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(54) Title: ANTHRAQUINONE DIOXIMES AND USES THEREOF

(57) Abstract: Anthraquinone dioximes and their derivatives are disclosed for use in treatment of diseases, especially cancer, such as colon and colorectal cancer. Methods of preparing such derivatives are also presented. Compositions of these compounds, as well as metabolites of said compounds and their use in gene modulation are also described.



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Anthraquinone Dioximes and Uses Thereof

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The present application is a continuation-in-part of PCT/US2008/006015, filed 9 May 2008, which claimed priority of U.S. Provisional Application 60/928,592, filed 10 May 2007 and U.S. Provisional
10 Application 60/999,153, filed 15 October 2007, the disclosures of which are hereby incorporated by reference in their entirety.

15

FIELD OF THE INVENTION

The present invention relates to the field of antitumor therapy using anthraquinone dioximes.

20

BACKGROUND OF THE INVENTION

The Wnt/beta-catenin signaling pathway is recognized as one of the
25 key signaling pathways in cancer and as a valid target for therapeutic intervention in many tumor types, especially colon tumors.

The cells of multicellular organisms have the ability to recognize and signal each other, sometimes from fair distances. Such signaling may be
30 accomplished by production of signaling molecules produced by one cell and which subsequently bind to a specific receptor on a different cell. Such signaling pathways have been implicated in various disease processes, including cancer. Wnt signaling, via receptor binding and subsequent increase in intracellular β -catenin, is referred to as the canonical pathway. Wnt proteins
35 form a family of highly conserved secreted signaling molecules that regulate

cell-to-cell interactions and have been implicated in cancer pathogenesis. Wnt proteins bind to receptors of the Frizzled and LRP families on the cell surface. Through several cytoplasmic relay components, the signal is transduced to β -catenin, which then enters the nucleus and forms a complex with TCF to
5 activate transcription of Wnt target genes.

In this pathway, Wnt polypeptides are either present on the surface of a signaling cell or released by that cell and eventually contact a specific cell-surface receptor of another cell. Such receptors on target cells include the
10 Frizzled/LRP receptor (LRP = LDL-receptor-related protein) and they transmit a signal to intracellular proteins, such as β -catenin, whose steady-state level is usually kept relatively low through continuous degradation (usually mediated by proteosomes). This is controlled by a complex containing the proteins GSK-3/APC/Axin (GSK-3 = glycogen synthase kinase and APC =
15 Adenomatous Polyposis Coli). The result of Wnt-binding at the surface of the target cell is to inhibit β -catenin degradation, whereupon the latter builds up, enters the nucleus and combines with transcriptional regulators to turn on genes.

20 It has been found that mutations that promote constitutive activation of the Wnt signaling pathway can lead to cancer. [for a review, see Logan and Nusse, "The Wnt Signaling Pathway in Development and Disease," in Ann. Rev. Cell Dev. Biol., 20:781-810 (2004)] For example, mutations in Axin2 may predispose an individual to colon cancer (Lammi et al., Am. J. Hum. Genet.,
25 74:1043-50 (2004)). In another such example, familial adenomatous polyposis (FAP), an inherited disease characterized by numerous polyps in the colon and rectum, is often caused by truncation of APC (another Wnt signaling-pathway protein), which promotes aberrant activation of the Wnt pathway. [see: Kinzler et al., Science, 253:661-665 (1991)] Mutations in APC and β -
30 catenin have also be detected in colon cancer and other tumor types (for a review see Giles et al., Biochim. Biophys. Acta, 1653:1-24 (2003)). In addition, mutations in Axin that cause loss of function have been identified in

hepatocellular carcinomas. [see: Satoh et al., Nat. Genet., 24:245-50 (2000)]
Thus, any mutation or other cellular event that serves to decouple Wnt
signaling and β -catenin regulation appears to be important in producing
cancer.

5

Because such cancer-genesis events have been linked to elevated
levels of β -catenin (i.e., situations where β -catenin levels are Wnt
independent), small organic compounds and other agents that serve to re-
establish this linkage or otherwise reduce β -catenin would prove useful in
10 abating the cancerous process and find use as anti-neoplastic agents. The
present invention provides such agents in the form of disulfonamide
derivatives of fluorene, anthracene, xanthene, dibenzosuberone and acridine
that reduce levels of beta-catenin in tumor cells.

15 Structurally related fluorene and anthracene derivatives with the
sulfonamide groups substituted with aromatic amines are known in the art
(see, for example, US 2004/0019042) as inhibitors of P2X3 and P2X2/3
containing receptors and have been found useful in the treatment and
prevention of disorders such as bladder overactivity, urinary incontinence or
20 pain. However, herein it is shown that novel structurally related compounds
can be prepared and used as modulators of the Wnt/ β -catenin pathway. It is
known that β -catenin is a regulator of the Wnt signally pathway. (see Willert
and Nusse, Current Opinion in Genetics and Development, 8:95-102 (1998).

25

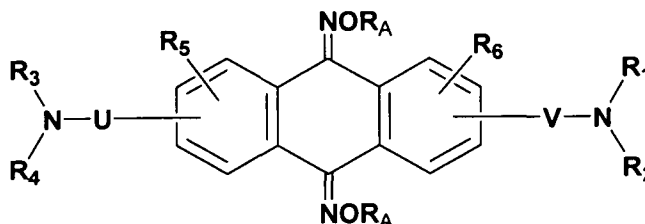
BRIEF SUMMARY OF THE INVENTION

30

The invention provides small organic compounds of the
anthraquinonedioxime family, useful for the treatment of cancer that interfere
with the Wnt signaling pathway and reduce levels of beta-catenin in cancer
cells, and methods for their synthesis. In specific embodiments, these

compounds include disulfonamide derivatives of anthraquinonedioxime that reduce levels of beta-catenin in tumor cells.

Compounds of the invention have the structure of Formula I:



Formula I

Wherein each R_A is independently selected from H, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, $-C(=O)R_B$, $-C(=O)OR_B$, $-C(=O)NR_BR_C$, $-C(=NR_B)R_C$, $-NR_BR_C$, heterocycloalkyl, aryl or polyaromatic, heteroaryl, arylalkyl and alkylaryl

wherein each of said R_B and R_C is independently H, alkyl, or heteroalkyl,

U and V are each independently selected from $C=O$, and $O=S=O$ and wherein when U is $C=O$, V is not $C=O$,

R_1 , R_2 , R_3 , and R_4 are each independently selected from H, alkyl, heteroalkyl, cycloalkyl, arylcycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, and each of said R_1 , R_2 and said R_3 , R_4 can independently combine to form heterocycloalkyl,

R_5 and R_6 are each independently selected from H, OH, SH, alkoxy, thioalkoxy, alkyl, halogen, CN, CF_3 , NO_2 , $COOR_D$, $CONR_DR_E$, NR_DR_E , NR_DCOR_E , $NR_DSO_2R_E$, and $NR_FCONR_DR_E$;

wherein R_D , R_E and R_F are independently H, alkyl, heteroalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or heterocycloalkyl;

and wherein when each R_A is NOH, and U and V are each O=S=O and one of R_1 or R_2 and one of R_3 or R_4 is phenyl or substituted phenyl, then the other of R_1 or R_2 and R_3 or R_4 is not H or alkyl,

including all pharmaceutically acceptable salts, esters, amides,
5 stereoisomers, geometric isomers, solvates or prodrugs thereof.

In specific embodiments, the compounds of the invention include those of Tables 1 to 4 and said compounds are contemplated by the invention either individually or in any combination thereof. Thus, the present invention
10 contemplates any one of said compounds alone, or any combination of these compounds or all of these compounds, as well as uses of any or all of these compounds, in any combination, to treat cancer by any mechanism. Each said compound is by itself an embodiment of the invention and any combination of said embodiments is itself a specific embodiment of the invention.

15

The present invention also provides therapeutic compositions of any of the compounds of the invention, such as the compounds of Tables 1 to 4, including individual compositions of any one of these compounds, or any combination of these compounds. Each said composition is by itself an
20 embodiment of the invention and any combination of said embodiments is itself a specific embodiment of the invention.

The present invention also relates to a method for ameliorating cancer or tumor metastasis in a mammal comprising administering to said mammal
25 an effective amount of a compound of the invention. Especially contemplated are uses of the compounds of Tables 1 to 4 for the treatment of cancer. Use of each said compound is by itself an embodiment of the invention and any combination of said embodiments is itself a specific embodiment of the invention.

30

DEFINITIONS

Unless expressly stated otherwise, each of the following terms has the
5 indicated meaning:

"Acyl" or "carbonyl" is a radical formed by removal of the hydroxy from a carboxylic acid (i.e., $R-C(=O)-$). Preferred acyl groups include acetyl, formyl, and propionyl, with acetyl being most preferred.

10

"Alkyl" means a saturated hydrocarbon radical having 1 to 15 carbon atoms, preferably 1 to 10 carbon atoms, more preferably 1 to 5 carbon atoms, most preferably 1 to 3 carbon atoms, that may be branched or unbranched. Non-limiting examples of alkyl radicals include methyl, ethyl, n-propyl,
15 isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, tert-amyl, pentyl, hexyl, heptyl, octyl and the like, wherein methyl, ethyl, n-propyl, and isopropyl represent specifically preferred examples.

The term "alkenyl," alone or in combination, refers to an optionally
20 substituted straight-chain, or optionally substituted branched-chain hydrocarbon radical having one or more carbon-carbon double-bonds and having 2 to 15 carbon atoms, preferably 2 to 10, more preferably 2 to 5 carbon atoms, more preferably two to about eighteen carbons. Examples of alkenyl radicals include ethenyl, propenyl, butenyl, 1,3-butadienyl and the like.

25

The term "alkynyl," alone or in combination, refers to an optionally substituted straight-chain or optionally substituted branched-chain hydrocarbon radical having one or more carbon-carbon triple-bonds and having 2 to 15 carbon atoms, preferably 2 to 10, more preferably 2 to 5
30 carbon atoms, more preferably from two to about twelve carbon atoms, from two to about six carbon atoms as well as those having from two to about four carbon atoms. Examples of alkynyl radicals include ethynyl, 2-propynyl, 2-butynyl, 1,3-butadiynyl and the like.

Preferred branched alkyl, alkenyl and alkynyl chains have one or two branches, preferably one branch, and each may be unsubstituted or substituted with from 1 to 4 substituents, preferably up to 3 substituents, more preferably 2 substituents and most preferably one substituent. Preferred
5 substituents are hydrocarbon, halo (preferably F, Cl, Br and I), hydroxy, aryloxy (e.g., phenoxy), heteroaryloxy, acyloxy (e.g., acetoxy), carboxy, aryl (e.g., phenyl), heteroaryl, cycloalkyl, heteroalkyl, heterocycloalkyl, spirocycle, amino, amido, acylamino, keto, thioketo, cyano, or any combination thereof. Preferred hydrocarbons are methyl, ethyl, propyl, isopropyl, butyl, vinyl,
10 allyl, butenyl, and exomethylenyl.

A "lower alkyl" is a shorter alkyl, e.g., one containing from one to about six carbon atoms.

Also, as referred to herein, a "lower" alkyl, alkenyl or alkynyl moiety (e.g., "lower alkyl") is a chain comprised of 1 to 10, preferably from 1 to 8,
15 carbon atoms in the case of alkyl and 2 to 10, preferably 2 to 8, carbon atoms in the case of alkene and alkyne.

