that compound **1** combination with bortezomib or carfilzomib was highly effective and synergistic in treating cancer related diseases.

Example 2 Compound **1** Enhances the Anti-Tumor Activity of Bortezomib Against Multiple Myeloma

Multiple myeloma (MM) is a malignancy of plasma cells, and is the second most common hematological malignancy in adults. Approximately 20,000 cases of MM are diagnosed each year in the United States, with over 11,000 reported deaths due to MM annually. Multiple myeloma is a disease of malignant plasma cells clinically characterized by lytic bone disease, renal insufficiency, hypercalcemia and anemia. While the advent of autologous stem cell transplantation and advances novel biological agents have improved patient outcomes from a 3-year median life expectancy to 5 years, MM remains incurable.

A Phase 1 protocol evaluating a combination therapy of an Hsp90 inhibitor (Compound **1**) and bortezomib is described as follows. The protocol is based on a standard 3 + 3 dose escalation design; however toxicity observed for both the first 2 cycles of single-agent Compound **1** and the first cycle of the combination is assessed for dose-limiting toxicities (DLT). Patients enter the study in cohorts of 3. If zero out of 3 evaluable patients has a DLT, then the next dose level is tested. If 2 out of 3 patients have a DLT, dose escalation ceases and the next lower dose level is expanded. If one out of three evaluable patients has a DLT, three additional patients are assessed at the same dose level. If one out of six evaluable patients has a DLT, then dose escalation continues. A dose that produces in DLT $\leq$ 1/6 is used for the expanded Phase 1 cohorts.

Treatment is administered on an outpatient basis. All patients receive run-in with 2 cycles of single agent Compound **1**. Patients who fail to achieve stable disease or better following one cycle, or minor response or better following 2 cycles, will have the option of adding escalating doses of bortezomib. Patients who do achieve stable disease or better following one cycle, or minor response or better following 2 cycles may continue on single agent Compound **1** until progression or unacceptable toxicity. Patients who experience DLT during the 2 run in cycles are discontinued therapy.

Single agent Compound **1** is given as indicated in the table below. Dose level 1 single agent and combination must be completed and fully evaluated for toxicity according to the standard 3+3 design outlined above, prior to initiation of dose level 2. Dose level 2 of Compound **1** is the same as dose level 1 (100 mg/m^2); therefore, if no DLT is experienced in dose level one, dose escalation may proceed to dose level 2 combination therapy.

Table 1

Cohort	**Compound 1**	**Bortezomib**	**Dexamethasone**
	IV Days 1, 4, 8, 11 every 3 weeks	IV Days 1, 4, 8, 11 every 3 weeks	Oral Prior to Bortezomib
1	100 mg/m^2	1.0 mg/m^2	20 + 20 mg (Day of and following bortezomib)
2	100 mg/m^2	1.3 mg/m^2	20 + 20 mg (Day of and following bortezomib)
3	120 mg/m^2	1.3 mg/m^2	20 + 20 mg (Day of and following bortezomib)
4	144 mg/m^2	1.3 mg/m^2	20 + 20 mg (Day of and following bortezomib)
5	173 mg/m^2	1.3 mg/m^2	20 + 20 mg (Day of and following bortezomib)

Subjects receive Compound **1** over 1 hour twice weekly on days 1, 4, 8 and 11. When bortezomib is added it is given by standard administration also on days 1, 4, 8, and 11 according to the dosing table below. A cycle is 21 days, and the dose levels are shown in Table 1.

Example 3 Compound **1** was advanced into phase 1 clinical investigations studying patients with refractory hematologic malignancies using two intravenous schedules of administration: weekly for 3 out of every 4 weeks and twice weekly without breaks dosing by one-hour infusion.

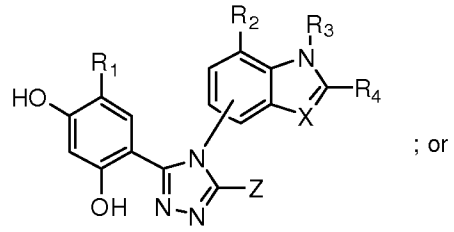
Dose limiting toxicities from the phase 1 program (including both solid tumors and refractory hematologic malignancies) include reversible fatigue and diarrhea. Unlike geldanamycin-based HSP90 inhibitors, severe hepatotoxicity has not been observed. Moderate tachycardia and PR interval prolongation can be seen following the infusion; Grade 1-2 infusional reactions can occur in 5% of patients. Efficacy signals (partial responses in colorectal cancer and melanoma; declines in peripheral and bone marrow blasts in AML and CML patients) have been observed.

Based on the preclinical data supporting the use of combined HSP90 and proteasome inhibition, the *in vitro* and *in vivo* anti-myeloma activity of single-agent Compound **1**, and clinical data demonstrating safety of Compound **1**, study was performed for the combination of Compound **1** with or without bortezomib in patients with relapsed/refractory multiple myeloma in a phase 1 trial.

All publications, patent applications, patents, and other documents cited herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples throughout the specification are illustrative only and not intended to be limiting in any way.

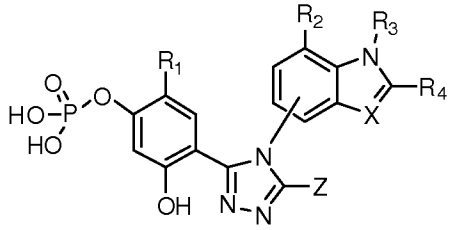
What is claimed is:

1. A composition comprising a proteasome inhibitor and an Hsp90 inhibitor according to the following formulae:



; or

(I)



(Ia)

or a tautomer, or a pharmaceutically acceptable salt thereof, wherein:

Z is OH, SH, or NH_2;

X is CR_4 or N;

R_1 is -H, -OH, -SH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, halo, cyano, nitro, guanidino, a haloalkyl, a heteroalkyl, an alkoxy or cycloalkoxy, a haloalkoxy, $-NR_{10}R_{11}$, $-OR_7$, $-C(O)R_7$, $-C(O)OR_7$, $-C(S)R_7$, $-C(O)SR_7$, $-C(S)SR_7$, $-C(S)OR_7$, $-C(S)NR_{10}R_{11}$, $-C(NR_8)OR_7$, $-C(NR_8)R_7$, $-C(NR_8)NR_{10}R_{11}$, $-C(NR_8)SR_7$, $-OC(O)R_7$, $-OC(O)OR_7$, $-OC(S)OR_7$, $-OC(NR_8)OR_7$, $-SC(O)R_7$, $-SC(O)OR_7$, $-SC(NR_8)OR_7$, $-OC(S)R_7$, $-SC(S)R_7$, $-SC(S)OR_7$, $-OC(O)NR_{10}R_{11}$, $-OC(S)NR_{10}R_{11}$, $-OC(NR_8)NR_{10}R_{11}$, $-SC(O)NR_{10}R_{11}$, $-SC(NR_8)NR_{10}R_{11}$, $-SC(S)NR_{10}R_{11}$, $-OC(NR_8)R_7$, $-SC(NR_8)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$,

