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(54) Title: INHIBITORS OF MITOTIC KINESIN

(57) **Abstract:** The present invention relates to compounds and methods useful as inhibitors of KSP for the treatment or prevention of cellular proliferative diseases.

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INHIBITORS OF MITOTIC KINESIN

This application claims the benefit of priority of United States provisional applications No. 60/699,521, filed July 15, 2005 and No. 60/761,613, filed January 24, 2006, both of which are hereby incorporated by reference as if written herein in their entirety.

FIELD OF THE INVENTION

The present invention is directed to new heterocyclic compounds and compositions and their application as pharmaceuticals for the treatment of disease. Methods of inhibition of mitotic kinesin KSP activity in a human or animal subject are also provided for the treatment of cellular proliferative diseases, such as cancer, hyperplasias, restenosis, cardiac hypertrophy, immune disorders and inflammation.

BACKGROUND OF THE INVENTION

The mitotic spindle is responsible for distribution of replicate copies of the genome to each of the two daughter cells that result from cell division. Disruption of the mitotic spindle can inhibit cell division, and induce cell death. Microtubules are the primary structural element of the mitotic spindle; they are the site of action of certain existing therapeutic agents used to treat cancer, such as taxanes and vinca alkaloids. Microtubules, however, exist as elements in other types of cellular structures (including tracks for intracellular transport in nerve processes). The therapeutic targeting of microtubules can, therefore, modulate processes in addition to cellular proliferation, leading to side effects that limit the usefulness of such drugs.

Improvement in the specificity of agents used to treat cancer is of considerable interest because of the therapeutic benefits that would be realized if the side effects associated with the administration of these agents could be reduced. Dramatic improvements in the treatment of cancer have been associated with identification of therapeutic agents acting through novel mechanisms. Examples of this include not only the taxanes, but also the camptothecin class of topoisomerase I inhibitors.

One novel anti-proliferative mechanism entails selective inhibition of mitotic kinesins, enzymes that are essential for assembly and function of the mitotic spindle, but are not generally part of other microtubule structures, such as in nerve processes. See, e.g., Guidebook to the Cytoskeletal and Motor Proteins, Kreis and Vale, Eds., pp. 389-394 (Oxford University Press 1999). Mitotic kinesins play essential roles during all phases of mitosis. These enzymes are "molecular motors" that transform energy released by hydrolysis of ATP into mechanical force that drives the directional movement of cellular cargoes along microtubules. The catalytic domain sufficient for this task is a compact structure of approximately 340 amino acids. During mitosis, kinesins organize microtubules into the bipolar structure that is the mitotic spindle. Kinesins mediate movement of chromosomes along spindle microtubules, as well as structural changes in the mitotic spindle associated with specific phases of mitosis. Experimental perturbation of mitotic kinesin function causes malformation or dysfunction of the mitotic spindle, frequently resulting in cell cycle arrest and cell death. Mitotic kinesins are attractive targets for the discovery and development of novel anti-mitotic chemotherapeutics.

Among the mitotic kinesins that have been identified is KSP. KSP belongs to an evolutionarily conserved kinesin subfamily of plus end-directed microtubule motors that assemble into bipolar homotetramers consisting of antiparallel homodimers. During mitosis, KSP associates with microtubules of the mitotic spindle. Microinjection of antibodies directed against KSP into human cells prevents spindle pole separation during prometaphase, giving rise to monopolar spindles and causing mitotic arrest and induction of programmed cell death. KSP and related kinesins in other, non-human, organisms, bundle antiparallel microtubules and slide them relative to one another, thus forcing the two spindle poles apart. KSP may also mediate in anaphase B spindle elongation and focusing of microtubules at the spindle pole.

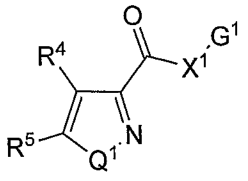
Human KSP (also termed HsEg5 or EG-5) has been described [Blangy, et al., Cell, 83:1159-69 (1995); Whitehead, et al., Arthritis Rheum., 39:1635-42 (1996); Galgio et al., J. Cell Biol., 135:339-414 (1996); Blangy, et al., J Biol. Chem., 272:19418-24 (1997); Blangy, et al., Cell Motil. Cytoskeleton, 40:174-82 (1998); Whitehead and Rattner, J. Cell Sci., 111:2551-61 (1998); Kaiser, et al., JBC 274:18925-31 (1999); GenBank accession numbers: X85137, NM004523 and U37426], and a fragment of the KSP gene (TRIP5) has been described [Lee, et al., Mol. Endocrinol., 9:243-54 (1995); GenBank accession number L40372]. Xenopus KSP homologs (Eg5), as well as Drosophila KLP61 F/KRP1 30 have been reported.

Recently, certain substituted quinazolinones have been described as inhibitors of mitotic kinesins for the treatment of cellular proliferative diseases (WO 01/30768 and WO 01/98278). It is an object of the present invention to provide novel inhibitors of mitotic kinesins such as KSP (particularly human KSP).

SUMMARY OF THE INVENTION

Novel compounds and pharmaceutical compositions that treat cellular proliferative diseases by inhibiting KSP have been found together with methods of synthesizing and using the compounds including methods for inhibiting or modulating KSP in a patient by administering the compounds.

The present invention discloses a class of compounds, useful in treating KSP-mediated disorders and conditions, defined by structural Formula I:



(I)

or a salt, ester, or prodrug thereof, wherein:

X^1 is selected from the group consisting of -O-, -S-, -N(R^3)-, -O[C(R^1)(R^2)]$_m$-, and -[C(R^1)(R^2)]$_m$-;

m is an integer from 1 to 5;

R^1 and R^2 are independently selected from the group consisting of hydrogen, lower acyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxyalkyl, lower alkylaminoalkyl, lower alkylcarbonyl, lower alkylthio, amido, lower aminoalkyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, lower cycloalkyl, lower cycloalkylalkyl, lower haloalkyl, lower perhaloalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, and heterocycloalkyl, any of which may be optionally substituted; or R^1 and R^2, together with the atoms to which they are attached, may be joined to form an optionally substituted lower cycloalkyl moiety;

R^3 is selected from the group consisting of hydrogen, lower acyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxyalkyl, lower alkylaminoalkyl, lower alkylcarbonyl, amido, lower aminoalkyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, lower cycloalkyl, lower cycloalkylalkyl, lower haloalkyl, lower perhaloalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, and heterocycloalkyl, any of which may be optionally substituted;

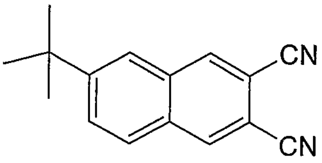
G^1 is selected from the group consisting of aryl, heteroaryl, heterocycloalkyl, and cycloalkyl, any of which may be optionally substituted;

R^4 and R^5 are independently selected from the group consisting of hydrogen, halogen, cyano, nitro, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower acylamino, lower alkoxycarbonyl, lower alkoxycarbonylalkyl, lower alkylaminocarbonyl, lower dialkylaminocarbonyl, lower alkylcarbonyl, lower alkylsulfonyl, lower alkylthio, lower alkylthioalkyl, lower aminoalkyl, carbamoyl, lower aminocarbonylalkyl, aralkoxycarbonyl, aralkanoyl, arylcarbonyl, carboxy, O-carbamyl, N-carbamyl, lower haloalkyl, lower perhaloalkyl, lower haloalkoxy, aryl, arylalkyl, arylalkenyl, arylalkynyl, heterocycloalkyl, heteroaryl, and heteroaralkyl, any of which may be optionally substituted; or R^4 and R^5, together with the atoms to which they are attached, may be joined to form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety, any of which may be substituted;

Q^1 is selected from the group consisting of O, N(R^6), and S; and

R^6 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower alkoxycarbonyl, lower alkoxycarbonylalkyl, lower alkylaminocarbonyl, lower dialkylaminocarbonyl, lower alkylcarbonyl, lower alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, lower aminoalkyl, carbamoyl, lower aminocarbonylalkyl, aralkoxycarbonyl, aralkanoyl, arylcarbonyl, carbamyl, lower haloalkyl, lower perhaloalkyl, lower haloalkoxy, aryl, arylalkyl, arylalkenyl, arylalkynyl, heterocycloalkyl, heteroaryl, and heteroaralkyl, any of which may be optionally substituted.

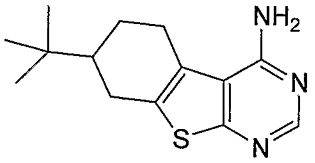
The present invention discloses a compound, useful in treating KSP-mediated disorders and conditions, defined as Example 4:



(4)

or a salt, ester, or prodrug thereof.

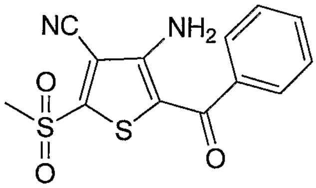
According to another embodiment, disclosed is a compound, useful in treating KSP-mediated disorders and conditions, defined as Example 5:



(5)

or a salt, ester, or prodrug thereof.