"Alkoxy" means an oxygen radical having a hydrocarbon chain substituent, where the hydrocarbon chain is an alkyl or alkenyl (i.e., -O-alkyl or -O-alkenyl). Examples of alkoxy radicals include methoxy, ethoxy, n-
20 propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, allyloxy and the like.

"Aryl" is an aromatic hydrocarbon ring. Aryl rings are monocyclic or fused bicyclic ring systems. Monocyclic aryl rings contain 6 carbon atoms in the ring. Monocyclic aryl rings are also referred to as phenyl rings. Bicyclic
25 aryl rings contain from 8 to 17 carbon atoms, preferably 9 to 12 carbon atoms, in the ring. Bicyclic aryl rings include ring systems wherein one ring is aryl and the other ring is aryl, cycloalkyl, or heterocycloalkyl. Preferred bicyclic aryl rings comprise 5-, 6- or 7-membered rings fused to 5-, 6-, or 7-membered rings. Aryl rings may be unsubstituted or substituted with from 1
30 to 4 substituents on the ring. Aryl may be substituted with halo, cyano, nitro, hydroxy, carboxy, amino, acylamino, alkyl, heteroalkyl, haloalkyl, phenyl, aryloxy, alkoxy, heteroalkyloxy, carbamyl, haloalkyl, methylenedioxy,

heteroaryloxy, or any combination thereof. Preferred aryl rings include naphthyl, tolyl, xylyl, and phenyl. The most preferred aryl ring radical is phenyl.

"Aryloxy" is an oxygen radical having an aryl substituent (i.e., -O-aryl).

- 5 Preferred aryloxy groups include, for example, phenoxy, naphthyloxy, methoxyphenoxy, and methylenedioxyphenoxy.

"Cycloalkyl" refers to a saturated hydrocarbon ring that is not aromatic. Cycloalkyl rings are monocyclic, or are fused, spiro, or bridged bicyclic or polycyclic ring systems. Monocyclic cycloalkyl rings contain from about 3 to
10 about 12 carbon atoms, preferably from 3 to 7 carbon atoms, in the ring. Bicyclic cycloalkyl rings contain from 7 to 17 carbon atoms, preferably from 7 to 12 carbon atoms, in the ring. Preferred bicyclic cycloalkyl rings comprise 4-, 5- 6- or 7-membered rings fused to 5-, 6-, or 7-membered rings. Cycloalkyl rings may be unsubstituted or substituted with from 1 to 4
15 substituents on the ring. Cycloalkyl may be substituted with halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, keto, hydroxy, carboxy, amino, acylamino, aryloxy, heteroaryloxy, or any combination thereof. Preferred cycloalkyl rings include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and cyclononyl rings.

- 20 The term "lower alkenyl" or "lower alkynyl" refers to an alkenyl or alkynyl radical, respectively, having from two to about six carbons in the carbon chain and not including substituents.

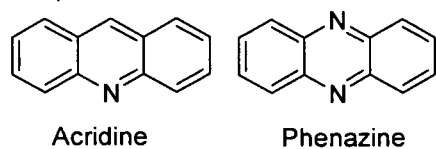
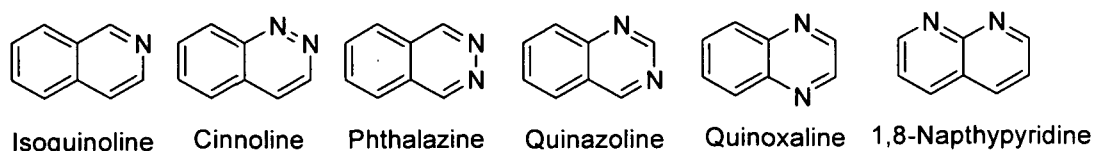
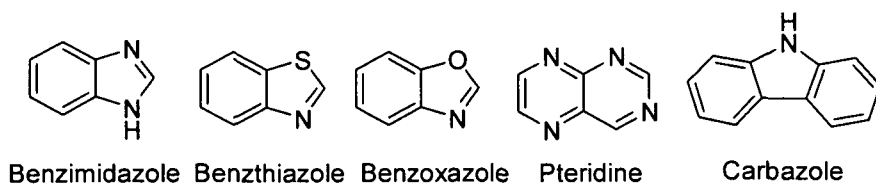
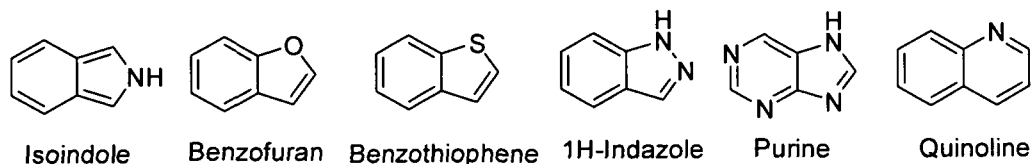
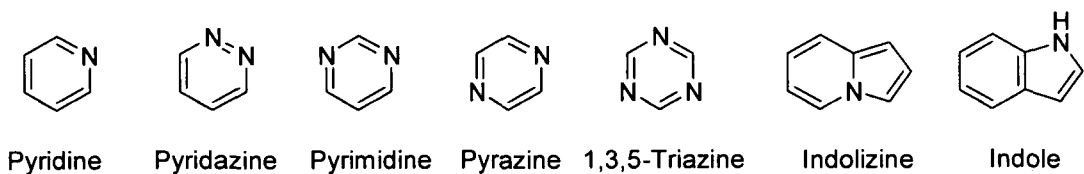
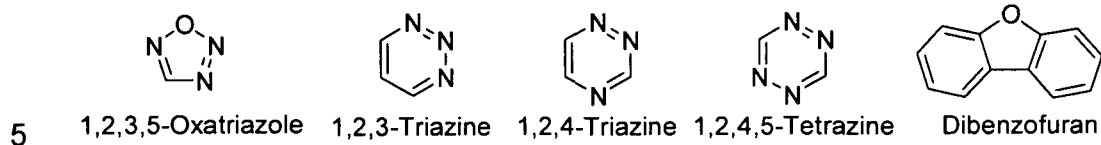
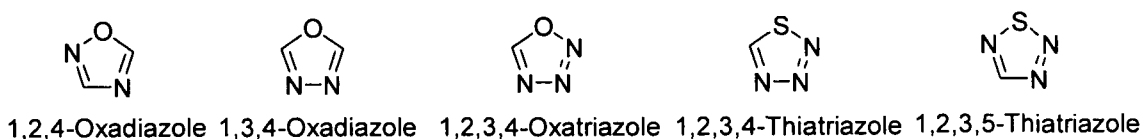
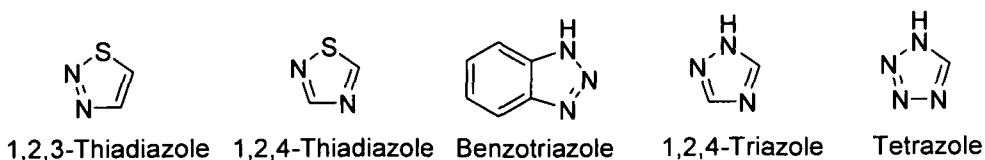
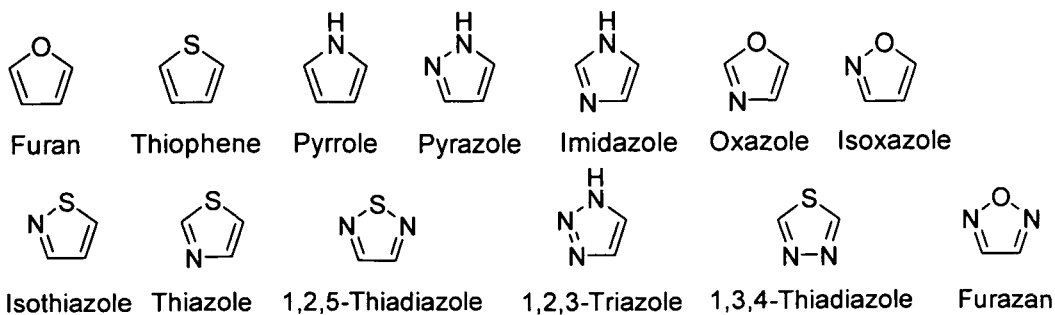
"Halo" or "halogen" is fluoro, chloro, bromo or iodo. Preferred halo are fluoro, chloro and bromo; more preferred typically are chloro and fluoro,
25 especially fluoro.

"Heteroatom" is a nitrogen, sulfur, or oxygen atom. Groups containing more than one heteroatom may contain different heteroatoms.

- "Heteroalkyl" is a saturated or unsaturated chain containing carbon and at least one heteroatom, wherein no two heteroatoms are adjacent.
30 Heteroalkyl chains contain from 2 to 15 member atoms (carbon and heteroatoms) in the chain, preferably 2 to 10, more preferably 2 to 5. For

example, alkoxy (i.e., -O-alkyl or -O-heteroalkyl) radicals are included in heteroalkyl. Heteroalkyl chains may be straight or branched. Preferred branched heteroalkyl have one or two branches, preferably one branch. Preferred heteroalkyl are saturated. Unsaturated heteroalkyl have one or more carbon-carbon double bonds and/or one or more carbon-carbon triple bonds. Preferred unsaturated heteroalkyls have one or two double bonds or one triple bond, more preferably one double bond. Heteroalkyl chains may be unsubstituted or substituted with from 1 to 4 substituents. Preferred substituted heteroalkyl are mono-, di-, or tri-substituted. Heteroalkyl may be substituted with lower alkyl, haloalkyl, halo, hydroxy, acyloxy, carboxy, amino, acylamino, amido, keto, thioketo, cyano, or any combination thereof. Where a group is described, for example, as an alkyl derivative, such as "-ethylpyridine" the dash "-" indicates the point of attachment of the substituent. Thus, "-ethylpyridine" means attachment of ethylpyridine via the ethyl portion of the group whereas "ethylpyridine-" means attachment via the pyridine ring.