$-NR_7C(S)R_7$, $-NR_7C(S)OR_7$, $-NR_7C(NR_8)R_7$, $-NR_7C(O)OR_7$, $-NR_7C(NR_8)OR_7$, $-NR_7C(O)NR_{10}R_{11}$, $-NR_7C(S)NR_{10}R_{11}$, $-NR_7C(NR_8)NR_{10}R_{11}$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-OS(O)_pOR_7$, $-OS(O)_pNR_{10}R_{11}$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, $-NR_7S(O)_pNR_{10}R_{11}$, $-NR_7S(O)_pOR_7$, $-S(O)_pNR_{10}R_{11}$, $-SS(O)_pR_7$, $-SS(O)_pOR_7$, $-SS(O)_pNR_{10}R_{11}$, $-OP(O)(OR_7)_2$, or $-SP(O)(OR_7)_2$;

R_2 is -H, -OH, -SH, $-NR_7H$, $-OR_{15}$, $-SR_{15}$, $-NHR_{15}$, $-O(CH_2)_mOH$, $-O(CH_2)_mSH$, $-O(CH_2)_mNR_7H$, $-S(CH_2)_mOH$, $-S(CH_2)_mSH$, $-S(CH_2)_mNR_7H$, $-OC(O)NR_{10}R_{11}$, $-SC(O)NR_{10}R_{11}$, $-NR_7C(O)NR_{10}R_{11}$, $-OC(O)R_7$, $-SC(O)R_7$, $-NR_7C(O)R_7$, $-OC(O)OR_7$, $-SC(O)OR_7$, $-NR_7C(O)OR_7$, $-OCH_2C(O)R_7$, $-SCH_2C(O)R_7$, $-NR_7CH_2C(O)R_7$, $-OCH_2C(O)OR_7$, $-SCH_2C(O)OR_7$, $-NR_7CH_2C(O)OR_7$, $-OCH_2C(O)NR_{10}R_{11}$, $-SCH_2C(O)NR_{10}R_{11}$, $-NR_7CH_2C(O)NR_{10}R_{11}$, $-OS(O)_pR_7$, $-SS(O)_pR_7$, $-NR_7S(O)_pR_7$, $-OS(O)_pNR_{10}R_{11}$, $-SS(O)_pNR_{10}R_{11}$, $-NR_7S(O)_pNR_{10}R_{11}$, $-OS(O)_pOR_7$, $-SS(O)_pOR_7$, $-NR_7S(O)_pOR_7$, $-OC(S)R_7$, $-SC(S)R_7$, $-NR_7C(S)R_7$, $-OC(S)OR_7$, $-SC(S)OR_7$, $-NR_7C(S)OR_7$, $-OC(S)NR_{10}R_{11}$, $-SC(S)NR_{10}R_{11}$, $-NR_7C(S)NR_{10}R_{11}$, $-OC(NR_8)R_7$, $-SC(NR_8)R_7$, $-NR_7C(NR_8)R_7$, $-OC(NR_8)OR_7$, $-SC(NR_8)OR_7$, $-NR_7C(NR_8)OR_7$, $-OC(NR_8)NR_{10}R_{11}$, $-SC(NR_8)NR_{10}R_{11}$, or $-NR_7C(NR_8)NR_{10}R_{11}$;

R_3 is -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, hydroxyalkyl, alkoxyalkyl, a haloalkyl, a heteroalkyl, $-C(O)R_7$, $-(CH_2)_mC(O)OR_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-S(O)_pR_7$, $-S(O)_pOR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_4 is -H, -OH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, hydroxyalkyl, alkoxyalkyl, halo, cyano, nitro, guanidino, a haloalkyl, a heteroalkyl, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, $-S(O)_pNR_{10}R_{11}$, or R_{43} and R_{44} taken together with the carbon atoms to which they are attached form an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heterocyclyl, or an optionally substituted heteroaryl;

R_7 and R_8, for each occurrence, are, independently, -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

R_{10} and R_{11}, for each occurrence, are independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R_{10} and R_{11}, taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

R_{15}, for each occurrence, is independently, a lower alkyl;
p, for each occurrence, is, independently, 1 or 2; and
m, for each occurrence, is independently, 1, 2, 3, or 4.

2. The composition of claim 1, wherein the Hsp90 inhibitor is selected from the group consisting of:

3-(2,4-dihydroxyphenyl)-4-(1-ethyl-indol-4-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxyphenyl)-4-(1-isopropyl-indol-4-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxyphenyl)-4-(indol-4-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxyphenyl)-4-(1-methoxyethyl-indol-4-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-isopropyl-indol-4-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxyphenyl)-4-(1-dimethylcarbamoyl-indol-4-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-propyl-indol-4-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1,2,3-trimethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(2,3-dimethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-acetyl-2,3-dimethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,

3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-propyl-2,3-dimethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-n-butyl-indol-4-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-n-pentyl-indol-4-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-n-hexyl-indol-4-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxy-5-cyclopropyl-phenyl)-4-(1-(1-methylcyclopropyl)-indol-4-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxy-5-cyclopropyl-phenyl)-4-(1,2,3-trimethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-methyl-3-ethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1-methyl-3-isopropyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1,2-dimethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(N-methyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxy-5-cyclopropyl-phenyl)-4-(1,3-dimethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxy-5-cyclopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1H-indol-5-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxy-5-ethyl-phenyl)-4-(1,2-dimethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,
3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-ethyl-indol-5-yl)-5-mercapto-[1,2,4]triazole, and
3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-propyl-indol-5-yl)-5-mercapto-[1,2,4]triazole,
5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate,
sodium 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl phosphate,

2-(3,4-dimethoxyphenethyl)-5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)phenyl dihydrogen phosphate,
5-hydroxy-2-isopropyl-4-(5-mercapto-4-(4-methoxybenzyl)-4H-1,2,4-triazol-3-yl)phenyl dihydrogen phosphate,
5-hydroxy-4-(5-hydroxy-4-(4-methoxybenzyl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate,
4-(4-(1,3-dimethyl-1H-indol-5-yl)-5-hydroxy-4H-1,2,4-triazol-3-yl)-2-ethyl-5-hydroxyphenyl dihydrogen phosphate,
or a tautomer, or a pharmaceutically acceptable salt thereof.