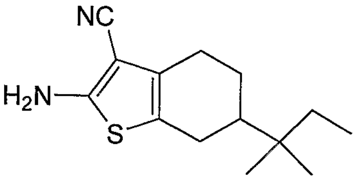
The present invention also discloses a compound, useful in treating KSP-mediated disorders and conditions, defined as Example 6:



(6)

or a salt, ester, or prodrug thereof.

According to another embodiment of the invention, disclosed is a compound, useful in treating KSP-mediated disorders and conditions, defined as Example 7:



(7)

or a salt, ester, or prodrug thereof.

Compounds according to the present invention possess useful KSPinhibiting or modulating activity, and may be used in the treatment or prophylaxis of a disease or condition in which KSP plays an active role. Thus, in broad aspect, the present invention also provides pharmaceutical compositions comprising one or more compounds of the present invention together with a pharmaceutically acceptable carrier, as well as methods of making and using the compounds and compositions. In certain embodiments, the present invention provides methods for inhibiting or modulating KSP. In other embodiments, the present invention provides methods for treating a KSP-mediated disorder in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of a compound or composition according to the present invention. The present invention also contemplates the use of compounds disclosed herein for use in the manufacture of a medicament for the treatment of a disease or condition ameliorated by the inhibition or modulation of KSP activity.

DETAILED DESCRIPTION OF THE INVENTION

In certain embodiments, the compounds of the present invention have structural Formula I, wherein:

X^1 is selected from the group consisting of -O-, -S-, and -N(R^3)-, and -[C(R^1)(R^2)]$_m$-;

m is 1;

R^1 and R^2 are independently selected from the group consisting of hydrogen, lower alkyl, aryl, arylalkyl, lower cycloalkyl, and lower cycloalkylalkyl, any of which may be optionally substituted; or R^1 and R^2, together with the atoms to which they are attached, may be joined to form an optionally substituted lower cycloalkyl moiety;

R^3 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, arylalkyl, lower cycloalkyl, lower cycloalkylalkyl, heteroaryl, heteroarylalkyl, and heterocycloalkyl, any of which may be optionally substituted;

G^1 is selected from the group consisting of aryl and heteroaryl, either of which may be optionally substituted;

R^4 and R^5 are independently selected from the group consisting of hydrogen, halogen, cyano, nitro, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower alkoxycarbonyl, lower alkoxycarbonylalkyl, lower alkylsulfonyl, lower alkylthio, carbamoyl, lower aminocarbonylalkyl, carboxy, lower perhaloalkyl, lower haloalkoxy, aryl, arylalkyl, heterocycloalkyl, heteroaryl,and heteroaralkyl, any of which may be optionally substituted; or R^4 and R^5, together with the atoms to which they are attached, may be joined to form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety, any of which may be substituted;

Q^1 is N(R^6); and

R^6 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, loweralkynyl, lower alkoxycarbonylalkyl, lower alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, arylcarbonyl, lower perhaloalkyl, aryl, arylalkyl, heterocycloalkyl, heteroaryl, and heteroaralkyl, any of which may be optionally substituted.

In further embodiments, the compounds of the present invention have structural Formula I, wherein:

X^1 is -S-;

G^1 is optionally substituted aryl;

R^4 and R^5 are independently selected from the group consisting of halogen, nitro, lower alkyl, lower perhaloalkyl, aryl, arylalkyl, heterocycloalkyl, heteroaryl, and heteroaralkyl, any of which may be optionally substituted;

Q^1 is $N(R^6)$; and

R^6 is selected from the group consisting of hydrogen, lower alkyl, lower alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryl, and heteroaryl, any of which may be optionally substituted.

In yet further embodiments, the compounds of the present invention have structural Formula I, wherein:

X^1 is -S-;

G^1 is selected from the group consisting of 4-bromophenyl, 4-methylphenyl, and 2,4-difluorophenyl;

R^4 is nitro;

R^5 is optionally substituted lower alkyl;

Q^1 is $N(R^6)$; and

R^6 is selected from optionally substituted lower alkyl and optionally substituted aryl.

In yet further embodiments, the compounds of the present invention have structural Formula I, wherein:

X^1 is -S-;

G^1 is selected from the group consisting of 4-bromophenyl, 4-methylphenyl, and 2,4-difluorophenyl;

R^4 is nitro;

R^5 is methyl;

Q^1 is $N(R^6)$; and

R^6 is methyl.

In another embodiment, the invention provides for compounds selected from the Examples 1 to 7.

As used herein, the terms below have the meanings indicated.

The term “acyl,” as used herein, alone or in combination, refers to a carbonyl attached to an alkenyl, alkyl, aryl, cycloalkyl, heteroaryl, heterocycle, or any other moiety were the atom attached to the carbonyl is carbon. An “acetyl” group refers to a $-C(O)CH_3$ group. Examples of acyl groups include formyl, alkanoyl and aroyl radicals.

The term "acylamino" embraces an amino radical substituted with an acyl group. An example of an "acylamino" radical is acetylamino ($CH_3C(O)NH-$).

The term “alkenyl,” as used herein, alone or in combination, refers to a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing from 2 to 20, preferably 2 to 6, carbon atoms. Alkenylene refers to a carbon-carbon double bond system attached at two or more positions such as ethenylene [(–CH=CH–),(–C::C–)]. Examples of suitable alkenyl radicals include ethenyl, propenyl, 2-methylpropenyl, 1,4-butadienyl and the like.

The term “alkoxy,” as used herein, alone or in combination, refers to an alkyl ether radical, wherein the term alkyl is as defined below. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

The term “alkoxyalkoxy,” as used herein, alone or in combination, refers to one or more alkoxy groups attached to the parent molecular moiety through another alkoxy group. Examples include ethoxyethoxy, methoxypropoxyethoxy, ethoxypentoxyethoxyethoxy and the like.

The term “alkoxyalkyl,” as used herein, alone or in combination, refers to an alkoxy group attached to the parent molecular moiety through an alkyl group. The term "alkoxyalkyl" also embraces alkoxyalkyl groups having one or more alkoxy groups attached to the alkyl group, that is, to form monoalkoxyalkyl and dialkoxyalkyl groups.

The term “alkoxycarbonyl,” as used herein, alone or in combination, refers to an alkoxy group attached to the parent molecular moiety through a carbonyl group. Examples of such "alkoxycarbonyl" groups include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl.

The term "alkoxycarbonylalkyl" embraces radicals having "alkoxycarbonyl", as defined above substituted to an alkyl radical. In certain embodiments, alkoxycarbonylalkyl radicals are "lower alkoxycarbonylalkyl" having lower alkoxycarbonyl radicals as defined above attached to one to six carbon atoms. Examples of such lower alkoxycarbonylalkyl radicals include methoxycarbonylmethyl.

The term “alkyl,” as used herein, alone or in combination, refers to a straight-chain or branched-chain alkyl radical containing from 1 to and including 20, preferably 1 to 10, and more preferably 1 to 6, carbon atoms. Alkyl groups may be optionally substituted as defined herein. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, noyl and the like. The term “alkylene,” as used herein, alone or in combination, refers to a saturated aliphatic group derived from a straight or branched chain saturated hydrocarbon attached at two or more positions, such as methylene ($-CH_2-$).

The term “alkylamino,” as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through an amino group. Suitable alkylamino groups may be mono- or dialkylated, forming groups such as, for example, N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino and the like.

The term "alkylaminocarbonyl" as used herein, alone or in combination, refers to an alkylamino group attached to the parent molecular moiety through a carbonyl group. Examples of such radicals include N-methylaminocarbonyl and N,N-dimethylcarbonyl.

The term “alkylcarbonyl” and “alkanoyl,” as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through a carbonyl group. Examples of such groups include methylcarbonyl and ethylcarbonyl.

The term “alkylidene,” as used herein, alone or in combination, refers to an alkenyl group in which one carbon atom of the carbon-carbon double bond belongs to the moiety to which the alkenyl group is attached.

The term “alkylsulfinyl,” as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through a sulfinyl group. Examples of alkylsulfinyl groups include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl.

The term “alkylsulfonyl,” as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through a sulfonyl group. Examples of alkylsulfinyl groups include methanesulfonyl, ethanesulfonyl, tert-butanesulfonyl, and the like.

The term “alkylthio,” as used herein, alone or in combination, refers to an alkyl thioether (R–S–) radical wherein the term alkyl is as defined above. Examples of suitable alkyl thioether radicals include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, iso-butylthio, sec-butylthio, tert-butylthio, ethoxyethylthio, methoxypropoxyethylthio, ethoxypentoxyethoxyethylthio and the like.

The term "alkylthioalkyl" embraces alkylthio radicals attached to an alkyl radical. Alkylthioalkyl radicals include "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms and an alkylthio radical as described above. Examples of such radicals include methylthiomethyl.