"Heteroaryl" is an aromatic ring containing carbon atoms and from 1 to about 6 heteroatoms in the ring. Heteroaryl rings are monocyclic or fused bicyclic ring systems. Monocyclic heteroaryl rings contain from about 5 to about 9 member atoms (carbon and heteroatoms), preferably 5 or 6 member atoms, in the ring. Bicyclic heteroaryl rings contain from 8 to 17 member atoms, preferably 8 to 12 member atoms, in the ring. Bicyclic heteroaryl rings include ring systems wherein one ring is heteroaryl and the other ring is aryl, heteroaryl, cycloalkyl, or heteroalkyl, heterocycloalkyl. Preferred bicyclic heteroaryl ring systems comprise 5-, 6- or 7-membered rings fused to 5-, 6-, or 7-membered rings. Heteroaryl rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Heteroaryl may be substituted with halo, cyano, nitro, hydroxy, carboxy, amino, acylamino, alkyl, heteroalkyl, haloalkyl, phenyl, alkoxy, aryloxy, heteroaryloxy, or any combination thereof. Preferred heteroaryl rings include, but are not limited to, the following:

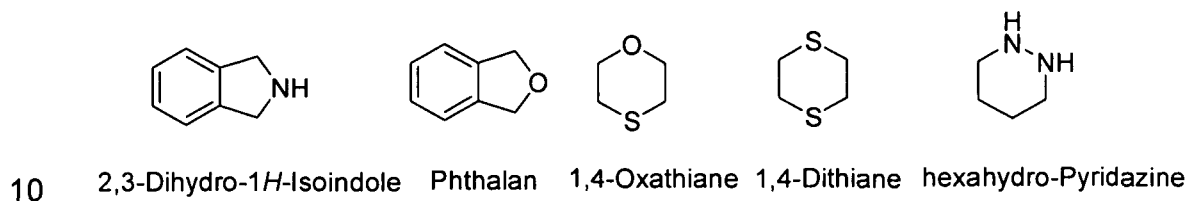
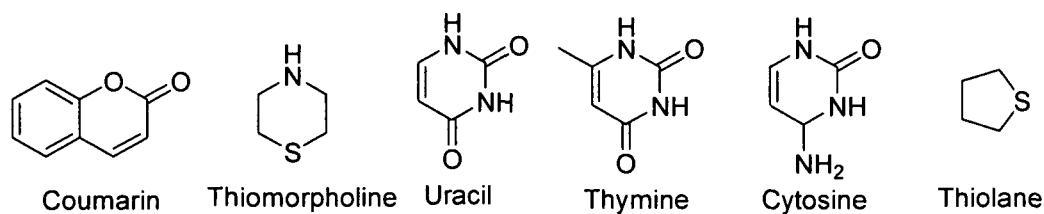
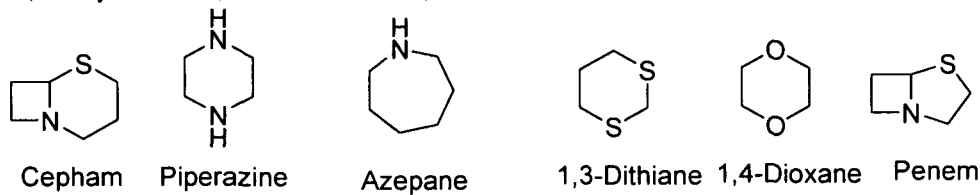
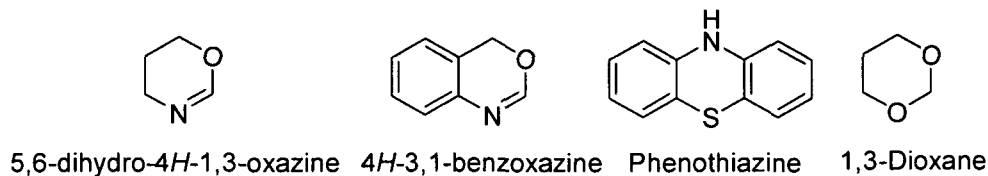
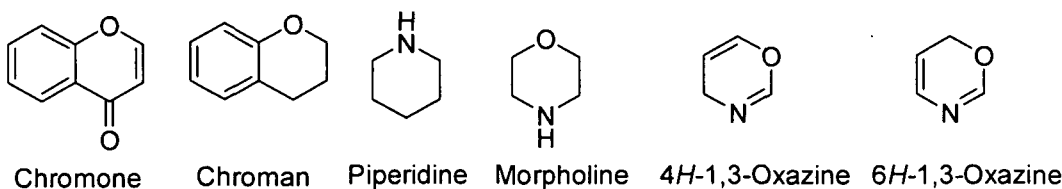
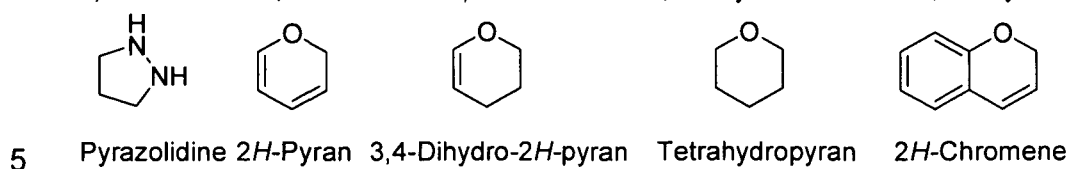
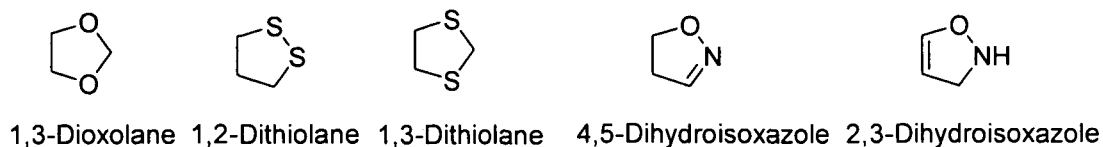
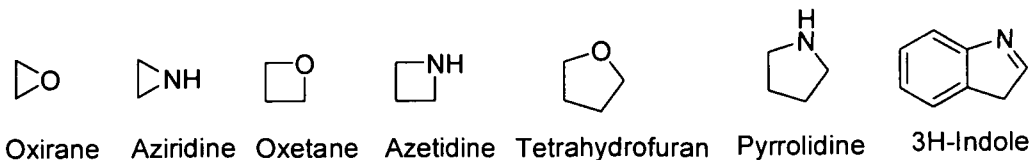


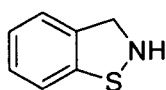
A fused heteroaryl radical may contain from two to four fused rings and where the ring of attachment is a heteroaromatic ring, the other individual rings within the fused ring system may be aromatic, heteroaromatic, alicyclic or heterocyclic. The term heteroaryl also includes mono-heteroaryls or fused
5 heteroaryls having from five to about twelve skeletal ring atoms, as well as those having from five to about ten skeletal ring atoms. The term "lower heteroaryl" refers to a heteroaryl having five to about ten skeletal ring atoms, e.g., pyridyl, thienyl, pyrimidyl, pyrazinyl, pyrrolyl, or furanyl.

"Heteroaryloxy" is an oxygen radical having a heteroaryl substituent
10 (i.e., -O-heteroaryl). Preferred heteroaryloxy groups include (for example) pyridyloxy, furanyloxy, (thiophene)oxy, (oxazole)oxy, (thiazole)oxy, (isoxazole)oxy, pyrimidinyloxy, pyrazinyloxy, and benzothiazolyloxy.

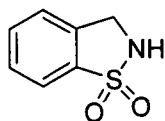
"Heterocycloalkyl" is a saturated or unsaturated ring containing carbon atoms and from 1 to 4 (preferably 1 to 3) heteroatoms in the ring.
15 Heterocycloalkyl rings are not aromatic. Heterocycloalkyl rings are monocyclic, or are fused, bridged, or spiro bicyclic ring systems. Monocyclic heterocycloalkyl rings contain from about 3 to about 9 member atoms (including both carbons and heteroatoms), preferably from 5 to 7 member atoms, in the ring. Bicyclic heterocycloalkyl rings contain from 7 to 17 member
20 atoms, preferably 7 to 12 member atoms, in the ring. Bicyclic heterocycloalkyl rings contain from about 7 to about 17 ring atoms, preferably from 7 to 12 ring atoms. Bicyclic heterocycloalkyl rings may be fused, spiro, or bridged ring systems. Preferred bicyclic heterocycloalkyl rings comprise 5-, 6- or 7-membered rings fused to 5-, 6-, or 7-membered
25 rings. Heterocycloalkyl rings may be unsubstituted (i.e., contain hydrogens as substituents of the ring atoms) or substituted (on either carbons or heteroatoms or both) with from 1 to 4 substituents selected from methyl, cyano, hydroxy, carboxy, keto, thioketo, amino, acylamino, acyl, amido, alkyl, heteroalkyl, phenyl, alkoxy, aryloxy or any combination thereof. Preferred
30 substituents on heterocycloalkyl include methyl, ethoxyl, and halo. A heterocycloalkyl ring may be attached as a substituent of a larger structure by

any chemically feasible atom of said heterocycloalkyl ring. Preferred heterocycloalkyl rings include, but are not limited to, the following:

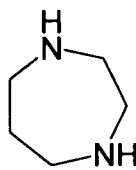




1,2-Benzisothiazoline



Benzylsultam



[1,4]Diazepane

The term "membered ring" can embrace any cyclic structure, including aromatic, heteroaromatic, alicyclic, heterocyclic and polycyclic fused ring systems as described below. The term "membered" is meant to denote the number of skeletal atoms that constitute the ring. Thus, for example, pyridine, pyran, and pyrimidine are six-membered rings and pyrrole, tetrahydrofuran, and thiophene are five-membered rings.

The term "alkylaryl," alone or in combination, refers to an aryl radical as defined above in which one H atom is replaced by an alkyl radical as defined above, such as, for example, tolyl, xylyl and the like.

The term "arylalkyl," or "aralkyl," alone or in combination, refers to an alkyl radical as defined above in which one H atom is replaced by an aryl radical as defined above, such as, for example, benzyl, 2-phenylethyl and the like.

The term "heteroarylalkyl" refers to an alkyl radical as defined above in which one H atom is replaced by a heteroaryl radical as defined above, each of which may be optionally substituted but wherein the aryl group is attached to a larger core structure with the alkyl group being the terminal moiety.

The term "alkylheteroaryl" refers to an alkyl radical as defined above in which one H atom is replaced by a heteroaryl radical as defined above, each of which may be optionally substituted but wherein the alkyl group is attached to a larger core structure with the heteroaryl group being the terminal moiety.

The term "alkylthio," alone or in combination, refers to an alkylthio radical, alkyl-S--, wherein the term alkyl is as defined above.

5 The term "arylthio," alone or in combination, refers to an arylthio radical, aryl-S--, wherein the term aryl is as defined above.

The term "heteroarylthio" refers to the group heteroaryl-S--, wherein the term heteroaryl is as defined above.

10 The term "acyloxy" refers to the ester group --OC(O)R, where R is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, alicyclic, heterocyclic, arylalkyl, or heteroarylalkyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, alicyclic, heterocyclic, arylalkyl or heteroarylalkyl may be optionally substituted.

15 The term "carboxy esters" refers to --C(O)OR where R is alkyl, aryl or arylalkyl, wherein the alkyl, aryl and arylalkyl groups may be optionally substituted.

20 The term "carboxamido" refers to the structure --C(O)NRR' where nitrogen is attached to the carbonyl carbon and each of R and R' are independently selected from the group consisting of H, alkyl, aryl, heteroaryl, alicyclic, heterocyclic, arylalkyl and heteroarylalkyl, wherein the alkyl, aryl, heteroaryl, alicyclic, heterocyclic, or arylalkyl groups may be optionally substituted.

25

The terms "alkylamino", refers to the group --NHR' where R is independently selected from alkyl.

30 The terms "dialkylamino", refers to the group --NRR' where R and R' are alkyls.

The term "sulfide" refers to a sulfur atom covalently linked to two atoms; the formal oxidation state of said sulfur is (II). The term "thioether" may be used interchangeably with the term "sulfide."

- 5 The term "sulfoxide" refers to a sulfur atom covalently linked to three atoms, at least one of which is an oxygen atom; the formal oxidation state of said sulfur atom is (IV).

- 10 The term "sulfone" refers to a sulfur atom covalently linked to four atoms, at least two of which are oxygen atoms; the formal oxidation state of said sulfur atom is (VI).

- 15 The terms "optional" or "optionally" mean that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "aryl optionally mono- or di-substituted with an alkyl" means that the alkyl may but need not be present, or either one alkyl or two may be present, and the description includes situations where the aryl is substituted with one or two alkyls and situations where the
20 aryl is not substituted with an alkyl.