3. The composition of claim 1, wherein the Hsp90 inhibitor is 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4] triazole or a tautomer or a pharmaceutically acceptable salt thereof.

4. The compositionof claim 1, wherein the Hsp90 inhibitor is 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate, or a tautomer, or a pharmaceutically acceptable salt thereof.

5. The composition of claim 1, wherein the proteasome inhibitor is epigallocatechin-3-gallate, salinosporamide A, carfilzomib, or bortezomib.

6. The composition of claim 1, wherein the Hsp90 inhibitor is 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4] triazole, or a tautomer or a pharmaceutically acceptable salt thereof, and the proteasome inhibitor is bortezomib.

7. The composition of claim 1, wherein the Hsp90 inhibitor is 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4] triazole, or a tautomer or a pharmaceutically acceptable salt thereof, and the proteasome inhibitor is carfilzomib.

8. The composition of claim 1, wherein the Hsp90 inhibitor is 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate, or a tautomer, or a pharmaceutically acceptable salt thereof, and the proteasome inhibitor is bortezomib.

9. The composition of claim 1, wherein the Hsp90 inhibitor is 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate, or a tautomer, or a pharmaceutically acceptable salt thereof, and the proteasome inhibitor is carfilzomib.

10. A method of treating a proliferative disorder in a subject, comprising administering to a subject an effective amount of the composition of claim 1.

11. The method of claim 10, wherein the proliferative disorder is cancer.

12. The method of claim 11, wherein the cancer is colorectal cancer, colon cancer, head and neck cancer, breast cancer, non-small cell lung cancer, prostate cancer, renal cell carcinoma, pancreatic cancer, ovarian cancer, peritoneal cancer, rectal cancer, kidney cancer, Hodgkin's lymphoma, bladder cancer, hepatocellular cancer, gastric cancer, squamous cell carcinoma, cervical cancer, uterine cancer, chronic lymphocytic leukemia, lymphoma, myeloma, multiple myeloma, solid tumor, hematological tumor, or gastrointestinal stromal tumor (GIST).

13. The method of claim 12, wherein the cancer is non-small cell lung cancer, colon cancer, multiple myeloma, or head and neck cancer.

14. The method of claim 13, wherein the cancer is metastatic non-small cell lung cancer.

15. The method of claim 13, wherein the cancer is colon cancer.

16. The method of claim 13, wherein the cancer is head and neck cancer.

17. The method of claim 13, wherein the cancer is multiple myeloma.

18. The method of claim 17, wherein the multiple myeloma is relapsed or refractory.

19. The method of any one of claims 10-18, wherein the subject is human.

20. A method for treating a subject with cancer, comprising administering to the subject an effective amount of a proteasome inhibitor and an effective amount of 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole, or a tautomer, or a pharmaceutically acceptable salt thereof, wherein the cancer is colorectal cancer, colon cancer, head and neck cancer, breast cancer, non-small cell lung cancer, prostate cancer, renal cell carcinoma, pancreatic cancer, ovarian cancer, peritoneal cancer, rectal cancer, kidney cancer, Hodgkin's lymphoma, bladder cancer, hepatocellular cancer, gastric cancer, squamous cell carcinoma, cervical cancer, uterine cancer, chronic lymphocytic leukemia, lymphoma, myeloma, multiple myeloma, solid tumor, hematological tumor, or gastrointestinal stromal tumor (GIST).

21. The method of claim 20, wherein the proteasome inhibitor is bortezomib or carfilzomib.

22. A method for treating a subject with cancer, comprising administering to the subject an effective amount of a proteasome inhibitor and an effective amount of 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate dihydrogen phosphate, or a tautomer, or a pharmaceutically acceptable salt thereof, wherein the cancer is colorectal cancer, colon cancer, head and neck cancer, breast cancer, non-small cell lung cancer, prostate cancer, renal cell carcinoma, pancreatic cancer, ovarian cancer, peritoneal cancer, rectal cancer, kidney cancer, Hodgkin's lymphoma, bladder cancer, hepatocellular cancer, gastric cancer, squamous cell carcinoma, cervical cancer, uterine cancer, chronic lymphocytic leukemia, lymphoma, myeloma, multiple myeloma, solid tumor, hematological tumor, or gastrointestinal stromal tumor (GIST).

23. The method of claim 22, wherein the proteasome inhibitor is bortezomib or carfilzomib.

24. A method of inhibiting the growth of a cancer or tumor cell in a subject, the method comprising the steps of: (a) contacting the cell with an effective amount of a compound of formulae (I) or (Ia) as defined in claim 1, and (b) exposing the cell to an effective amount of a proteasome inhibitor, wherein the proteasome inhibitor is selected from the group consisting of epigallocatechin-3-gallate, salinosporamide A, carfilzomib, or bortezomib.

25. The method of claim 24, wherein the compound is 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4] triazole, or a tautomer or a pharmaceutically acceptable salt thereof and the proteasome inhibitor is bortezomib or carfilzomib.

26. The method of claim 24, wherein the compound is 5-hydroxy-4-(5-hydroxy-4-(1-methyl-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-2-isopropylphenyl dihydrogen phosphate, or a tautomer, or a pharmaceutically acceptable salt thereof, and the proteasome inhibitor is bortezomib or carfilzomib.