The term “alkynyl,” as used herein, alone or in combination, refers to a straight-chain or branched chain hydrocarbon radical having one or more triple bonds and containing from 2 to 20, preferably from 2 to 6, more preferably from 2 to 4, carbon atoms. “Alkynylene” refers to a carbon-carbon triple bond attached at two positions such as ethynylene (–C:::C–, –C≡C–). Examples of alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl, and the like.

The term “amido,” as used herein, alone or in combination, refers to an amino group as described below attached to the parent molecular moiety through a carbonyl group. The term “C-amido” as used herein, alone or in combination, refers to a -C(=O)-NR$_2$ group with R as defined herein. The term “N-amido” as used herein, alone or in combination, refers to a RC(=O)NH- group, with R as defined herein.

The term “amino,” as used herein, alone or in combination, refers to —NRR$'$, wherein R and R$'$ are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkenyl, arylalkyl, cycloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocycloalkenyl, and heterocycloalkyl, wherein the aryl, the aryl part of the arylalkenyl, the arylalkyl, the heteroaryl, the heteroaryl part of the heteroarylalkenyl and the heteroarylalkyl, the heterocycle, and the heterocycle part of the heterocycloalkenyl and the heterocycloalkyl can be optionally substituted as defined herein with one, two, three, four, or five substituents.

The term “aminoalkyl,” as used herein, alone or in combination, refers to an amino group attached to the parent molecular moiety through an alkyl group. Examples include aminomethyl, aminoethyl and aminobutyl.

The terms “aminocarbonyl” and “carbamoyl,” as used herein, alone or in combination, refer to an amino-substituted carbonyl group, wherein the amino group can be a primary or secondary amino group containing substituents selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like.

The term "aminocarbonylalkyl," as used herein, alone or in combination, refers to an aminocarbonyl radical attached to an alkyl radical, as described above. An example of such radicals is aminocarbonylmethyl. The term "amidino" denotes an $-C(NH)NH_2$ radical. The term "cyanoamidino" denotes an $-C(N-CN)NH_2$ radical.

The term “aralkenyl” or “arylalkenyl,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkenyl group.

The term “aralkoxy” or “arylalkoxy,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

The term “aralkyl” or “arylalkyl,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkyl group.

The term “aralkylamino” or “arylalkylamino,” as used herein, alone or in combination, refers to an arylalkyl group attached to the parent molecular moiety through a nitrogen atom, wherein the nitrogen atom is substituted with hydrogen.

The term “aralkylidene” or “arylalkylidene,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkylidene group

The term “aralkylthio” or “arylalkylthio,” as used herein, alone or in combination, refers to an arylalkyl group attached to the parent molecular moiety through a sulfur atom.

The term “aralkynyl” or “arylalkynyl,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkynyl group.

The term “aralkoxycarbonyl,” as used herein, alone or in combination, refers to a radical of the formula aralkyl-O–C(O)– in which the term “aralkyl,” has the significance given above. Examples of an aralkoxycarbonyl radical are benzyloxycarbonyl (Z or Cbz) and 4-methoxyphenylmethoxycarbonyl (MOS).

The term “aralkanoyl,” as used herein, alone or in combination, refers to an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as benzoyl, phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminohydrocinnamoyl, 4-methoxyhydrocinnamoyl, and the like. The term “aroyl” refers to an acyl radical derived from an arylcarboxylic acid, “aryl” having the meaning given below. Examples of such aroyl radicals include substituted and unsubstituted benzoyl or napthoyl such as benzoyl, 4-chlorobenzoyl, 4-carboxybenzoyl, 4-(benzyloxycarbonyl)benzoyl, 1-naphthoyl, 2-naphthoyl, 6-carboxy-2-naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, 3-(benzyloxyformamido)-2-naphthoyl, and the like.

The term "aryl," as used herein, alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as benzyl, phenyl, naphthyl, anthracenyl, phenanthryl, indanyl, indenyl, annulenyl, azulenyl, tetrahydronaphthyl, and biphenyl.

The term "arylamino" as used herein, alone or in combination, refers to an aryl group attached to the parent moiety through an amino group, such as methylamino, N-phenylamino, and the like.

The terms “arylcarbonyl” and “aroyl,” as used herein, alone or in combination, refer to an aryl group attached to the parent molecular moiety through a carbonyl group.

The term “aryloxy,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an oxygen atom.

The term “arylsulfonyl,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through a sulfonyl group.

The term “arylthio,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through a sulfur atom.

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes --CO_2H.

The terms “benzo” and “benz,” as used herein, alone or in combination, refer to the divalent radical C_6H_4= derived from benzene. Examples include benzothiophene and benzimidazole.

The term “O-carbamyl” as used herein, alone or in combination, refers to a -OC(O)NRR’, group-with R and R’ as defined herein.

The term “N-carbamyl” as used herein, alone or in combination, refers to a ROC(O)NR’- group, with R and R’ as defined herein.

The term “carbonyl,” as used herein, when alone includes formyl [–C(O)H] and in combination is a –C(O)– group.

The term “carboxy,” as used herein, refers to –C(O)OH or the corresponding “carboxylate” anion, such as is in a carboxylic acid salt. An “O-carboxy” group refers to a RC(O)O– group, where R is as defined herein. A “C-carboxy” group refers to a –C(O)OR groups where R is as defined herein.

The term “cyano,” as used herein, alone or in combination, refers to –CN.

The term “cycloalkyl,” as used herein, alone or in combination, refers to a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety contains from 3 to 12, preferably five to seven, carbon atom ring members and which may optionally be a benzo fused ring system which is optionally substituted as defined herein. Examples of such cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, octahydronaphthyl, 2,3-dihydro-1H-indenyl, adamantyl and the like. “Bicyclic” and “tricyclic” as used herein are intended to include both fused ring systems, such as decahydonapthalene, octahydronapthalene as well as the multicyclic (multicentered) saturated or partially unsaturated type. The latter type of isomer is exemplified in general by bicyclo[2,2,2]octane, bicyclo[2,2,2]octane, bicyclo[1,1,1]pentane, camphor and bicyclo[3,2,1]octane.

The term “ester,” as used herein, alone or in combination, refers to a carboxyl group bridging two moieties linked at carbon atoms.

The term “ether,” as used herein, alone or in combination, refers to an oxy group bridging two moieties linked at carbon atoms.

The term “halo,” or “halogen,” as used herein, alone or in combination, refers to fluorine, chlorine, bromine, or iodine.

The term “haloalkoxy,” as used herein, alone or in combination, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term “haloalkyl,” as used herein, alone or in combination, refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. “Haloalkylene” refers to a halohydrocarbyl group attached at two or more positions. Examples include fluoromethylene (–CFH–), difluoromethylene ($-CF_2-$), chloromethylene (–CHCl–) and the like.

The term "heteroalkyl," as used herein, alone or in combination, refers to a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, fully saturated or containing from 1 to 3 degrees of unsaturation, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. Up to two heteroatoms may be consecutive, such as, for example, -CH2-NH-OCH3.

The term "heteroaryl," as used herein, alone or in combination, refers to 3 to 7 membered, preferably 5 to 7 membered, unsaturated heterocyclic rings wherein at least one atom is selected from the group consisting of O, S, and N. Heteroaryl groups are exemplified by: unsaturated 3 to 7 membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.]tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo[1,5-b]pyridazinyl, etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic groups containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic groups containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.]etc.; unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.]; unsaturated 3 to 6-membered heteromonocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.]and isothiazolyl; unsaturated condensed heterocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.]and the like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuryl, benzothienyl, and the like.

The term "heteroaralkenyl" or "heteroarylalkenyl," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through an alkenyl group.

The term "heteroaralkoxy" or "heteroarylalkoxy," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through an alkoxy group.

The term "heteroarylalkyl," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through an alkyl group.

The term "heteroaralkylidene" or "heteroarylalkylidene," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through an alkylidene group.

The term "heteroaryloxy," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through an oxygen atom.

The term "heteroarylsulfonyl," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through a sulfonyl group.

The terms "heterocycloalkyl" and, interchangeably, "heterocycle," as used herein, alone or in combination, each refer to a saturated, partially unsaturated, or fully unsaturated monocyclic, bicyclic, or tricyclic heterocyclic radical containing at least one, preferably 1 to 4, and more preferably 1 to 2 heteroatoms as ring members, wherein each said heteroatom may be independently selected from the group consisting of nitrogen, oxygen, and sulfur, and wherein there are preferably 3 to 8 ring members in each ring, more preferably 3 to 7 ring members in each ring, and most preferably 5 to 6 ring members in each ring. "Heterocycloalkyl" and "heterocycle" are intended to include sulfones, sulfoxides, N-oxides of tertiary nitrogen ring members, and carbocyclic fused and benzo fused ring systems; additionally, both terms also include systems where a heterocycle ring is fused to an aryl group, as defined herein, or an additional heterocycle group. Heterocycle groups of the invention are exemplified by aziridinyl, azetidinyl, 1,3-benzodioxolyl, dihydroisoindolyl, dihydroisoquinolinyl, dihydrocinnolinyl, dihydrobenzodioxinyl, dihydro[1,3]oxazolo[4,5-b]pyridinyl, benzothiazolyl, dihydroindolyl, dihydropyridinyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, isoindolinyl, morpholinyl, piperazinyl, pyrrolidinyl, tetrahydropyridinyl, piperidinyl, thiomorpholinyl, and the like. The heterocycle groups may be optionally substituted unless specifically prohibited.