- "Independently selected" groups are groups present in the same structure that need not all represent the same substitution. For example, where two substituents are represented as NOR_A and each R_A is said to be
25 independently selected from H, methyl, ethyl, etc., this means that where one R_A is methyl, the other R_A may be methyl but could be H or ethyl (or any other recited substitution). Typical embodiments appear in Table 2.

- 30 Some of the compounds of the present invention may contain one or more chiral centers and therefore may exist in enantiomeric and diastereomeric forms. The scope of the present invention is intended to cover all isomers per se, as well as mixtures of cis and trans isomers, mixtures of diastereomers and racemic mixtures of enantiomers (optical isomers) as well.

Further, it is possible using well known techniques to separate the various forms, and some embodiments of the invention may feature purified or enriched species of a given enantiomer or diastereomer.

5 A "pharmacological composition" refers to a mixture of one or more of the compounds described herein, or pharmaceutically acceptable salts thereof, with other chemical components, such as pharmaceutically acceptable carriers and/or excipients. The purpose of a pharmacological composition is to facilitate administration of a compound to an organism.

10

 The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject agent from one organ, or
15 portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and
20 potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11)
25 polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible
30 substances employed in pharmaceutical formulations. A physiologically acceptable carrier should not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound.

The term "excipient" refers to an inert substance added to a pharmacological composition to further facilitate administration of a compound. Examples of excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

As used herein, the term "therapeutic effect" includes, but is not limited to, the inhibition, in whole or in part, of the growth of cells characteristic of a proliferative disorder, e.g., colon cancer. A therapeutic effect may also include amelioration of one or more of the symptoms of the disease, other than cell growth or size of the cell mass, and may include 1) a reduction in the number of cells; 2) a reduction in cell size; 3) inhibition (i.e., slowing, preferably stopping) of cell infiltration (i.e., metastasis) into peripheral organs; 3) inhibition or slowing of cell growth; and/or 4) relieving one or more symptoms associated with the disease, such as cancer. Any amount or dose of a compound disclosed herein that results in such a therapeutic effect is deemed to be a "therapeutically effective dose" or a "therapeutically effective amount" of said compound.

As it relates to cancer, the phrase "effective amount" means an amount sufficient to effect a desired response, or to ameliorate a symptom or sign, with respect to metastasis or primary tumor progression, size, or growth. Typical mammalian treatment recipients include mice, rats, cats, dogs, and primates, including humans. An effective amount for a particular patient may vary depending on factors such as the condition being treated, the overall health of the patient, the method, route, and dose of administration and the severity of side affects. Preferably, the effect will result in a change in quantitation of at least about 10%, preferably at least 20%, 30%, 50%, 70%, or even 90% or more. When in combination, an effective amount is in ratio to a combination of components and the effect is not limited to individual components alone.

A "solvate" is a complex formed by the combination of a solute (e.g., a metalloprotease inhibitor) and a solvent (e.g., water). See J. Honig et al., The Van Nostrand Chemist's Dictionary, p. 650 (1953).

5 The terms "optical isomer", "geometric isomer" (e.g., a cis and/or trans isomer), "stereoisomer", and "diastereomer" have the accepted meanings (see, e.g., Hawley's Condensed Chemical Dictionary, 11th Ed.). The illustration of specific protected forms and other derivatives of the compounds of the instant invention is not intended to be limiting. The
10 application of other useful protecting groups, salt forms, prodrugs etc., is within the ability of the skilled artisan.

A "prodrug" is a form of a drug that must undergo chemical conversion by metabolic processes before becoming an active, or fully active,
15 pharmacological agent. A prodrug is not active, or is less active, in its ingested or absorbed or otherwise administered form. For example, a prodrug may be broken down by bacteria in the digestive system into products, at least one of which will become active as a drug. Alternatively, it may be administered systemically, such as by intravenous injection, and subsequently
20 be metabolized into one or more active molecules.

As used herein, the term " IC_{50} " refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response in an assay that measures such response. In some method
25 embodiments of the invention, the " IC_{50} " value of a compound of the invention can be greater for normal cells than for cells exhibiting a proliferative disorder, e.g., breast cancer cells. The value depends on the assay used.

By a "standard" is meant a positive or negative control. A negative
30 control in the present case refers to a normal as opposed to a cancerous cell, e.g., a sample possessing Wnt/ β -catenin pathway activity that correlates with a normal cell. A negative control may also include a sample that contains no

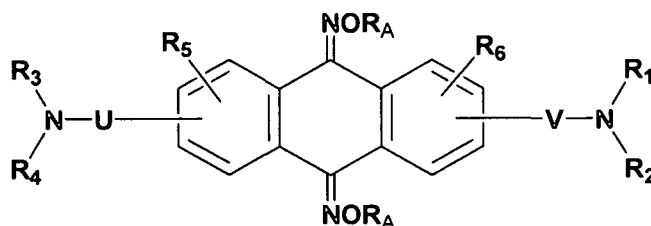
such pathway. By contrast, a positive control does contain such pathway, preferably of an amount that correlates with overexpression as found in proliferative disorders, e.g., breast cancers. The controls may be from cell or tissue samples, or else contain purified ligand (or absent ligand), immobilized
 5 or otherwise. In some embodiments, one or more of the controls may be in the form of a diagnostic "dipstick."

By "selectively targeting" is meant affecting one type of cell to a greater extent than another, e.g., in the case of cancerous cells versus non-
 10 cancerous cells.

DETAILED DESCRIPTION OF THE INVENTION

15

The present invention provides a compound having the structure of Formula I



20

Formula I

Wherein each R_A is independently selected from H, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, $-C(=O)R_B$, $-C(=O)OR_B$, $-C(=O)NR_BR_C$, $-C(=NR_B)R_C$, -
 25 NR_BR_C , heterocycloalkyl, aryl or polyaromatic, heteroaryl, arylalkyl and alkylaryl

wherein each of said R_B and R_C is independently H, alkyl, or heteroalkyl,

U and V are each independently selected from C=O, and O=S=O and
 30 wherein when U is C=O, V is not C=O,

R_1 , R_2 , R_3 , and R_4 are each independently selected from H, alkyl, heteroalkyl, cycloalkyl, arylcycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, and each of said R_1 , R_2 and said R_3 , R_4 can independently combine to form heterocycloalkyl,

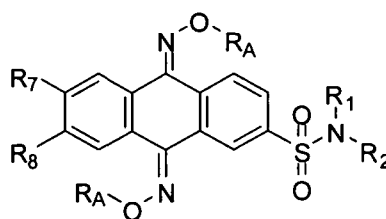
5 R_5 and R_6 are each independently selected from H, OH, SH, alkoxy, thioalkoxy, alkyl, halogen, CN, CF_3 , NO_2 , $COOR_D$, $CONR_D R_E$, $NR_D R_E$, $NR_D COR_E$, $NR_D SO_2 R_E$, and $NR_F CONR_D R_E$; wherein R_D , R_E and R_F are independently H, alkyl, heteroalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, 10 cycloalkyl, or heterocycloalkyl;

and wherein when each R_A is NOH, and U and V are each O=S=O and one of R_1 or R_2 and one of R_3 or R_4 is phenyl or substituted phenyl, then the other of R_1 or R_2 and R_3 or R_4 is not H or alkyl,

including all pharmaceutically acceptable salts, esters, amides, 15 stereoisomers, geometric isomers, solvates or prodrugs thereof.

In one preferred embodiment, X and Y are each NOH.

20 In one such embodiment, the invention provides a compound (an anthraquinone derivative) having the structure of Formula II



Formula II

25

wherein R_7 and R_8 are independently selected from H and $SO_2 NR_3 R_4$, wherein one of R_7 and R_8 is hydrogen and wherein the other substituents have the meaning defined for Formula I.

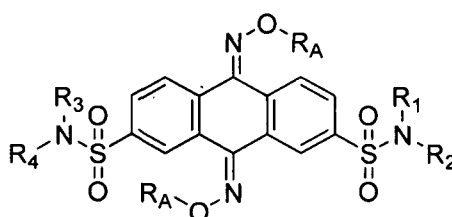
In specific examples of the compounds of Formula I, U and V are each O=S=O.

In all embodiments of Formula I, when X and Y are both NOH, and U and V are each O=S=O and one of R₁ or R₂ and one of R₃ or R₄ is phenyl then the other of R₁ or R₂ and R₃ or R₄ is not H or alkyl.

In specific embodiments of Formula II, R₁, R₂, R₃, and R₄ are each independently selected from H, alkyl, cycloalkyl, alkenyl, or alkynyl. In other such examples, R_A is hydrogen and R₁, R₂, R₃, and R₄ are each independently selected from H, alkyl, cycloalkyl, alkenyl, or alkynyl. In additional examples, NR₁R₂ and NR₃R₄ are independently 6- to 15-membered, preferably a 6 to 10 membered heterocycle, preferably a heterocycloalkyl, most preferably an 8 or 9 membered ring.

15

In one specific embodiment, a compound of the invention has the structure of Formula III

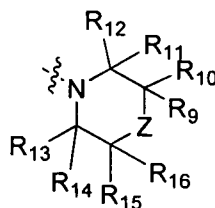


Formula III

20

wherein NR₁R₂ and NR₃R₄ are independently 6- to 12-membered heterocycloalkyl containing one nitrogen in the ring and wherein the R groups are defined as for Formula II. In preferred embodiments, at least one R_A is H, or both are H. In another preferred embodiment of Formula III, NR₁R₂ and NR₃R₄ are independently selected from Formula IV

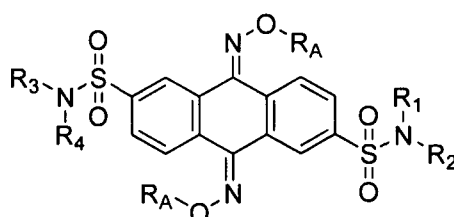
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Formula IV

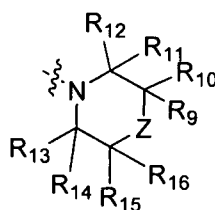
wherein Z is $(\text{CR}_{17}\text{R}_{18})_m$ and $m = 1-4$, R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{15} , R_{16} , R_{17} , and R_{18} are independently H, methyl, ethyl, propyl, butyl, methoxy or ethoxy.

- 5 In one embodiment, a compound of the invention has the structure of Formula V



10 **Formula V**

- wherein NR_1R_2 and NR_3R_4 are independently 6- to 12-membered heterocycloalkyl containing one nitrogen in the ring and the other R groups are as defined for Formula II. In preferred embodiments thereof, at least one R_A is H or both are H. In another such embodiment thereof, NR_1R_2 and NR_3R_4 are independently from formula VI:



20 **Formula VI**

20

wherein Z is $(\text{CR}_{17}\text{R}_{18})_m$ and $m = 1-4$, R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{15} , R_{16} , R_{17} , and R_{18} are independently H, methyl, ethyl, propyl, butyl, methoxy or ethoxy.

25

In one embodiment of the invention, a compound of the invention has the structure of a compound shown in Table 1 so that each said structure is

alone a separate embodiment of the invention. In preferred examples of such embodiments, the invention specifically contemplates a compound selected from compounds 1-1, 1-2, 1-3, 1-4, 1-5, 1-6, 1-22, 1-26, 1-37, 1-44, 1-45, 1-46, 1-49, 1-51, 1-56, 1-77, 1-95 of Table 1.