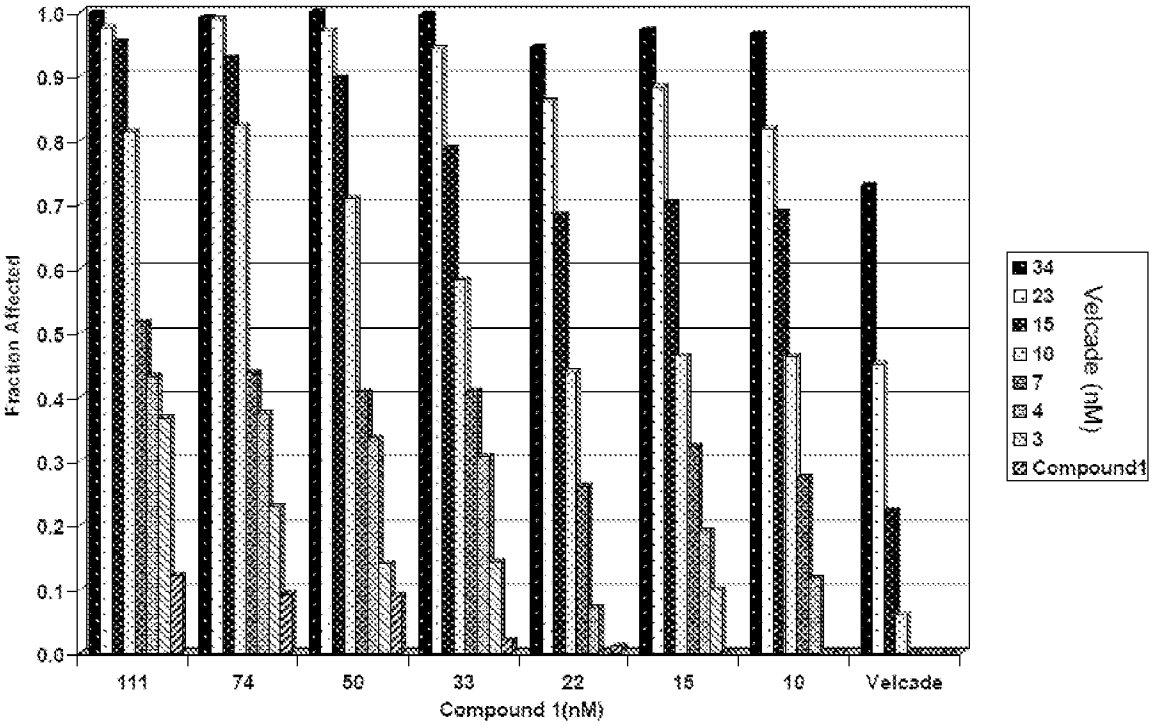

Fraction Affected
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
111
74
50
33
22
15
10
Velcade
Compound 1(nM)
34
23
15
10
7
4
3
Compound1
Velcade (nM)

Fig. 1

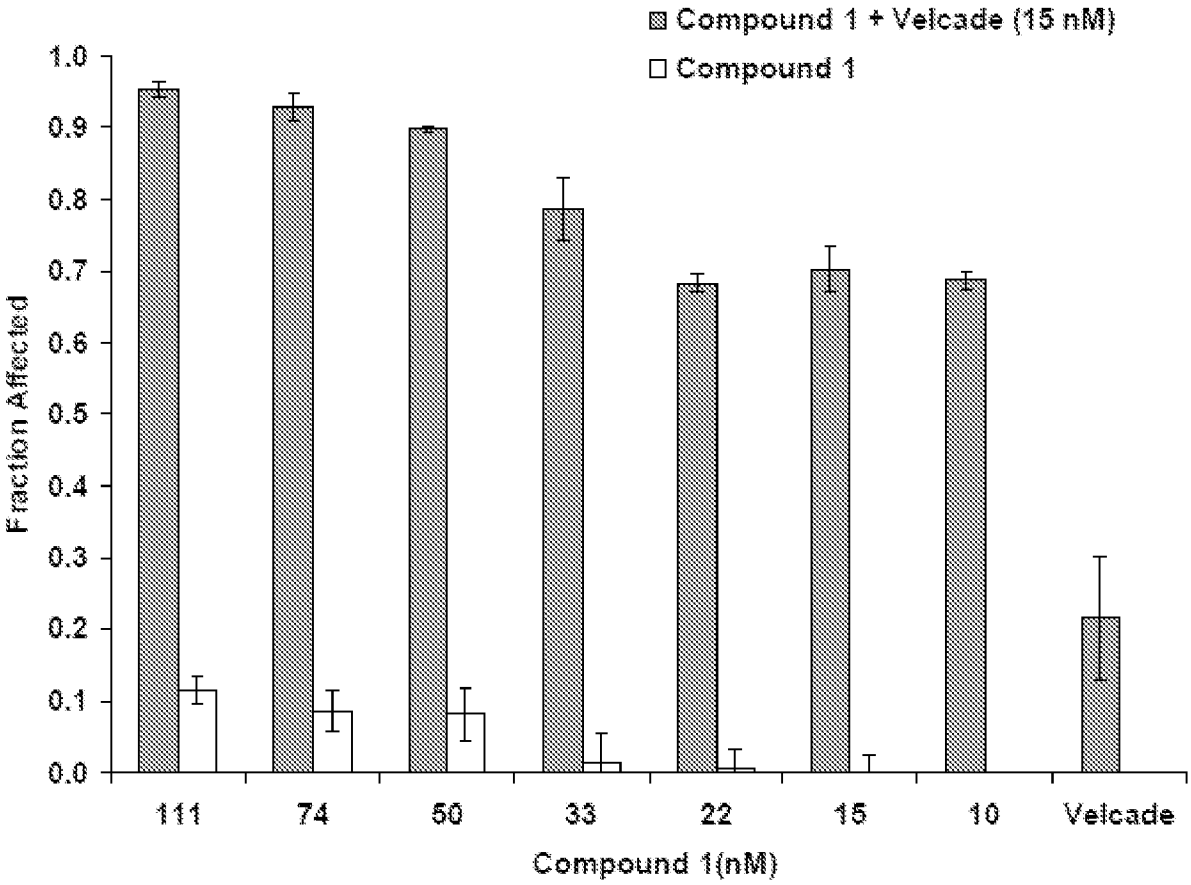

Compound 1 + Velcade (15 nM)
Compound 1
Fraction Affected
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
111
74
50
33
22
15
10
Velcade
Compound 1(nM)