The term "heterocycloalkylalkenyl," as used herein, alone or in combination, refers to a heterocycle group attached to the parent molecular moiety through an alkenyl group.

The term "heterocycloalkylalkoxy," as used herein, alone or in combination, refers to a heterocycle group attached to the parent molecular group through an oxygen atom.

The term "heterocycloalkylalkylidene," as used herein, alone or in combination, refers to a heterocycle group attached to the parent molecular moiety through an alkylidene group.

The term "hydrazinyl" as used herein, alone or in combination, refers to two amino groups joined by a single bond, i.e., –N–N–.

The term "hydroxy," as used herein, alone or in combination, refers to –OH.

The term "hydroxyalkyl," as used herein, alone or in combination, refers to a hydroxy group attached to the parent molecular moiety through an alkyl group.

The term "imino," as used herein, alone or in combination, refers to =N–.

The term "iminohydroxy," as used herein, alone or in combination, refers to =N(OH) and =N–O–.

The phrase "in the main chain" refers to the longest contiguous or adjacent chain of carbon atoms starting at the point of attachment of a group to the compounds of this invention.

The term "isocyanato" refers to a –NCO group.

The term "isothiocyanato" refers to a –NCS group.

The phrase "linear chain of atoms" refers to the longest straight chain of atoms independently selected from carbon, nitrogen, oxygen and sulfur.

The term "lower," as used herein, alone or in combination, means containing from 1 to and including 6 carbon atoms.

The term "mercaptoalkyl" as used herein, alone or in combination, refers to an R'SR– group, where R and R' are as defined herein.

The term "mercaptomercaptyl" as used herein, alone or in combination, refers to a RSR'S– group, where R and R' are as defined herein.

The term "mercaptyl" as used herein, alone or in combination, refers to an RS– group, where R is as defined herein.

The term "nitro," as used herein, alone or in combination, refers to $–NO_2$.

The terms "oxy" or "oxa," as used herein, alone or in combination, refer to –O–.

The term "oxo," as used herein, alone or in combination, refers to =O.

The term "perhaloalkoxy" refers to an alkoxy group where all of the hydrogen atoms are replaced by halogen atoms.

The term "perhaloalkyl" as used herein, alone or in combination, refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.

The terms "sulfonate," "sulfonic acid," and "sulfonic," as used herein, alone or in combination, refer the $–SO_3H$ group and its anion as the sulfonic acid is used in salt formation.

The term "sulfanyl," as used herein, alone or in combination, refers to –S–.

The term "sulfinyl," as used herein, alone or in combination, refers to –S(O)–.

The term "sulfonyl," as used herein, alone or in combination, refers to $–SO_2–$.

The term "N-sulfonamido" refers to a $RS(=O)_2NR'$- group with R and R' as defined herein.

The term "S-sulfonamido" refers to a $-S(=O)_2NRR'$, group, with R and R' as defined herein.

The terms "thia" and "thio," as used herein, alone or in combination, refer to a –S– group or an ether wherein the oxygen is replaced with sulfur. The oxidized derivatives of the thio group, namely sulfinyl and sulfonyl, are included in the definition of thia and thio.

The term "thiol," as used herein, alone or in combination, refers to an –SH group.

The term "thiocarbonyl," as used herein, when alone includes thioformyl –C(S)H and in combination is a –C(S)– group.

The term "N-thiocarbamyl" refers to an ROC(S)NR'– group, with R and R'as defined herein.

The term "O-thiocarbamyl" refers to a –OC(S)NRR', group with R and R'as defined herein.

The term "thiocyanato" refers to a –CNS group.

The term "trihalomethanesulfonamido" refers to a $X_3CS(O)_2NR$– group with X is a halogen and R as defined herein.

The term "trihalomethanesulfonyl" refers to a $X_3CS(O)_2$– group where X is a halogen.

The term "trihalomethoxy" refers to a X_3CO– group where X is a halogen.

The term "trisubstituted silyl," as used herein, alone or in combination, refers to a silicone group substituted at its three free valences with groups as listed herein under the definition of substituted amino. Examples include trimethysilyl, tert-butyldimethylsilyl, triphenylsilyl and the like.

When a group is defined to be "null," what is meant is that said group is absent.

The term "optionally substituted" means the anteceding group may be substituted or unsubstituted. When substituted, the substituents of an "optionally substituted" group may include, without limitation, one or more substituents independently selected from the following groups or a particular designated set of groups, alone or in combination: lower alkyl, lower alkenyl, lower alkynyl, lower heteroalkyl, lower heterocycloalkyl, lower haloalkyl, lower haloalkenyl, lower haloalkynyl, lower perhaloalkyl, lower perhaloalkoxy, lower cycloalkyl, phenyl, aryl, aryloxy, lower alkoxy, lower haloalkoxy, oxo, lower acyloxy, carbonyl, lower carboxyester, lower carboxamido, cyano, hydrogen, halogen, hydroxy, amino, lower alkylamino, arylamino, amido, thiol, lower alkylthio, arylthio, lower alkylsulfinyl, lower alkylsulfonyl, arylsulfinyl, arylsulfonyl, arylthio, sulfonate, sulfonic acid, trisubstituted silyl, N_3, $NHCH_3$, $N(CH_3)_2$, SH, SCH_3, CO_2CH_3, $C(O)NH_2$, pyridinyl, thiophene, furanyl, lower carbamate, and lower urea. Two substituents may be joined together to form a fused five-, six-, or seven-menbered carbocyclic or heterocyclic ring consisting of zero to three heteroatoms, for example forming methylenedioxy or ethylenedioxy. An optionally substituted group may be unsubstituted (e.g., -$CH2CH_3$), fully substituted (e.g., -CF_2CF_3), monosubstituted (e.g., -CH_2CH_2F) or substituted at a level anywhere in-between fully substituted and monosubstituted (e.g., -CH_2CF_3). Where substituents are recited without qualification as to substitution, both substituted and unsubstituted forms are encompassed. Where a substituent is qualified as "substituted," the substituted form is specifically intended. Additionally, different sets of optional substituents to a particuar moiety may be defined as needed; in these cases, the optional substitution will be as defined, often immediately following the phrase, "optionally substituted with."

The term R or the term R', appearing by itself and without a number designation, unless otherwise defined, refers to a moiety selected from the group consisting of alkyl, cycloalkyl, heteroalkyl, aryl, heteroaryl and heterocycloalkyl. Such R and R' groups should be understood to be optionally substituted as defined herein. Whether an R group has a number designation or not, every R group, including R, R' and R^n where n=(1, 2, 3, ...n), every substituent, and every term should be understood to be independent of every other in terms of selection from a group. Should any variable, substituent, or term (e.g. aryl, heterocycle, R, etc.) occur more than one time in a formula or generic structure, its definition at each occurrence is independent of the definition at every other occurrence.

Asymmetric centers exist in the compounds of the present invention. These centers are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. It should be understood that the invention encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric, and epimeric forms,as well as d-isomers and 1-isomers, and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns, or any other appropriate method known in the art. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art. Additionally, the compounds of the present invention may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. Additionally, compounds may exist as tautomers; all tautomeric isomers are provided by this invention. Additionally, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

The term "bond" refers to a covalent linkage between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. A bond may be single, double, or triple unless otherwise specified.

The term "combination therapy" means the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

"KSP inhibitor" is used herein to refer to a compound that exhibits an IC_{50} with respect to KSP activity of no more than about 100 μM and more typically not more than about 50 μM, as measured in the KSP ATP depletion assay described generally hereinbelow. "IC_{50}" is that concentration of inhibitor which reduces the activity of an enzyme / (e.g., KSP) to half-maximal level. Representative compounds of the present invention have been discovered to exhibit inhibition against KSP. Compounds of the present invention preferably exhibit an IC_{50} with respect to KSP of no more than about 10 μM, more preferably, no more than about 5 μM, even more preferably not more than about 1 μM, and most preferably, not more than about 200 nM, as measured in the KSP ATP depletion as assay described herein.

The phrase "therapeutically effective" is intended to qualify the amount of active ingredients used in the treatment of a disease or disorder. This amount will achieve the goal of reducing or eliminating the said disease or disorder.