5

In another preferred embodiment, a compound of the invention has the structure of a compound of Table 3. Specific examples of such preferred embodiment are compounds 3-1, 3-2, 3-3, 3-4, 3-7, 3-8, 3-11, 3-13, 3-14, 3-16, 3-21, 3-28, 3-38, 3-39 and 3-40 of Table 3.

10

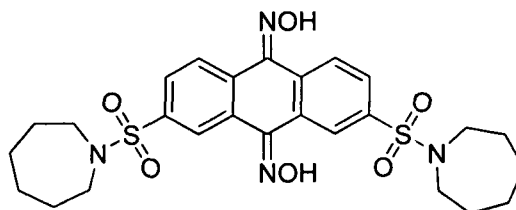
Other preferred embodiments, the compounds are those with structures shown in Tables 2 and/or 4.

Specific embodiments of the invention utilize any of such compounds, including combination of such compounds, or combinations of one or more of such compounds with one or more additional therapeutic agents, preferably an anticancer agent (e.g., those used in Example 12), in treating any or all of the cancers recited herein, such as one or more of colon cancer, adenocarcinoma, rectal cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, adenomatous polyposis, and hepatocellular carcinoma, with colon and colorectal cancer being especially preferred.

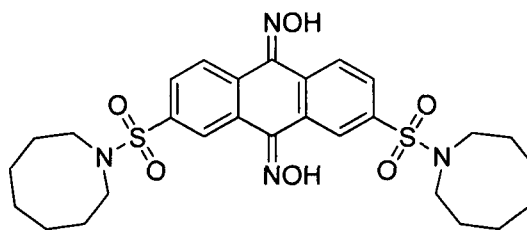
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One preferred embodiment of the invention is 2,7-bis(azepan-1-ylsulfonyl)anthracene-9,10-dione dioxime:

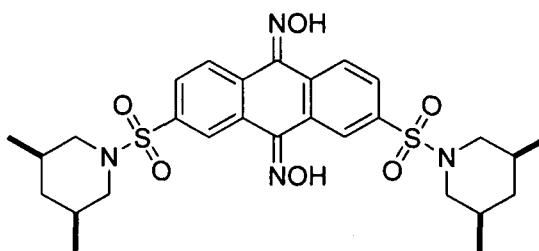
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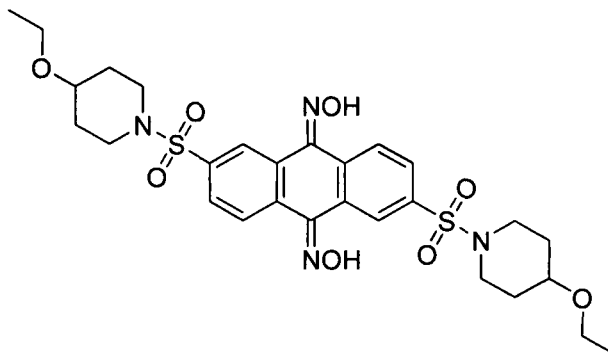
One preferred embodiment of the invention is 2,7-bis(azocan-1-ylsulfonyl)anthracene-9,10-dione dioxime:



One preferred embodiment of the invention is 2-((3R,5S)-3,5-dimethylpiperidin-1-ylsulfonyl)-7-((3S,5R)-3,5-dimethylpiperidin-1-ylsulfonyl)anthracene-9,10-dione dioxime:

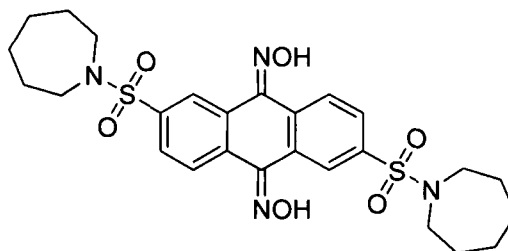


One preferred embodiment of the invention is 2,6-bis(4-ethoxypiperidin-1-ylsulfonyl)anthracene-9,10-dione dioxime:



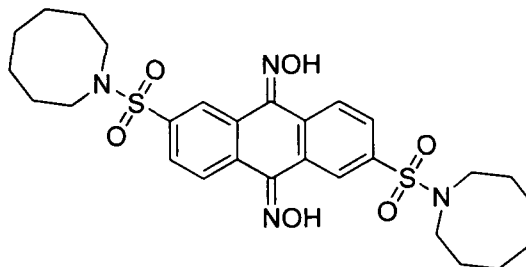
10

One preferred embodiment of the invention is 2,6-bis(azepan-1-ylsulfonyl)anthracene-9,10-dione dioxime:

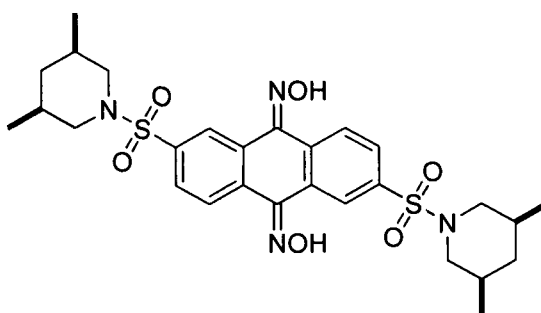


15

One preferred embodiment of the invention is 2,6-bis(azocan-1-ylsulfonyl)anthracene-9,10-dione dioxime:



5 One preferred embodiment of the invention is 2,6-bis((3R,5S)-3,5-dimethylpiperidin-1-ylsulfonyl)anthracene-9,10-dione dioxime:



10 The present invention also relates to compositions of compounds, including pharmaceutically acceptable salts thereof, having the structures defined above for Formulas I to VI (with substituents as disclosed therein), preferably compounds of Tables 1 to 4, in a therapeutically effective amount in a pharmaceutically acceptable carrier:

15

The compounds of said compositions may also contain a multi-ring cycloalkyl or heterocycloalkyl bridge structure (as in Tables 1 to 4) containing a total of up to 12 atoms and up to 4 heteroatoms selected from N and O.

20 The present invention also provides therapeutic compositions of any of the compounds of the invention, such as the compounds of Tables 1 to 4.

The compounds of the invention may be in the form of pharmaceutically acceptable salts, esters, amides, stereoisomers, geometric

isomers, solvates or prodrugs thereof. Where a compound of the invention is a stereoisomer, the latter may be an enantiomer or a diastereomer. Where said compound is a enantiomer (or contains a chiral center, for example, a chiral carbon atom), the form of the compound used for pharmaceutical purposes may include either enantiomer or the racemate, although one of said enantiomers may be preferred, such as where it is the active form or is more active than the other enantiomer. Where said compound of the invention is a geometric isomer (e.g., contains a carbon pair with substituents attached in cis- or trans- configuration), either the cis- form, or the trans- form, may be preferred for pharmaceutical use, although mixtures of the cis- and trans- forms may be used in the methods of the invention to the extent they have the desired pharmaceutical effect.

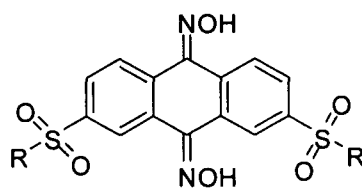
A "pharmaceutically-acceptable salt" is a cationic salt formed at any acidic (e.g., carboxylic acid) group, or an anionic salt formed at any basic (e.g., amino) group. Many such salts are known in the art, as described in WO 87/05297 (Johnston et al., published September 11, 1987 incorporated by reference herein). Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydriodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate; palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Preferred cationic salts include the alkali metal salts (such as sodium and potassium), and alkaline earth metal salts (such as magnesium and calcium) and organic salts. Preferred anionic salts include the halides (such as chloride salts), sulfonates, carboxylates, phosphates, and the like.

This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

5 In another aspect, the present invention relates to compositions of any of the compounds of the invention, preferably wherein such compound is present in a pharmaceutically acceptable carrier and in a therapeutically effective amount. Such compositions will generally comprise an amount of such compound that is not toxic (i.e., an amount that is safe for therapeutic
10 uses).

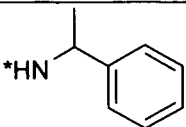
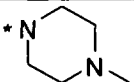
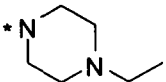
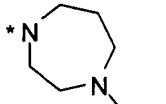
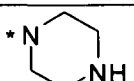
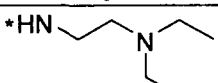
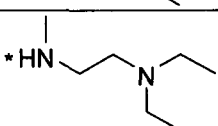
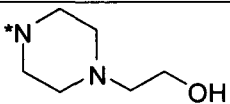
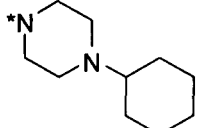
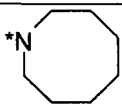
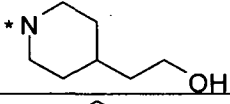
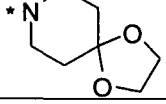
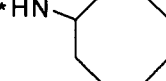
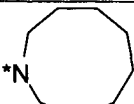
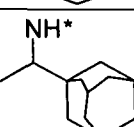
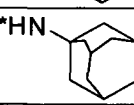
The present invention also contemplates metabolites of any of the novel compounds of the invention, such metabolites representing second compound formed by one or more *in vivo* metabolic reactions on a first
15 compound following administration of the latter to a mammal wherein the first compound is a novel compound of the invention. In preferred embodiments, said first compound is any of the compounds disclosed herein as having a structure as defined for Formulas I to VI, with the substituents disclosed for those formulas, and even more preferably any compound of Tables 1, 2, 3 or
20 4, including all pharmaceutically acceptable salts thereof.

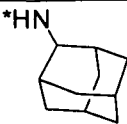
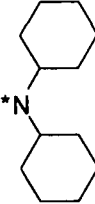
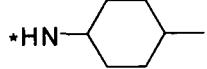
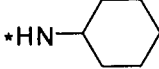
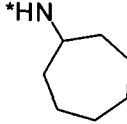
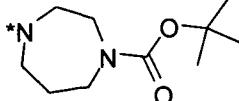
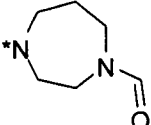
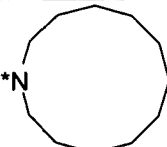
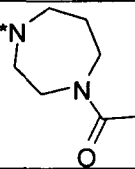
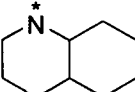
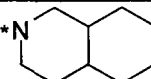
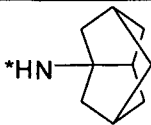
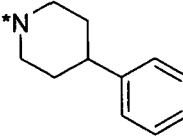
Selected examples of compounds of the invention include, but are not limited to, any or all of the compounds of Tables 1-4, including all pharmaceutically acceptable salts thereof as well as metabolites of any said
25 compounds produced by normal mammalian, especially human, metabolism of said compounds after administration to said mammal as a therapeutic agent. Any and all such compounds are specifically claimed for their use in any and all of the methods of the invention. In each indicated structure, the ligand is attached via the atom marked with an asterisk (*). For example, in
30 Table 1 (anthraquinone dioximes) the sulfur atoms of the indicated formula (i.e., the "core structure") are attached to the indicated R group at the asterisked nitrogen of the R column of the table; similarly for the other tables.