Fig. 2

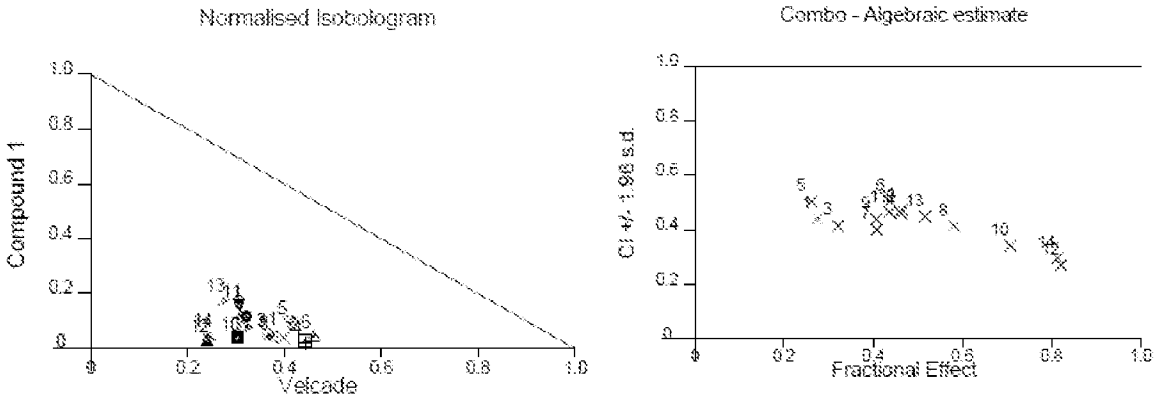

Normalised Isobologram
Compound 1
Veicade
0
0.2
0.4
0.6
0.8
1.0
Combo - Algebraic estimate
CI +/- 1.96 s.d.
Fractional Effect

Fig. 3

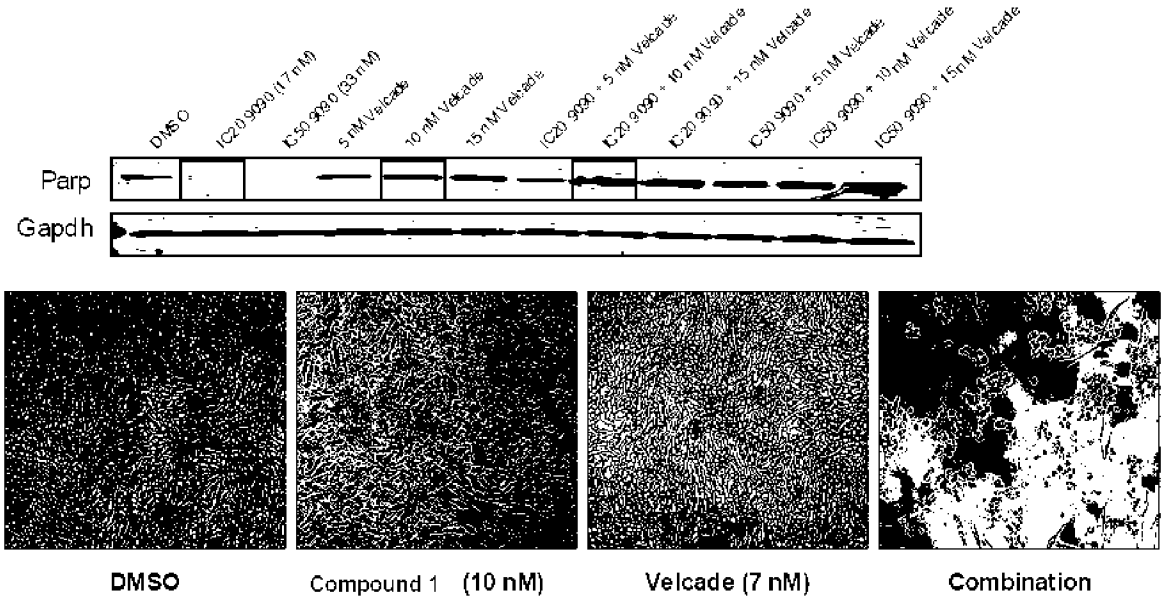
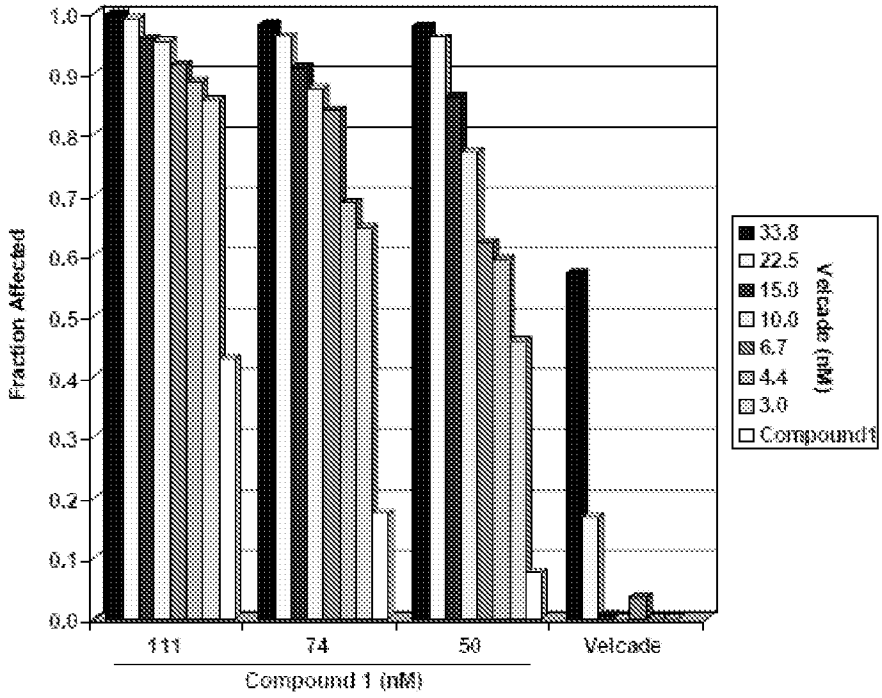

DMSO
IC20 9930 (7 nM)
IC50 9930 (33 nM)
5 nM Velcade
10 nM Velcade
15 nM Velcade
(C20) 9930 + 5 nM Velcade
IC20 9930 + 10 nM Velcade
IC20 9930 + 15 nM Velcade
(C50) 9930 + 5nM Velcade
(C50) 9930 + 10 nM Velcade
(C50) 9930 + 15nM Velcade
Parp
Gapdh
DMSO
Compound 1 (10 nM)
Velcade (7 nM)
Combination

Fig. 4


Fraction Affected
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0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
111
74
50
Velcade
Compound 1 (nM)
33.8
22.5
15.0
10.0
6.7
4.4
3.0
Compound 1
Velcade (nM)