As used herein, reference to "treatment" of a patient is intended to include prophylaxis. The term “patient” means all mammals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, pigs, and rabbits. Preferably, the patient is a human.

The term "prodrug" refers to a compound that is made more active in vivo. The present compounds can also exist as prodrugs, as described in *Hydrolysis in Drug and Prodrug Metabolism : Chemistry, Biochemistry, and Enzymology* (Testa, Bernard and Mayer, Joachim M. Wiley-VHCA, Zurich, Switzerland 2003). Prodrugs of the compounds described herein are structurally modified forms of the compound that readily undergo chemical changes under physiological conditions to provide the compound. Additionally, prodrugs can be converted to the compound by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to a compound when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the compound, or parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound. The term “therapeutically acceptable prodrug,” refers to those prodrugs or zwitterions which are suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

The term “therapeutically acceptable salt,” as used herein, represents salts or zwitterionic forms of the compounds of the present invention which are water or oil-soluble or dispersible; which are suitable for treatment of diseases without undue toxicity, irritation, and allergic-response; which are commensurate with a reasonable benefit/risk ratio; and which are effective for their intended use. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting the appropriate compound in the form of the free base with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, L-ascorbate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, formate, fumarate, gentisate, glutarate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, malonate, DL-mandelate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, phosphonate, picrate, pivalate, propionate, pyroglutamate, succinate, sulfonate, tartrate, L-tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate (p-tosylate), and undecanoate. Also, basic groups in the compounds of the present invention can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form therapeutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Salts can also be formed by coordination of the compounds with an alkali metal or alkaline earth ion. Hence, the present invention contemplates sodium, potassium, magnesium, and calcium salts of the compounds of the compounds of the present invention and the like.

Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of therapeutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, *N,N*-dimethylaniline, *N*-methylpiperidine, *N*-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, *N,N*-dibenzylphenethylamine, 1-ephenamine, and *N,N'*-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

The compounds of the present invention can exist as therapeutically acceptable salts. The present invention includes compounds listed above in the form of salts, in particular acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable. However, salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question. For a more complete discussion of the preparation and selection of salts, refer to *Pharmaceutical Salts: Properties, Selection, and Use* (Stahl, P. Heinrich. Wiley-VCHA, Zurich, Switzerland, 2002).

While it may be possible for the compounds of the subject invention to be administered as the raw chemical, it is also possible to present them as a pharmaceutical formulation. Accordingly, the subject invention provides a pharmaceutical formulation comprising a compound or a pharmaceutically acceptable salt, ester, prodrug or solvate thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences. The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, intraarticular, and intramedullary), intraperitoneal, transmucosal, transdermal, rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound of the subject invention or a pharmaceutically acceptable salt, ester, prodrug or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

Pharmaceutical preparations which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures.

Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, pastilles, or gels formulated in conventional manner. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or tragacanth.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter, polyethylene glycol, or other glycerides.

Compounds of the present invention may be administered topically, that is by non-systemic administration. This includes the application of a compound of the present invention externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as gels, liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the formulation.

For administration by inhalation the compounds according to the invention are conveniently delivered from an insufflator, nebulizer pressurized packs or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

Preferred unit dosage formulations are those containing an effective dose, as herein below recited, or an appropriate fraction thereof, of the active ingredient.

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

The compounds of the invention may be administered orally or via injection at a dose of from 0.1 to 500 mg/kg per day. The dose range for adult humans is generally from 5 mg to 2 g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

The compounds of the subject invention can be administered in various modes, *e.g.* orally, topically, or by injection. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. The specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diets, time of administration, route of administration, rate of excretion, drug combination, the precise disorder being treated, and the severity of the indication or condition being treated. Also, the route of administration may vary depending on the condition and its severity.

In certain instances, it may be appropriate to administer at least one of the compounds described herein (or a pharmaceutically acceptable salt, ester, or prodrug thereof) in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds herein is hypertension, then it may be appropriate to administer an anti-hypertensive agent in combination with the initial therapeutic agent. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (i.e., by itself the adjuvant may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, by way of example only, the benefit of experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. By way of example only, in a treatment for diabetes involving administration of one of the compounds described herein, increased therapeutic benefit may result by also providing the patient with another therapeutic agent for diabetes. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

Specific, non-limiting examples of possible combination therapies include use of the compounds of the present invention as defined above or a pharmaceutically acceptable salt thereof; with at least one active ingredient selected from chemotherapeutic agents including, but not limited to, the group consisting of aromatase inhibitors, antiestrogen, anti-androgen, gonadorelin agonists, topoisomerase 1and 2 inhibitors, microtubule active agents, alkylating agents, antineoplastic antimetabolites, or platinum-containing compounds, lipid or protein kinase targeting agents, protein or lipid phosphatase targeting agents, anti-angiogenic agents, agents that induce cell differentiation, bradykinin 1 receptor and angiotensin II antagonists, cyclooxygenase inhibitors, heparanase inhibitors, lymphokines or cytokine inhibitors, bisphosphonates, rapamycin derivatives, anti-apoptotic pathway inhibitors, apoptotic pathway agonists, PPAR agonists, inhibitors of Ras isoforms, telomerase inhibitors, protease inhibitors, metalloproteinase inhibitors, aminopeptidase inhibitors, and biologic drugs including but not limited to antibodies, cytokines and growth factors.

In certain aspects of the invention, the chemotherapeutic agents include, but are not limited to the group consisting of the actinomycins (e.g. actinomycin C_2, C_3, D, and F_1), alkylating agents (e.g. cyclophosphamide, melphalan, estramustine), ansa macrolides (e.g. maytansinol, rifamycin, and streptovaricin), anthracycline derivatives (e.g. doxorubicin, daunorubicin, epirubicin, idarubicin, detorubicin, carminomycin, idarubicin, epirubicin, esorubicin, and mitoxantrone), bleomycins (e.g. bleomycin A, A_2, and B), camptothecins (e.g. Irinotecan®, Topotecan®, 9-aminocamptothecin, 10,11-methylenedioxycamptothecin, 9-nitrocamptothecin, and TAS103), combretastatins (e.g. combretastatin, combretastatin A-2, and combretastatin A-4), diynenes (e. g. calicheamicins , neocarcinostatins), epothilones (e.g. epothilone A B, C, and semi-synthetic variants), enzymes, proteins and antibodies (e.g. Herceptin®, Rituxan®, asparaginase, interleukins, interferons, leuprolide, and pegaspargase), fluoropyrimidines (e.g. 5-fluorouracil (5-FU), fluorodeoxyuridine, ptorafur, 5'-deoxyfluorouridine, UFT, and S-1 capecitabine), hormones and hormonal analogues (e.g. diethylstilbestrol, tamoxifen, toremefine, tolmudex, thymitaq, flutamide, fluoxymesterone, bicalutamide, finasteride, estradiol, trioxifene, dexamethasone, leuproelin acetate, estramustine, droloxifene, medroxyprogesterone, megesterol acetate, aminoglutethimide, testolactone, testosterone, diethylstilbestrol, and hydroxyprogesterone), the mitomycins (e.g. mitomycins A, B and C, porfiromycin), platinum analogues (e.g. cisplatin, carboplatin, oxaliplatin, tetraplatin, platinum-DACH, ormaplatin, CI-973, and JM-216), podophyllotoxin and epipodophyllotoxins (e.g. etoposide and teniposide), protein kinase inhibitors (e.g. Tarceva®, Iressa®, Imatinib®, Miltefosine® and Perifosine®), pteridines (e.g. aminopterin, methotrexate, methopterin, dichloro-methotrexate), purines (e.g. 6-mercaptopurine, thioguanine, azattuoprine, allopurinol, cladribine, fludarabine, pentostatin, and 2-chloroadenosine), pyrimidine nucleosides (e.g. deoxycytidine, cytosine arabinoside, cytarabine, azacitidine, 5-azacytosine, gencitabine, and 5-azacytosine-arabinoside), vinca alkaloids (e.g. vincristine, vinblastine, vinorelbine, leurosine, leurosidine and vindesine), and taxanes (e.g. paclitaxel, taxotere and docetaxel).

In some aspects of the invention, the chemotherapeutic agents for the treatment of multiple myeloma include, but are not limited to, alkylating agents (e.g., melphalan), anthracyclines (e.g. doxorubicin, daunorubicin, epirubicin, idarubicin, and mitoxantrone), corticosteroids (e.g. dexamethasome), IMiDs (eg. thalidomide, lenalidomide), protease inhibitors (e.g. bortezomib, NPI0052), IGF-1 inhibitors, CD40 antibodies, Smac mimetics (e.g. telomestatin), FGF3 modulator (e.g. CHIR258), mTOR inhibitor (Rad 001), HDAC inhibitors (eg. SAHA, Tubacin), IKK inhibitors, P38MAPK inhibitors, HSP90 inhibitors (e.g. 17-AAG), and Akt inhibitors (e.g. Perifosine).