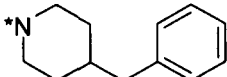
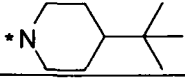
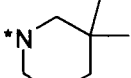
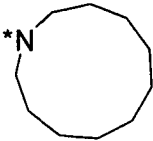
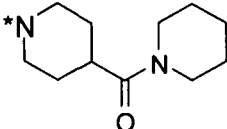
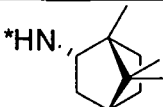
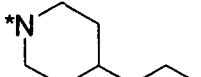
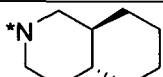
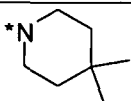
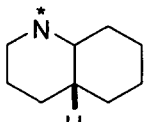
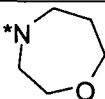
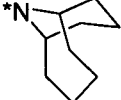
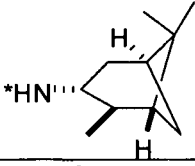
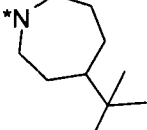
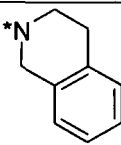
Table 1

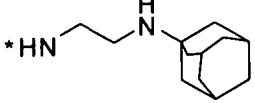
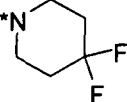
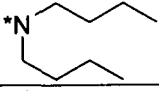
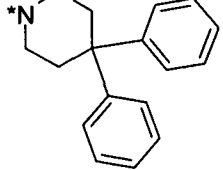
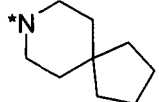
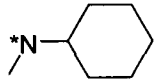
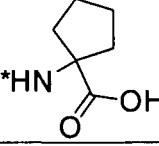
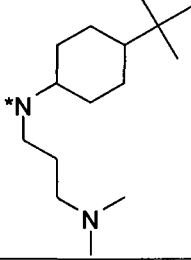
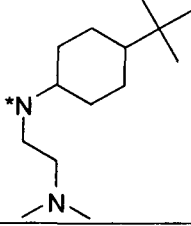
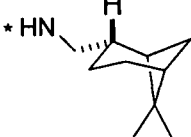
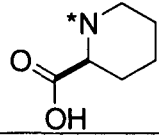
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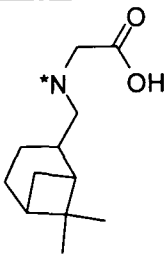
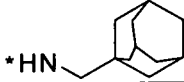
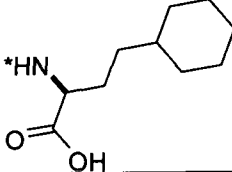
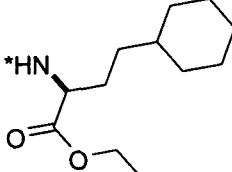
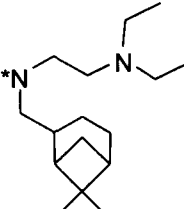
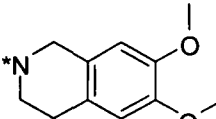
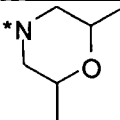
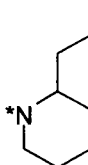
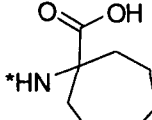
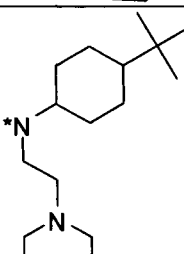
Compound	R	MW
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1-2		560.6
1-3		536.5
1-4		560.6
1-5		560.6
1-6		588.7
1-7		676.7
1-8		562.6
1-9		590.7
1-10		604.7
1-11		590.7
1-12		622.7

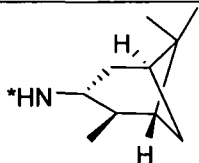
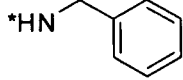
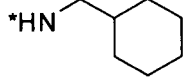
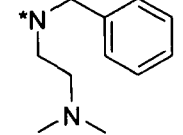
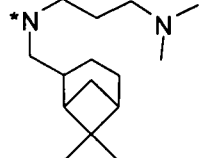
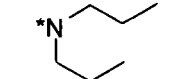
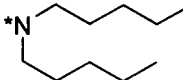
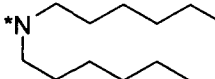
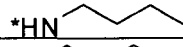
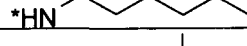
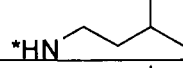
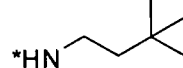
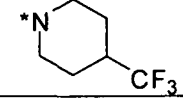
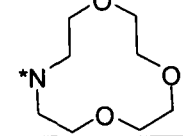
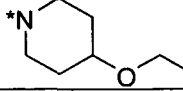
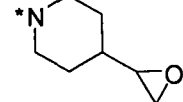
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1-14		562.6
1-15		590.7
1-16		618.7
1-17		534.6
1-18		594.7
1-19		622.7
1-20		622.7
1-21		698.8
1-22		588.7
1-23		620.7
1-24		648.7
1-25		616.7
1-26		616.7
1-27		720.9
1-28		664.8

1-29		664.8
1-30		724.9
1-31		672.8
1-32		588.7
1-33		560.6
1-34		588.7
1-35		762.8
1-36		618.6
1-37		700.9
1-38		646.7
1-39		640.8
1-40		640.8
1-41		636.7
1-42		684.8

1-43		712.8
1-44		644.8
1-45		588.7
1-46		672.8
1-47		754.9
1-48		668.8
1-49		616.7
1-50		640.8
1-51		588.7
1-52		640.8
1-53		564.6
1-54		640.8
1-55		668.8
1-56		672.8
1-57		628.7

1-58		750.9
1-59		604.5
1-60		620.8
1-61		837.01
1-62		640.8
1-63		588.7
1-64		620.6
1-65		843.1
1-66		815.1
1-67		668.8
1-68		620.6
1-69		508.6

1-70		784.9
1-71		692.8
1-72		732.8
1-73		788.9
1-74		867.2
1-75		748.8
1-76		592.6
1-77		616.7
1-78		676.7
1-79		871.2

1-80		696.9
1-81		576.6
1-82		588.7
1-83		718.8
1-84		839.1
1-85		564.7
1-86		676.9
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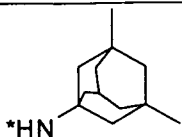
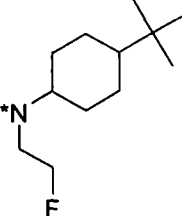
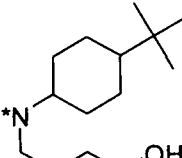
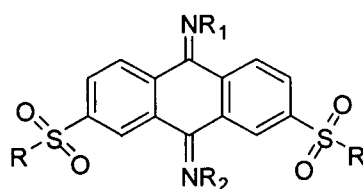
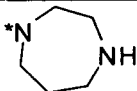
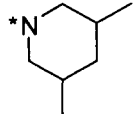
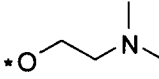
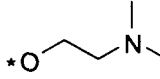
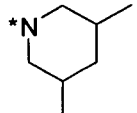
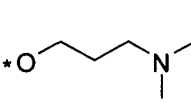
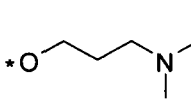
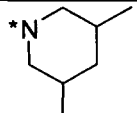
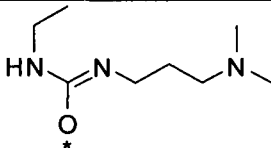
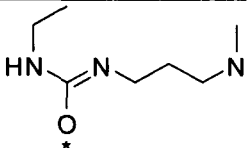
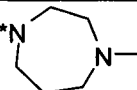
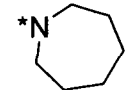
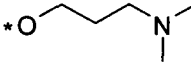
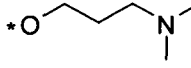
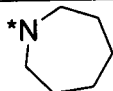
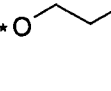
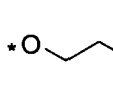
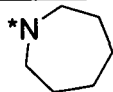
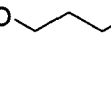
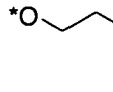
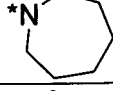
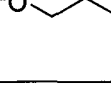
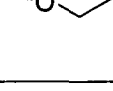
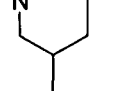
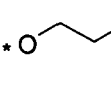
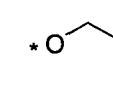
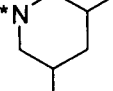
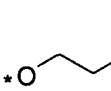
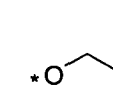
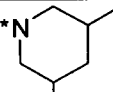
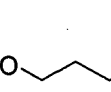
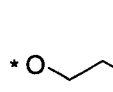
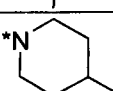
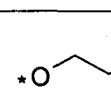
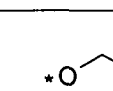
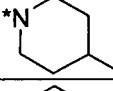
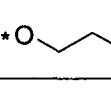
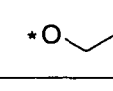
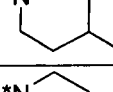
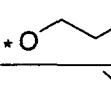
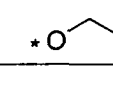
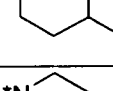
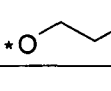
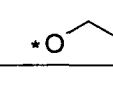
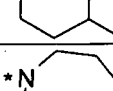
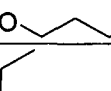
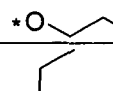
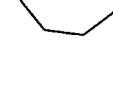
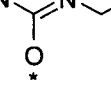
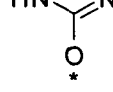
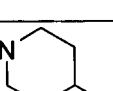
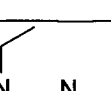
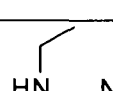
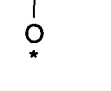
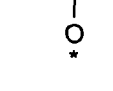
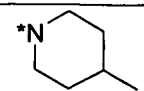
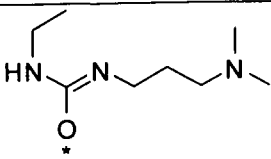
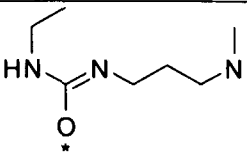
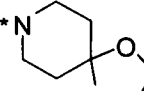
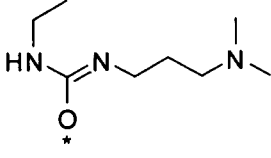
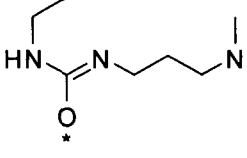
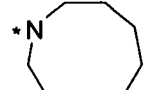
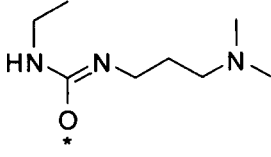
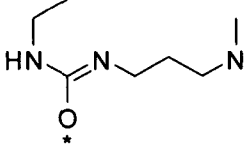
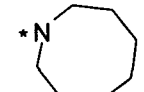
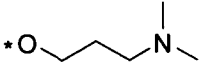
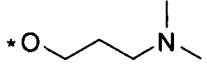
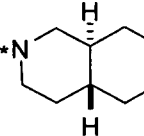
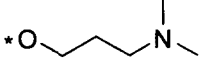
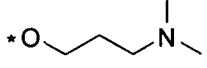
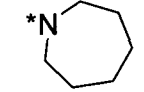
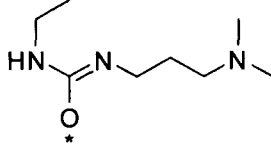
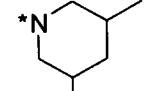
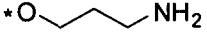
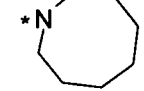
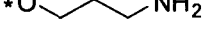
1-97		720.9
1-98		764.9
1-99		817.1