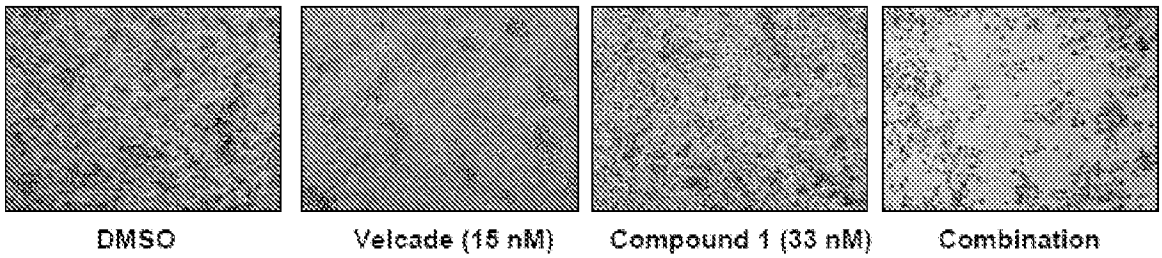
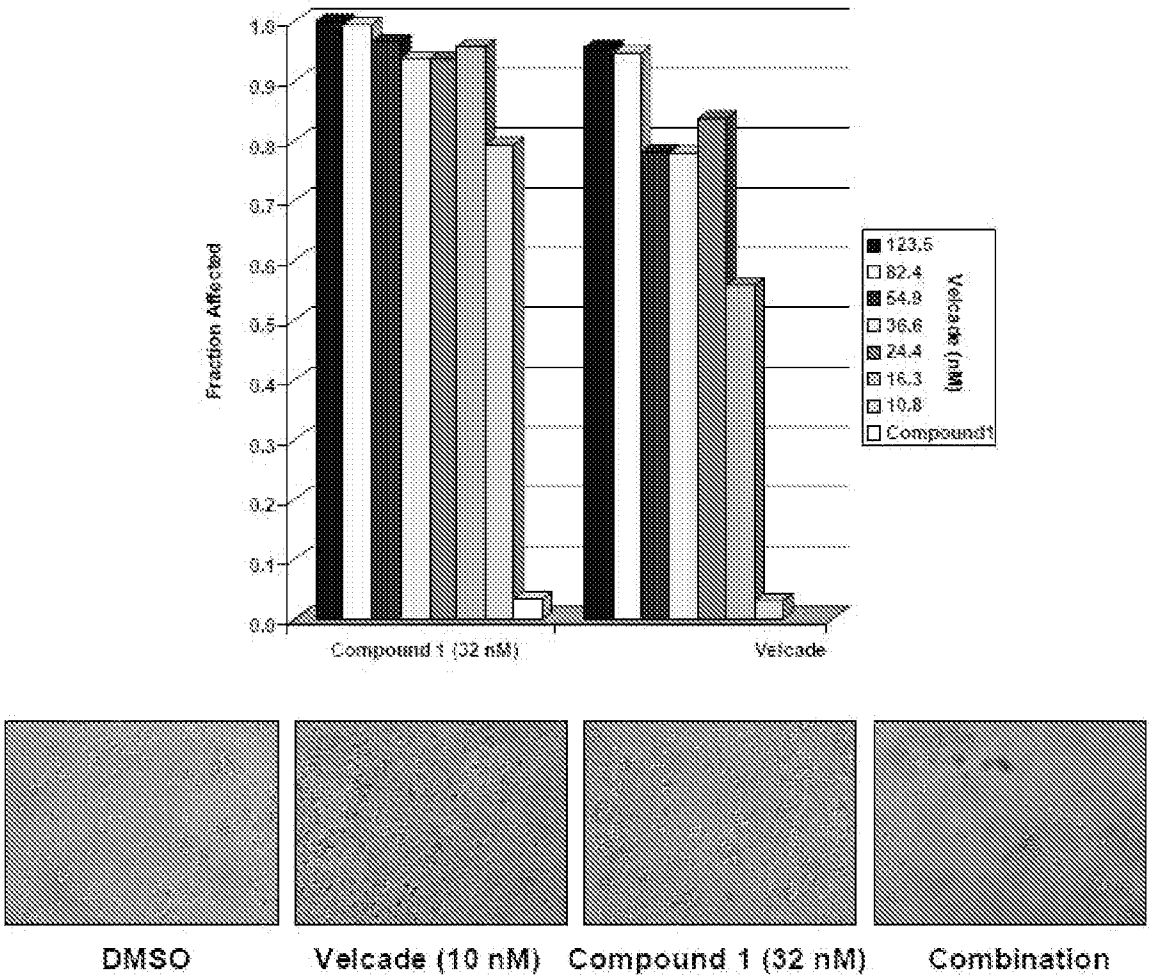

DMSO
Velcade (15 nM)
Compound 1 (33 nM)
Combination

Fig. 5


Fraction Affected
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0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Compound 1 (32 nM)
Velcade
Velcade (nM)
123.5
82.4
54.8
36.6
24.4
16.3
10.8
Compound 1
DMSO
Velcade (10 nM)
Compound 1 (32 nM)
Combination