Further, the preferred chemotherapeutic agents used in combination with the compounds of the present invention include without limitation melphalan, doxorubicin (including lyophilized), dexamethasone, prednisone, thalidomide, lenalidomide, bortezomib, and NPI0052.

In any case, the multiple chemotherapeutic agents (at least one of which is a compound of the present invention) may be administered in any order or even simultaneously. If simultaneously, the multiple chemotherapeutic agents may be provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). One of the chemotherapeutic agents may be given in multiple doses, or both may be given as multiple doses. If not simultaneous, the timing between the multiple doses may be any duration of time ranging from a few minutes to four weeks.

Thus, in another aspect, the present invention provides methods for treating KSP-mediated disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of the present invention effective to reduce or prevent said disorder in the subject in combination with at least one additional agent for the treatment of said disorder that is known in the art. In a related aspect, the present invention provides therapeutic compositions comprising at least one compound of the present invention in combination with one or more additional agents for the treatment of KSP-mediated disorders.

In certain aspects of the invention, the disease is a hyperproliferative condition of the human or animal body, including, but not limited to cancer, hyperplasias, restenosis, inflammation, immune disorders, cardiac hypertrophy, atherosclerosis, pain, migraine, angiogenesis-related conditions or disorders, proliferation induced after medical conditions, including but not limited to surgery, angioplasty, or other conditions.

In further embodiments, said hyperproliferative condition is selected from the group consisting of hematologic and nonhematologic cancers. In yet further embodiments, said hematologic cancer is selected from the group consisting of multiple myeloma, leukemias, and lymphomas. In yet further embodiments, said leukemia is selected from the group consisting of acute and chronic leukemias. In yet further embodiments, said acute leukemia is selected from the group consisting of acute lymphocytic leukemia (ALL) and acute nonlymphocytic leukemia (ANLL). In yet further embodiments, said chronic leukemia is selected from the group consisting of chronic lymphocytic leukemia (CLL) and chronic myelogenous leukemia (CML). In further embodiments, said lymphoma is selected from the group consisting of Hodgkin's lymphoma and non-Hodgkin's lymphoma. In further embodiments, said hematologic cancer is multiple myeloma. In other embodiments, said hematologic cancer is of low, intermediate, or high grade. In other embodiments, said nonhematologic cancer is selected from the group consisting of: brain cancer, cancers of the head and neck, lung cancer, breast cancer, cancers of the reproductive system, cancers of the digestive system, pancreatic cancer, and cancers of the urinary system. In further embodiments, said cancer of the digestive system is a cancer of the upper digestive tract or colorectal cancer. In further embodiments, said cancer of the urinary system is bladder cancer or renal cell carcinoma. In further embodiments, said cancer of the reproductive system is prostate cancer.

Additional types of cancers which may be treated using the compounds and methods described herein include: cancers of oral cavity and pharynx, cancers of the respiratory system, cancers of bones and joints, cancers of soft tissue, skin cancers, cancers of the genital system, cancers of the eye and orbit, cancers of the nervous system, cancers of the lymphatic system, and cancers of the endocrine system. In certain embodiments, these cancer s may beselected from the group consisting of: cancer of the tongue, mouth, pharynx, or other oral cavity; esophageal cancer, stomach cancer, or cancer of the small intestine; colon cancer or rectal, anal, or anorectal cancer; cancer of the liver, intrahepatic bile duct, gallbladder, pancreas, or other biliary or digestive organs; laryngeal, bronchial, and other cancers of the respiratory organs; heart cancer, melanoma, basal cell carcinoma, squamous cell carcinoma, other non-epithelial skin cancer; uterine or cervical cancer; uterine corpus cancer; ovarian, vulvar, vaginal, or other female genital cancer; prostate, testicular, penile or other male genital cancer; urinary bladder cancer; cancer of the kidney; renal, pelvic, or urethral cancer or other cancer of the genito-urinary organs; thyroid cancer or other endocrine cancer; chronic lymphocytic leukemia; and cutaneous T-cell lymphoma, both granulocytic and monocytic.

Yet other types of cancers which may be treated using the compounds and methods described herein include: adenocarcinoma, angiosarcoma, astrocytoma, acoustic neuroma, anaplastic astrocytoma, basal cell carcinoma, blastoglioma, chondrosarcoma, choriocarcinoma, chordoma, craniopharyngioma, cutaneous melanoma, cystadenocarcinoma, endotheliosarcoma, embryonal carcinoma, ependymoma, Ewing's tumor, epithelial carcinoma, fibrosarcoma, gastric cancer, genitourinary tract cancers, glioblastoma multiforme, hemangioblastoma, hepatocellular carcinoma, hepatoma, Kaposi's sarcoma, large cell carcinoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, medullary thyroid carcinoma, medulloblastoma, meningioma mesothelioma, myelomas, myxosarcoma neuroblastoma, neurofibrosarcoma, oligodendroglioma, osteogenic sarcoma, epithelial ovarian cancer, papillary carcinoma, papillary adenocarcinomas, parathyroid tumors, pheochromocytoma, pinealoma, plasmacytomas, retinoblastoma, rhabdomyosarcoma, sebaceous gland carcinoma, seminoma, skin cancers, melanoma, small cell lung carcinoma, squamous cell carcinoma, sweat gland carcinoma, synovioma, thyroid cancer, uveal melanoma, and Wilm's tumor.

In some aspects of the invention, the disease to be treated by the methods of the present invention may be a hematologic disorder. In certain embodiments, said hematologic disorder is selected from the group consisting of sickle cell anemia, myelodysplastic disorders (MDS), and myeloproliferative disorders. In further embodiments, said myeloproliferative disorder is selected from the group consisting of polycythemia vera, myelofibrosis and essential thrombocythemia.

In some aspects of the invention, the disease to be treated by the methods of the present invention may be a neurological disorder. In certain embodiments, said neurologic disorder is selected from the group consisting of Parkinson's disease, Alzheimer's disease, Alzheimer's dementia, and central nervous system damage resulting from stroke, ischemia and trauma. In other embodiments, said neurological disorder is selected from the group consisting of epilepsy, neuropathic pain, depression and bipolar disorders.

In some aspects of the invention, the disease to be treated by the methods of the present invention may be a cardiovascular condition. In certain embodiments, said cardiovascular condition is selected from the group consisting of atherosclerosis, cardiac hypertrophy, idiopathic cardiomyopathies, heart failure, angiogenesis-related conditions or disorders, and proliferation induced after medical conditions, including, but not limited to restenosis resulting from surgery and angioplasty.

In some aspects of the invention, the disease to be treated by the methods of the present invention may be an autoimmune disease. In certain embodiments, the autoimmune disease to be treated may be selected from the group consisting of: autoimmune disease that targets the nervous system, e.g., multiple sclerosis, myasthenia gravis, autoimmune neuropathies such as Guillain-Barré syndrome, autoimmune uveitis; autoimmune disease that targets the gastrointestinal system, e.g., Crohn's disease, ulcerative colitis, primary biliary cirrhosis; autoimmune hepatitis; autoimmune disease that targets the blood, e.g., autoimmune hemolytic anemia, pernicious anemia, autoimmune thrombocytopenia; autoimmune disease that targets endocrine glands, e.g., Type 1 or immune-mediated diabetes mellitus, Grave's disease, Hashimoto's thyroiditis, autoimmune oophoritis and orchitis, autoimmune disease of the adrenal gland; autoimmune disease that targets blood vessels, e.g., temporal arteritis, anti-phospholipid syndrome, vasculitides such as Wegener's granulomatosis, Behcet's disease; autoimmune disease that targets multiple organs including the musculoskeletal system, e.g., rheumatoid arthritis, scleroderma, polymyositis, dermatomyositis, spondyloarthropathies such as ankylosing spondylitis, Sjogren's syndrome; autoimmune disease that targets skin, e.g., psoriasis, dermatitis herpetiformis, pemphigus vulgaris, or vitiligo. In further embodiments, said autoimmune disease is selected from the group consisting of systemic lupus erythromatosus (SLE), multiple sclerosis (MS), and systemic lupus nephritis.

In some aspects of the invention, the disease to be treated by the methods of the present invention may be a dermatologic disorder. In certain embodiments, said dermatologic disorder is selected from the group consisting of fungal infections, psoriasis, melanoma, basal cell carcinoma, squamous cell carcinoma, and other non-epithelial skin cancers.

In some aspects of the invention, the disease to be treated by the methods of the present invention may be an ophthalmologic disorder. In certain embodiments, the present invention provides methods and compositions for the treatment of ophthalmic diseases and other diseases in which angiogenesis plays a role in pathogenesis, such as glaucoma, retinal ganglion degeneration, occular ischemia, retinitis, retinopathies, uveitis, ocular photophobia, and of inflammation and pain associated with acute injury to the eye tissue. In further embodiments, said ophthalmologic disorder is selected from the group consisting of dry eye, closed angle glaucoma and wide angle glaucoma.