Table 2

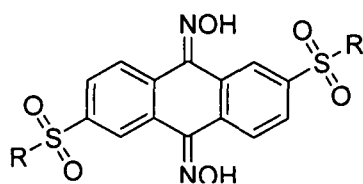
Compound	R	R₁	R₂	MW
2-1				590.7
2-2				730.9
2-3				759.03
2-4				899.2
2-5				618.7
2-6				730.9

2-7				817.1
2-8				702.9
2-9				674.8
2-10				783.05
2-11				811.1
2-12				839.1
2-13				702.9
2-14				730.9
2-15				755
2-16				783.1
2-17				811.1
2-18				899.2
2-19				931.2
2-20				702.9

2-21				871.1
2-22				959.1
2-23				927.2
2-24				759.03
2-25				811.1
2-26				715.9
2-27				645.8
2-28				645.8

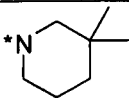
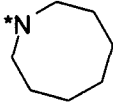
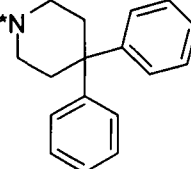
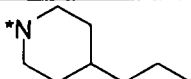
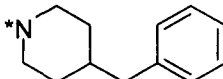
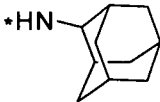
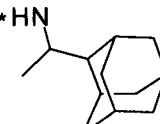
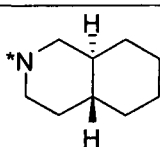
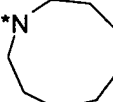
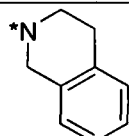
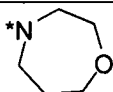
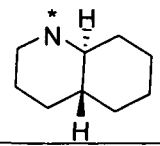
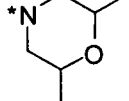
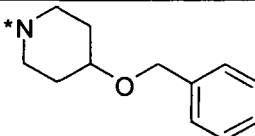
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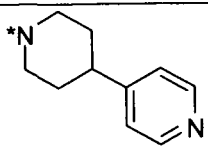
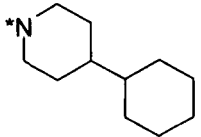
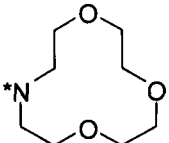
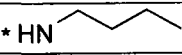
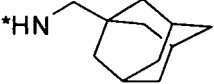
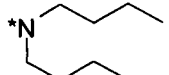
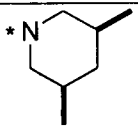
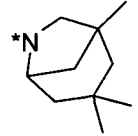
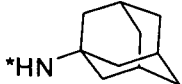
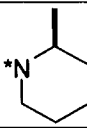
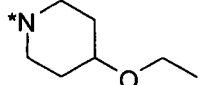
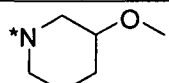
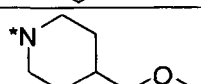
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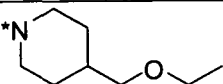
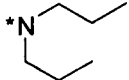
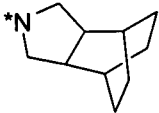
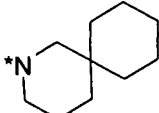
Table 3

5

Compound	R	MW
3-1		560.6
3-2		560.6
3-3		532.6
3-4		588.7
3-5		676.7
3-6		590.7
3-7		560.6
3-8		588.7
3-9		640.8
3-10		684.8
3-11		644.8
3-12		668.8

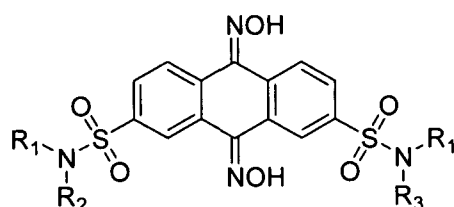
3-13		588.7
3-14		588.7
3-15		837.01
3-16		616.7
3-17		712.8
3-18		664.8
3-19		720.9
3-20		640.8
3-21		616.7
3-22		628.7
3-23		564.6
3-24		640.8
3-25		592.6
3-26		744.8

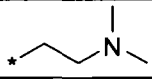
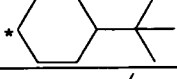
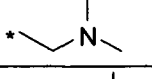
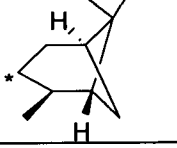
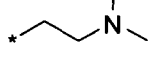
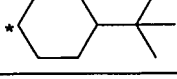
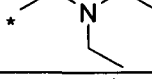
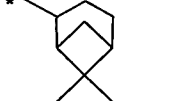
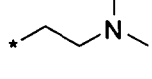
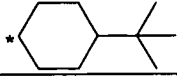
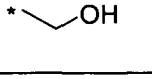
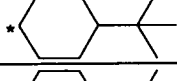
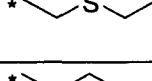
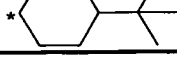
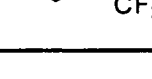
3-27		686.8
3-28		588.7
3-29		696.9
3-30		668.8
3-31		718.7
3-32		508.6
3-33		692.8
3-34		620.8
3-35		644.8
3-36		668.8
3-37		664.8
3-38		560.6
3-39		620.7
3-40		592.6
3-41		620.7

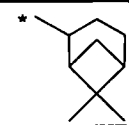
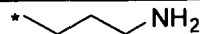
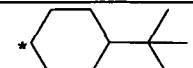
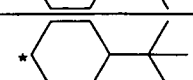
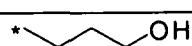
3-42		648.7
3-43		564.7
3-44		672.8
3-45		664.8
3-46		668.8

5

Table 4



Compound	R ₁	R ₂	R ₃	MW
4-1		H		758.1
4-2		H		744.0
4-3		H		754.0
4-4		H		772.1
4-5		H		754.0
4-6		H		717.0
4-7		H		761.1
4-8		H		783.0

4-9		H		740.0
4-10		H		718.9
4-11		H		745.0

In accordance with the foregoing, the present invention is directed to use of the compounds of the invention as active ingredients for medicaments, in particular for medicaments useful for the treatment of tumors. The compounds of the invention will thus be present in pharmaceutical compositions containing, for example, compounds of Formula I as active ingredients, in admixture with pharmaceutically acceptable vehicles and excipients, which includes any pharmaceutical agent that does not itself induce the production of antibodies harmful to the individual receiving the composition, and which may be administered without undue toxicity. Pharmaceutically acceptable carriers include, but are not limited to, liquids such as water, saline, glycerol and ethanol, and the like, including carriers useful in forming sprays for nasal and other respiratory tract delivery or for delivery to the ophthalmic system. A thorough discussion of pharmaceutically acceptable carriers, diluents, and other excipients is presented in REMINGTON'S PHARMACEUTICAL SCIENCES (Mack Pub. Co., N.J. current edition). Use of such carriers is well known to those skilled in the art and will not be described further herein.

20

Also in accordance with the foregoing, the present invention relates to a method for preventing or treating a disease associated with a change in levels of expression of particular sets of genes in a mammal comprising administering to said mammal an effective amount of a compound of the invention.

25

Compounds according to the present invention have, for example, the effect of reducing size and/or number of tumors, especially primary tumors, in a mammal, especially a human, in need of such treatment. A statistically

significant change in the numbers of primary tumor or metastasizing cells will typically be at least about 10%, preferably 20%, 30%, 50%, 70%, 90%, or more.

5 In accordance with the present invention, the agents described herein may be combined with other treatments of the medical conditions described herein, such as other chemotherapies, radiation treatments, immunotherapy, surgical treatments, and the like. The compounds of the invention may also be administered in combination with such other agents as painkillers, diuretics,
10 antidiuretics, antivirals, antibiotics, nutritional supplements, anemia therapeutics, blood clotting therapeutics, bone therapeutics, and psychiatric and psychological therapeutics.

 Determination of the appropriate treatment dose is made by the
15 clinician, e.g., using parameters or factors known in the art to affect treatment or predicted to affect treatment. Generally, the dose begins with an amount somewhat less than the optimum dose and it is increased by small increments thereafter until the desired or optimum effect is achieved relative to any negative side effects.

20

 The specific dose of compound administered according to this invention to obtain therapeutic and/or prophylactic effect will, of course, be determined by the particular circumstances surrounding the case, including, for example, the specific compound administered, the route of administration,
25 the condition being treated, and the individual being treated. A typical daily dose (administered in single or divided doses) will contain a dosage level of from about 0.01 mg/kg to about 50-100 mg/kg of body weight of an active compound of the invention. Preferred daily doses generally will be from about 0.05 mg/kg to about 25 mg/kg and ideally from about 0.1 mg/kg to about 10
30 mg/kg. Factors such as clearance rate, half-life and maximum tolerated dose (MTD), while not specifically recited herein, may be readily determined by one of ordinary skill in the art using standard procedures.

An effective amount of a therapeutic will modulate the symptoms typically by at least about 10%; usually by at least about 20%; preferably at least about 30%; or more preferably at least about 50%. Alternatively, modulation of migration will mean that the migration or trafficking of various cancer cell types is affected. Such will result in, e.g., statistically significant and quantifiable changes in the numbers of cells being affected. This may be a decrease in the numbers of target cells being attracted within a time period or target area. Rate of primary tumor progression, size, or growth may also be monitored.

10

In another aspect, the present invention relates to a method for preventing or treating a disorder modulated by altered gene expression, such as one or more of cancer, cardiovascular disorders, arthritis, osteoporosis, inflammation, periodontal disease and skin disorders, comprising administering to a mammal in need of such treatment or prevention a therapeutically effective amount of a compound of the invention.

In a preferred embodiment, the present invention relates to a method of preventing, treating or ameliorating cancer or tumor metastasis in a mammal comprising administering to said mammal an effective a compound of the invention, preferably where said mammal is a human.

Compounds of the invention may also be administered in combination (simultaneously or sequentially) with other chemotherapeutic agents. Such combination administration preferably results in a synergistic effect. In one preferred embodiment of the methods of the invention a compound of the invention is administered with an agent such as HMG CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitor, for example, atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, and the like (useful in the treatment of cardiovascular disorders (e.g., atherosclerosis) as described in WO 2006/083214). Other preferred agents for co-administration include 5-fluorouracil and oxaliplatin. Procedures for such co-administration are provided in Example 12 (see data in Table 8).

The compounds of the invention will commonly exert a therapeutic effect by modulation of one or more genes found in a cell, especially a mammalian cell, such as a cancer cell, preferably colon cancer and most preferably adenocarcinoma. Thus, a compound, or compounds, of the invention can be used to determine or demarcate a set of genes by determining modulation of such set of genes by one or more compounds of the invention. For example, where a set of genes is found to be up regulated in cancer cells versus otherwise normal cells, especially normal cells of the same tissue or organ as the cancer cells, a set of genes can be determined by their common property of being modulated (based on a change in expression of the genes, such as a change in rate or amount of RNA transcribed or the amount of polypeptide produced by said expression) by contacting such genes, or a cell containing such genes, with one or more of the compounds of the invention. The extent of such modulation may, of course, be related to the amount of said compound, or compounds, used in the contacting. Such modulation may include the increased expression of all the determined genes (i.e., the genes of the set), the decreased expression of all genes of the set, or the increase in expression of some of the genes of the set and decreased expression of others. Thus, a gene not modulated by the test compound (the compound used in contacting the genes or cell containing them) is not considered a member of the set.