Fig. 6

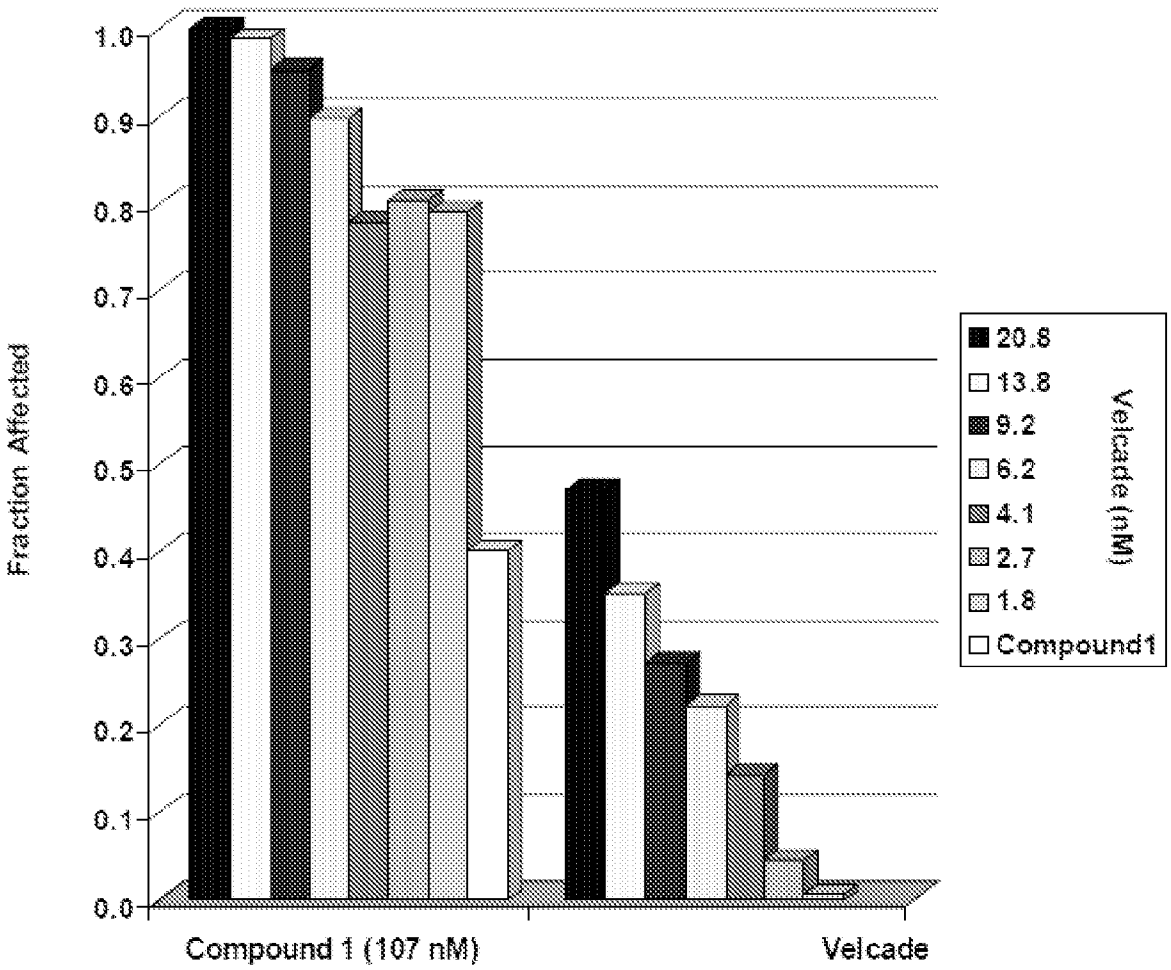
Fraction Affected
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Compound 1 (107 nM)
Velcade
20.8
13.8
9.2
6.2
4.1
2.7
1.8
Compound1
Velcade (nM)

Fig. 7

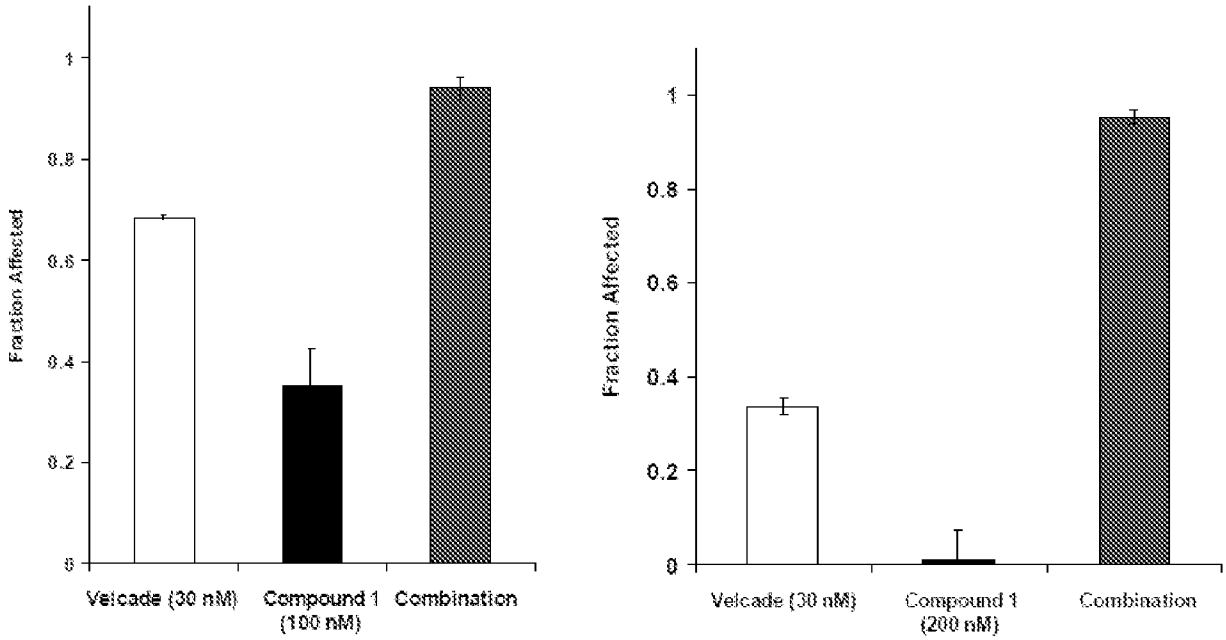
Fraction Affected
1
0.8
0.6
0.4
0.2
0
Velcade (30 nM)
Compound 1 (100 nM)
Combination
Fraction Affected
1
0.8
0.6
0.4
0.2
0
Velcade (30 nM)
Compound 1 (200 nM)
Combination