In some aspects of the invention, the disease to be treated by the methods of the present invention may be an inflammatory condition. In some embodiments, the inflammatory condition is selected from the group consisting of Rheumatoid Arthritis (RA), Inflammatory Bowel Disease (IBD), ulcerative colitis and psoriasis.

In further accordance with the present invention, methods and compositions are provided for treating disease states characterized by tissue damage, where the disease states include, but are not limited to, vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury, myocardial ischemia, and the like.

In another aspect of the present invention, methods and compositions are provided for treating the fibrosis which occurs with radiation therapy.

In accordance with another aspect, methods and compositions of the invention are used for treating subjects having adenomatous polyps, including those with familial adenomatous polyposis (FAP). Additionally, the present compounds and methods can be used to prevent polyps from forming in patients at risk of FAP.

In yet another aspect, the present invention provides methods and compositions of the invention are used for treating a neurological or polyglutamine-repeat disorder including, but not limited to, Huntington's disease, Spinocerebellar ataxia 1 (SCA 1), Machado-Joseph disease (MJD)/Spinocerebella ataxia 3 (SCA 3), Kennedy disease/Spinal and bulbar muscular atrophy (SBMA) and Dentatorubral pallidolusyian atrophy (DRPLA).

Besides being useful for human treatment, the compounds and formulations of the present invention are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

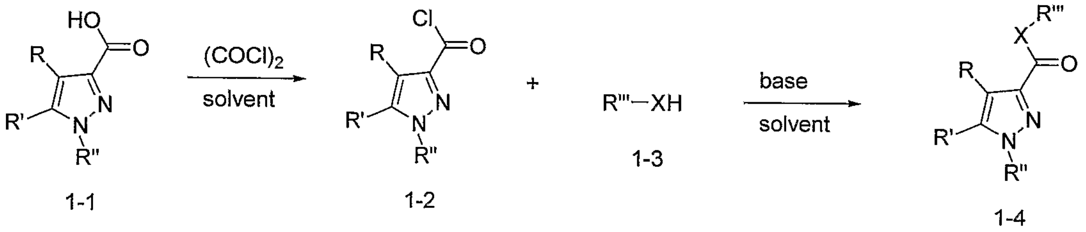
All references, patents or applications, U.S. or foreign, cited in the application are hereby incorporated by reference as if written herein.

GENERAL SYNTHETIC METHODS FOR PREPARING COMPOUNDS

The following schemes and examples can be used to practice the present invention. Starting materials are commercially available, made by known procedures, or prepared as illustrated herein.

One of the principal routes for preparation of compounds within the scope of the instant invention is depicted in Scheme 1. According to this route, pyrazoles 1-1, which are commercially available or prepared using known procedures, are converted to acid chlorides 1-2 using reagents such as oxalyl chloride in solvents such as dichloromethane. Acid chlorides 1-2 are then reacted with compounds 1-3, which can be thiols, amines or alcohols, to give mitotic kinesin inhibitors 1-4. These compounds can exist as mixtures of stereoisomers. These can be separated by a variety of methods, including by HPLC using a column with a chiral stationary phase.

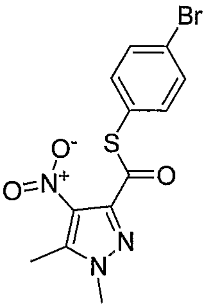
SCHEME 1



Examples 1-3 can be synthesized using the following general synthetic procedure set forth in Scheme I. In some cases the order of carrying out the foregoing reaction scheme may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

EXAMPLE 1

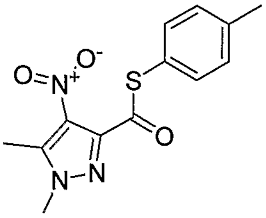
1,5-Dimethyl-4-nitro-1H-pyrazole-3-carbothioic acid S-(4-bromo-phenyl) ester



MS(ESI): 357.21 (M+H$^+$)

EXAMPLE 2

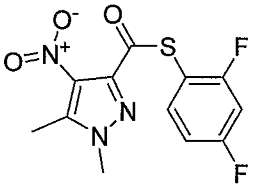
1,5-Dimethyl-4-nitro-1H-pyrazole-3-carbothioic acid S-p-tolyl ester



MS(ESI): 292.34 (M+H$^+$)

EXAMPLE 3

1,5-Dimethyl-4-nitro-1H-pyrazole-3-carbothioic acid S-(2,4-difluoro-phenyl) ester

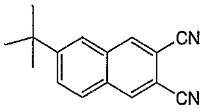
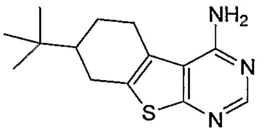
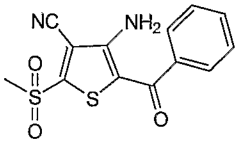
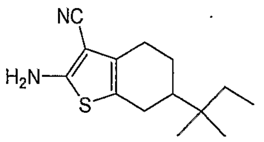


MS(ESI): 314.29 (M+H$^+$)

Examples 4-7 described herein and shown in Table 1 can be prepared according to methods known in the art. In addition, most of the following compounds are commercially available.

Table 1

Example	Structure	Name

4		6-tert-Butylnaphthalene-2,3-dicarbonitrile
5		7-(1,1-Dimethylethyl)-5,6,7,8-tetrahydro-[1]benzothieno[2,3-d]pyrimidin-4-amine
6		4-Amino-5-benzoyl-2-(methylsulfonyl)thiophene-3-carbonitrile
7		2-Amino-6-tert-pentyl-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile

The compounds below have not yet been made, but can generally be made using both literature methods and those methods described above. It is expected that these compounds, when made, will have activity in the assays described below. The compounds are represented herein using the Simplified Molecular Input Line Entry System, or SMILES. SMILES is a modern chemical notation system, developed by David Weininger and Daylight Chemical Information Systems, Inc., that is built into all major commercial chemical structure drawing software packages. Software is not needed to interpret SMILES text strings, and an explanation of how to translate SMILES into structures can be found in Weininger, D., *J. Chem. Inf. Comput. Sci.* 1988, *28*, 31-36.

[O-][N+](C(C(C(SC1=CC=CC=C1)=O)=NN2C)=C2C)=O
[O-][N+](C(C(C(SC1=CC=C(C(F)(F)F)C=C1)=O)=NN2C)=C2C)=O
[O-][N+](C(C(C(SC1=C(F)C=CC(F)=C1)=O)=NN2C)=C2C)=O
[O-][N+](C(C(C(OC(C=C1)=CC=C1Br)=O)=NN2C)=C2C)=O
[O-][N+](C(C(C(OC1=CC=C(C)C=C1)=O)=NN2C)=C2C)=O
[O-][N+](C(C(C(OC1=C(F)C=C(F)C=C1)=O)=NN2C)=C2C)=O
[O-][N+](C(C(C(NC(C=C1)=CC=C1Br)=O)=NN2C)=C2C)=O
[O-][N+](C(C(C(NC1=CC=C(C)C=C1)=O)=NN2C)=C2C)=O
[O-][N+](C(C(C(NC1=C(F)C=C(F)C=C1)=O)=NN2C)=C2C)=O
O=C(SC(C=C1)=CC=C1Br)C(C(C(F)(F)F)=C2C)=NN2C
O=C(SC1=CC=C(C)C=C1)C(C(C(F)(F)F)=C2C)=NN2C
O=C(SC1=C(F)C=C(F)C=C1)C(C(C(F)(F)F)=C2C)=NN2C

O=C(SC(C=C1)=CC=C1Br)C(C(C(F)(F)F)=C2C)=NN2C3=CC=CC=C3
O=C(SC1=CC=C(C)C=C1)C(C(C(F)(F)F)=C2C)=NN2CC
O=C(SC1=C(F)C=C(F)C=C1)C(C(C(F)(F)F)=C2CC)=NN2C
O=C(SC(C=C1)=CC=C1Br)C(C=C2C)=NN2C
O=C(SC1=CC=C(C)C=C1)C(C=C2C)=NN2C
O=C(SC1=C(F)C=C(F)C=C1)C(C=C2C)=NN2C

Examples 1-7 have been shown to be KSP inhibitors by using the following assays. The other compounds listed above, which have not yet been made and/or tested, are predicted to have activity in these assays as well.

The activity of the compounds as KSP inhibitors can be illustrated in the following assay.

Biological Activity Assay

In vitro KSP ATP depletion assay

KSP is expressed in and purified from E. coli bacteria as recombinant C-terminal His6-tagged human KSP (amino acids 1-386, Genbank accession NM_004523) and stored in (20mM PIPES buffer, pH 7.3, 200mM NaCl, 1mM $MgCl_2$, 0.1mM TCEP [Tris(2-carboxyethyl)phosphine]). KSP stock is diluted in PME (25mM PIPES buffer, pH 7.0, 5mM $MgCl_2$, 0.1mM EDTA) containing 0.3mg/ml BSA and 0.005% Brij 35 (PME++). Taxol-stabilized microtubules are prepared as follows. 20µl of 2mM taxol (EMD Biosciences, cat. 580555) in DMSO is added to 2ml of PM (25mM PIPES buffer, pH 7.0, 5mM $MgCl_2$) to make PM/taxol. 10mg of lyophilized microtubules (Cytoskeleton, Inc., cat. MT001-XL) are dissolved in PM/taxol and allowed to incubate at room temperature (~22°C) for 20 minutes, followed by immediate use or flash-freezing in liquid N_2 and storage at -80°C.

2.5µl KSP (10nM) is dispensed into wells of a 1536 multi-well black solid plate. The plate is centrifuged for 1' at ~200 x g. 60nl of 100X concentration of test compound in DMSO is dispensed to the wells by passive pin transfer and incubated for 10 minutes at room temperature. 2.5µl of PME++ containing 1mM taxol-stabilized microtubules and 6µM ATP is then dispensed and the combined reaction is allowed to incubate at room temperature for 2 hours. The assay plate is sealed between reagent additions and during the combined reaction incubation. After 2 hours, 2.5µl of PKLight assay reagent (Cambrex, cat. LT07-501) is dispensed. After a further 10 minute incubation at room temperature, luminescence is measured on a Molecular Devices Analyst multi-mode plate reader (or other suitable plate reader). An increase in luminescence signal correlates with an increase in final ATP concentration, which correlates with KSP inhibition. Negative control activity is measured with DMSO lacking any test compound. Positive control activity is measured with 1-[3-(2,5-Difluoro-phenyl)-5-(3-hydroxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-ethanone (Cox, C. D. et al., Bioorg. Med. Chem. Lett., 15:2041-2045 (2005)). Efficacy is measured as a percentage of positive control activity. The invention is illustrated by the examples and the associated in vitro activity shown in Table 2. The IC_{50} values reported below were derived from the preceding in vitro protocol. The symbol (-) denotes an IC_{50} value of ≤ 10 μM while the symbol (+) denotes an IC_{50} value of >10 μM.

Table 2. Biological Activity

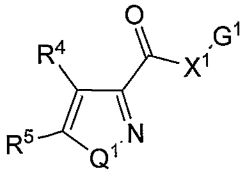
Example#	IC$_{50}$: (-): <= 10μM (+): > 10μM
1	(-)
2	(-)
3	(-)
4	(-)
5	(-)
6	(-)
7	(-)

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

CLAIMS

What is claimed is:

1. A method of inhibiting KSP in a patient in need thereof comprising the administration of a compound of structural Formula I:



(I)

or a salt, ester, or prodrug thereof, wherein:

X^1 is selected from the group consisting of -O-, -S-, $-N(R^3)-$, $-O[C(R^1)(R^2)]_m-$, and $-[C(R^1)(R^2)]_m-$;

m is an integer from 1 to 5;

R^1 and R^2 are independently selected from the group consisting of hydrogen, lower acyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxyalkyl, lower alkylaminoalkyl, lower alkylcarbonyl, lower alkylthio, amido, lower aminoalkyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, lower cycloalkyl, lower cycloalkylalkyl, lower haloalkyl, lower perhaloalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, and heterocycloalkyl, any of which may be optionally substituted; or R^1 and R^2, together with the atoms to which they are attached, may be joined to form an optionally substituted lower cycloalkyl moiety;

R^3 is selected from the group consisting of hydrogen, lower acyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxyalkyl, lower alkylaminoalkyl, lower alkylcarbonyl, amido, lower aminoalkyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, lower cycloalkyl, lower cycloalkyl alkyl, lower haloalkyl, lower perhaloalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, and heterocycloalkyl, any of which may be optionally substituted;

G^1 is selected from the group consisting of aryl, heteroaryl, heterocycloalkyl, and cycloalkyl, any of which may be optionally substituted;

R^4 and R^5 are independently selected from the group consisting of hydrogen, halogen, cyano, nitro, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower acylamino, lower alkoxycarbonyl, lower alkoxycarbonylalkyl, lower alkylaminocarbonyl, lower dialkylaminocarbonyl, lower alkylcarbonyl, lower alkylsulfonyl, lower alkylthio, lower alkylthioalkyl, lower aminoalkyl, carbamoyl, lower aminocarbonylalkyl, aralkoxycarbonyl, aralkanoyl, arylcarbonyl, carboxy, O-carbamyl, N-carbamyl, lower haloalkyl, lower perhaloalkyl, lower haloalkoxy, aryl, arylalkyl, arylalkenyl, arylalkynyl, heterocycloalkyl, heteroaryl, and heteroaralkyl, any of which may be optionally substituted; or R^4 and R^5, together with the atoms to which they are attached, may be joined to form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety, any of which may be substituted;

Q^1 is selected from the group consisting of O, $N(R^6)$, and S; and

R^6 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower alkoxycarbonyl, lower alkoxycarbonylalkyl, lower alkylaminocarbonyl, lower dialkylaminocarbonyl, lower alkylcarbonyl, lower alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, lower aminoalkyl, carbamoyl, lower aminocarbonylalkyl, aralkoxycarbonyl, aralkanoyl, arylcarbonyl, carbamyl, lower haloalkyl, lower perhaloalkyl, lower haloalkoxy, aryl, arylalkyl, arylalkenyl, arylalkynyl, heterocycloalkyl, heteroaryl, and heteroaralkyl, any of which may be optionally substituted.

2. The method as recited in Claim 1, wherein:

X^1 is selected from the group consisting of -O-, -S-, and $-N(R^3)-$, and $-[C(R^1)(R^2)]_m-$;

m is 1;

R^1 and R^2 are independently selected from the group consisting of hydrogen, lower alkyl, aryl, arylalkyl, lower cycloalkyl, and lower cycloalkylalkyl, any of which may be optionally substituted; or R^1 and R^2, together with the atoms to which they are attached, may be joined to form an optionally substituted lower cycloalkyl moiety;

R^3 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, arylalkyl, lower cycloalkyl, lower cycloalkylalkyl, heteroaryl, heteroarylalkyl, and heterocycloalkyl, any of which may be optionally substituted;

G^1 is selected from the group consisting of aryl and heteroaryl, either of which may be optionally substituted;

R^4 and R^5 are independently selected from the group consisting of hydrogen, halogen, cyano, nitro, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower alkoxycarbonyl, lower alkoxycarbonylalkyl, lower alkylsulfonyl, lower alkylthio, carbamoyl, lower aminocarbonylalkyl, carboxy, lower perhaloalkyl, lower haloalkoxy, aryl, arylalkyl, heterocycloalkyl, heteroaryl, and heteroaralkyl, any of which may be optionally substituted; or R^4 and R^5, together with the atoms to which they are attached, may be joined to form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety, any of which may be substituted;

Q^1 is $N(R^6)$; and

R^6 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxycarbonylalkyl, lower alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, arylcarbonyl, lower perhaloalkyl, aryl, arylalkyl, heterocycloalkyl, heteroaryl, and heteroaralkyl, any of which may be optionally substituted.

3. The method as recited in Claim 2, wherein:

X^1 is -S-;

G^1 is optionally substituted aryl;

R^4 and R^5 are independently selected from the group consisting of halogen, nitro, lower alkyl, lower perhaloalkyl, aryl, arylalkyl, heterocycloalkyl, heteroaryl, and heteroaralkyl, any of which may be optionally substituted;and

R^6 is selected from the group consisting of hydrogen, lower alkyl, lower alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryl, and heteroaryl, any of which may be optionally substituted.

4. The method as recited in Claim 3, wherein:

   G^1 is selected from the group consisting of 4-bromophenyl, 4-methylphenyl, and 2,4-difluorophenyl;

   R^4 is nitro;

   R^5 is optionally substituted lower alkyl; and

   R^6 is selected from the group consisting of optionally substituted lower alkyl and optionally substituted aryl.

5. The method as recited in Claim 4, wherein R^5 and R^6 are methyl.
6. The method as recited in Claim 1 selected from the group consisting of Examples 1-3.
7. A method of inhibiting KSP in a patient in need thereof comprising the administration of a compound consisting of Examples 4 to 6, or a salt, ester, or prodrug thereof.
8. A method of inhibiting KSP in a patient in need thereof comprising the administration of a compound consisting of Example 7, or a salt, ester, or prodrug thereof.
9. The compound as recited in Claims 1, 7, and 8 for use in the manufacture of a medicament for the prevention or treatment of a disease or condition ameliorated by the inhibition of KSP.
10. A pharmaceutical composition comprising a compound as recited in Claims 1and 7, together with a pharmaceutically acceptable carrier.
11. A method of inhibiting KSP activity in a patient in need thereof comprising the administration of a therapeutically effective amount of a compound as recited in Claims 1, 7, and 8 to said patient.