Fig. 8

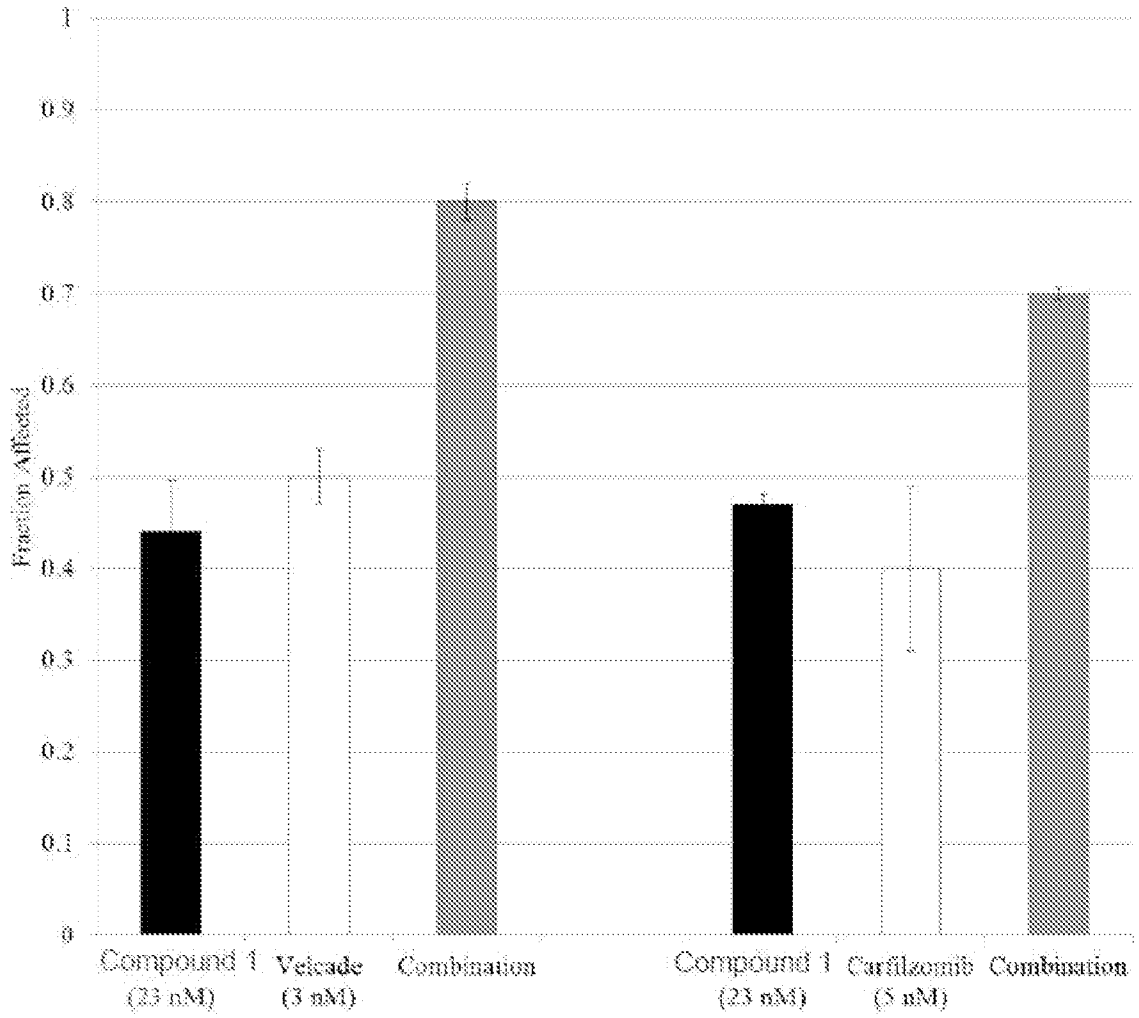
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Fraction Affected
Compound 1 (23 nM)
Velcade (3 nM)
Combination
Compound 1 (23 nM)
Carfilzomib (5 nM)
Combination

Fig. 9

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/020722

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4196 A61K31/5377 A61K31/675 A61K31/69 A61K45/06
A61P35/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2011/146803 A1 (SYNTA PHARMACEUTICALS CORP [US]; VUKOVI VOJO [US]) 24 November 2011 (2011-11-24) claims 1-6, 19-20 pages 33-34	1-26
X,P	WO 2011/149824 A1 (SYNTA PHARMACEUTICALS CORP [US]; BLACKMAN RONALD K [US]; FOLEY KEVIN P) 1 December 2011 (2011-12-01) claims 1-29	1-26
X	WO 2006/055760 A1 (SYNTA PHARMACEUTICALS CORP [US]; YING WEIWEN [US]; JAMES DAVID [US]; Z) 26 May 2006 (2006-05-26)	1-4, 10-20,22
Y	claims 1, 16-17, 25-27, 40, 46-47, 51, 53 pages 29-31 pages 127-134	5-7,21, 24-26

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 February 2012	21/02/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Renard, Delphine

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 2009/023211 A1 (SYNTA PHARMACEUTICALS CORP [US]; YING WEIWEN [US]; SUN LIJUN [US]; KOY) 19 February 2009 (2009-02-19) compound 3 page 99, line 2 - page 108, line 3 claims 1, 80, 86, 87 -----	1,2,4, 10-19,22 5,8,9, 23-26
Y	YAO QING ET AL: "The Hsp90 inhibitor 17-AAG sensitizes human leukemia cells to proteasome inhibitor PS-341", BLOOD, AMERICAN SOCIETY OF HEMATOLOGY, US, vol. 102, no. 11, 16 November 2003 (2003-11-16), pages 622A-623A, XP009113885, ISSN: 0006-4971 the whole document -----	1-26
Y	G. ROUE ET AL: "The Hsp90 inhibitor IPI-504 overcomes bortezomib resistance in mantle cell lymphoma in vitro and in vivo by down-regulation of the prosurvival ER chaperone BiP/Grp78", BLOOD, vol. 117, no. 4, 24 November 2010 (2010-11-24), pages 1270-1279, XP55018931, ISSN: 0006-4971, DOI: 10.1182/blood-2010-04-278853 pages 1271, 12 abstract -----	1-26
Y	LI Y ET AL: "New developments in Hsp90 inhibitors as anti-cancer therapeutics: Mechanisms, clinical perspective and more potential", DRUG RESISTANCE UPDATES, CHURCHILL LIVINGSTONE, EDINBURGH, GB, vol. 12, no. 1-2, 1 February 2009 (2009-02-01), pages 17-27, XP026070000, ISSN: 1368-7646, DOI: 10.1016/J.DRUP.2008.12.002 [retrieved on 2009-03-27] page 20; figure 1; compounds epigallocatechin-3-gallate Hsp90 inhibitors and cancer treatment; pages 22-23 ----- -/--	1-5, 10-20, 22,24

1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HUANJIE YANG ET AL: "Clinical development of novel proteasome inhibitors for cancer treatment", EXPERT OPINION ON INVESTIGATIONAL DRUGS, INFORMA HEALTHCARE, UNITED KINGDOM, vol. 18, no. 7, 1 July 2009 (2009-07-01), pages 957-971, XP002665665, ISSN: 1744-7658, DOI: 10.1517/13543780903002074 figure 3 page 962, left-hand column -----	1-26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/020722

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011146803 A1	24-11-2011	NONE	
WO 2011149824 A1	01-12-2011	NONE	
WO 2006055760 A1	26-05-2006	AU 2005306484 A1	26-05-2006
		BR PI0518315 A2	11-11-2008
		CA 2586612 A1	26-05-2006
		CN 101072759 A	14-11-2007
		EP 1817295 A1	15-08-2007
		EP 2295416 A2	16-03-2011
		EP 2298748 A2	23-03-2011
		JP 2008520702 A	19-06-2008
		KR 20070086353 A	27-08-2007
		NZ 555158 A	30-09-2010
		US 2006167070 A1	27-07-2006
		US 2011009397 A1	13-01-2011
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