Thus, the present invention relates to a gene set wherein expression of each member of said gene set is modulated as a result of contacting said gene set with a compound of the invention. In specific embodiments, expression of each member of said gene set is increased as a result of said contacting or is decreased as a result of said contacting. In another preferred embodiment, the gene set is present in a cell. Such a gene set will commonly be related to a specific disease process, such as a set of genes all of which are modulated by a compound of the invention wherein such compound has a specific therapeutic effect, such as being an anti-neoplastic agent. Such a gene set is shown in Table 5. Any subset of the genes of Table 5 may also form a gene set as contemplated by the invention.

Table 5.

Gene No.	Gene Name
1	Activating transcription factor 3
2	AHNAK nucleoprotein 2
3	Aldo-keto reductase family 1, member C2 (dihydrodiol dehydrogenase 2; bile acid binding protein; 3-alpha hydroxysteroid dehyd
4	Basic helix-loop-helix domain containing, class B, 2
5	CD200 molecule
6	Chemokine (C-C motif) ligand 20
7	Chromosome 13 open reading frame 15
8	Cytidine deaminase
9	Dehydrogenase/reductase (SDR family) member 9
10	DNA-damage-inducible transcript 3
11	DnaJ (Hsp40) homolog, subfamily B, member 9
12	DnaJ (Hsp40) homolog, subfamily C, member 12
13	Dopa decarboxylase (aromatic L-amino acid decarboxylase)
14	Dual specificity phosphatase 1
15	Dual specificity phosphatase 5
16	Epithelial membrane protein 3
17	GABA(A) receptor-associated protein like 1
18	GABA(A) receptors associated protein like 3
19	Growth differentiation factor 15
20	GTP binding protein overexpressed in skeletal muscle
21	Helicase, lymphoid-specific
22	Heme oxygenase (decycling) 1
23	Histone cluster 2, H2be
24	hypothetical protein MGC14376
25	IL8
26	Interferon stimulated exonuclease gene 20kDa
27	Interleukin 32
28	Interleukin 8
29	Laminin, alpha 3
30	Lysosomal trafficking regulator
31	NADPH oxidase 1
32	Optineurin
33	Protein phosphatase 1, regulatory (inhibitor) subunit 15A
34	PTEN induced putative kinase 1
35	Ras homolog gene family, member F (in filopodia)
36	Sclerostin domain containing 1
37	Sequestosome 1
38	Small proline-rich protein 1A
39	Small proline-rich protein 1B (cornifin)
40	Small proline-rich protein 3
41	Solute carrier family 7, (cationic amino acid transporter, y+ system) member 11
42	SPC25, NDC80 kinetochore complex component, homolog (S. cerevisiae)
43	S-phase kinase-associated protein 2 (p45)
44	Tubulin, alpha 1a

In another aspect, the present invention is drawn to a method of preventing, treating or ameliorating cancer or tumor metastasis in a mammal comprising administering to said mammal an effective amount of a compound

that modulates expression of one or more genes of Table 5. In preferred
embodiments, such compounds have the structure of Formula I, II, III and V,
with the substituents disclosed herein for those formulas, and even more
preferably any compound of Tables 1, 2, 3 or 4, including all pharmaceutically
5 acceptable salts thereof.

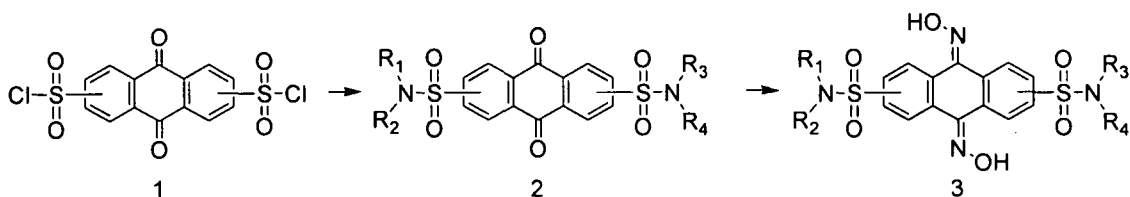
The present invention also relates to a method for ameliorating cancer
or tumor metastasis in a mammal comprising administering to said mammal
an effective amount of a compound of the invention. Especially contemplated
10 are uses of the compounds of Table 1. In selected embodiments, said cancer
is a sarcoma or said cancer is a carcinoma. Specific cancers contemplated by
the methods of the invention include, but are not limited to, one or more of
colon cancer, adenocarcinoma, rectal cancer, colorectal cancer, breast
cancer, lung cancer, ovarian cancer, adenomatous polyposis, and
15 hepatocellular carcinoma, with colon cancer and colorectal cancer being a
preferred embodiment.

The invention also provides convenient methods for the synthesis of
compound of Formula I, according to the general synthetic pathway presented
20 in Scheme 1. The starting sulfonyl chlorides 1 can be obtained by direct
chlorosulfonylation of the corresponding aromatic ring system or by
chlorination of an appropriate sulfonic acid derivative. Compounds 1 are
reacted with 6 or 7-membered cyclic amines to give secondary sulfonamides
2. Compounds 2 can be additionally transformed into derivatives 3 which in
25 some cases serve as prodrugs with modified physico-chemical and
pharmacological properties such as solubility in water, modified protein
binding properties, stability in plasma, toxicity, and others.

EXAMPLES

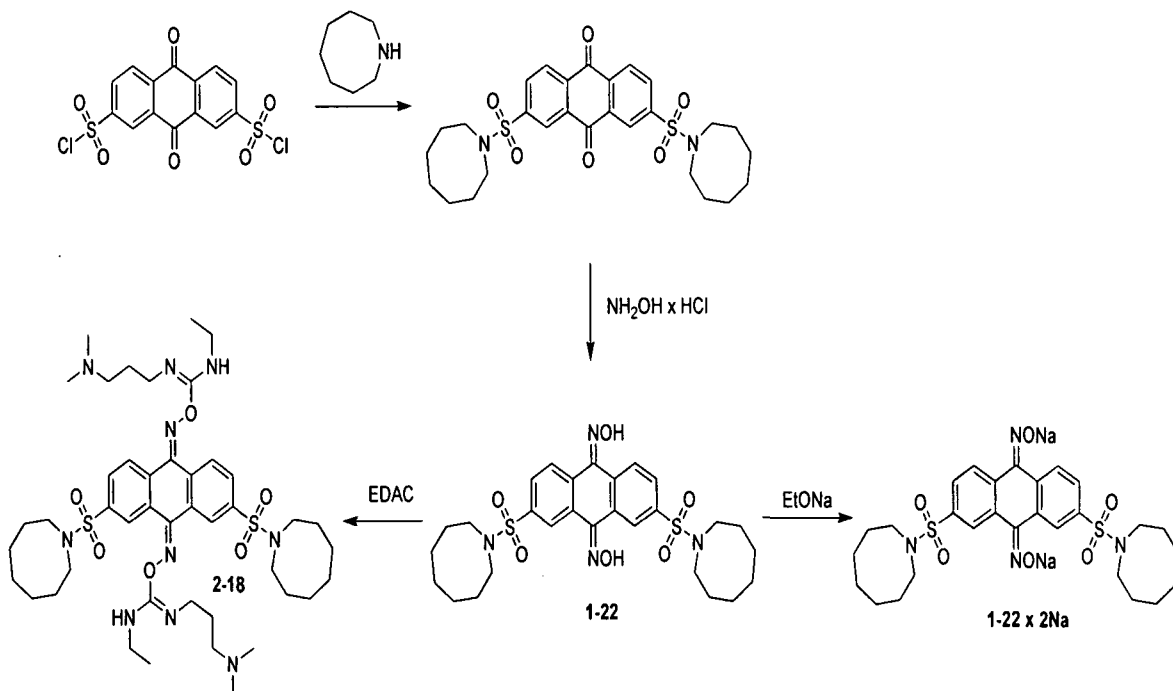
Most of the compounds disclosed herein were prepared from the corresponding sulfonyl chloride derivatives according to the general synthetic pathway presented in Scheme 1.

Scheme 1



The following Schemes and Examples are intended as an illustration of and not a limitation upon the scope of the invention as defined in the appended claims.

Scheme 2



EXAMPLE 1

2,7-bis(azocan-1-ylsulfonyl)anthracene-9,10-dione

5 Anthraquinone-2,7-disulfonylchloride (1215 mg , 3 mmole) was dissolved in 100 mL DCM. The solution was cooled to -50°C. To this solution was added 1 mL (8 mmole) of heptamethyleneimine, followed by 1 mL of diisopropylethylamine. The reaction mixture was stirred at room temperature for 4 hrs. Solvent was evaporated and the residue was treated with 1N HCl,
10 filtered off, washed with water and dried. Crude material was crystallized from chloroform-hexane to give 1.014 g (91%) of yellow compound as desired compound. $^1\text{H-NMR}$ (CDCl_3) : 8.70 (2H, d, C1 and C8), 8.47 (2H, d, C4 and C5), 8.22 (2H, dd, C3 and C6), 3.22 (8H, m), 1.70 (20H, m).

15

EXAMPLE 2

2,7-bis(azocan-1-ylsulfonyl)anthracene-9,10-dione dioxime (1-22)

The product from Example 1 (1.0 g, 1.706 mmole), 5 mL of pyridine and
20 hydroxylamine hydrochloride (1.5 g, 21.5 mmole) was stirred at 95°C for 36 hrs. Pyridine was evaporated and the residue was stirred with 1 N HCl (50 mL) for several minutes. White product was collected by filtration, washed with water and dried. Crude material was then crystallized from DCM-hexane to give 970 mg (97%) of a white compound **1-22**. $^1\text{H-NMR}$ (CDCl_3) : 9.05 (1H, dd),
25 8.75 (1H, dd), 8.35 (1H, dd), 8.05 (1H, dd), 7.90 (2H, m), 3.20 (8H, m), 1.70 (20H, m).

EXAMPLE 3

2,7-bis(azocan-1-ylsulfonyl)anthracene-9,10-dione dioxime disodium salt (2-22 x 2Na)

A mixture of compound **1-22** (620 mg, 1.0 mmole), 35 mL of DCM and 2.2 mL of 1M sodium ethoxide in ethanol was stirred with heating until a clear solution
35 was formed. To the solution was added 100 mL of ether and the mixture was

sonicated for 5 min. Yellow solid of product was collected by filtration, washed with ether and dried to give 660 mg (100%) of the title compound.

5

EXAMPLE 4

**9,10-bis(N'-(3-(dimethylamino)propyl)-N-ethylcarbamidoyloxyimino)-
2,7-bis(azocan-1-ylsulfonyl)-9,10-dihydro-anthracene tetrahydrochloride
(3-18)**

10

Compound 1-22 (442 mg, 0.75 mmole), 4 mL of anhydrous chloroform and 400 mg of EDAC were stirred at 60°C for 1 hr. The reaction mixture was condensed and chromatographed by HPLC. Combined fractions containing the desired product ($MH^+=899$) were acidified by addition of 5 mL of 1N HCl and evaporated to dryness. The product was dissolved in distilled water and lyophilized to give 530 mg (68%) of white title compound.

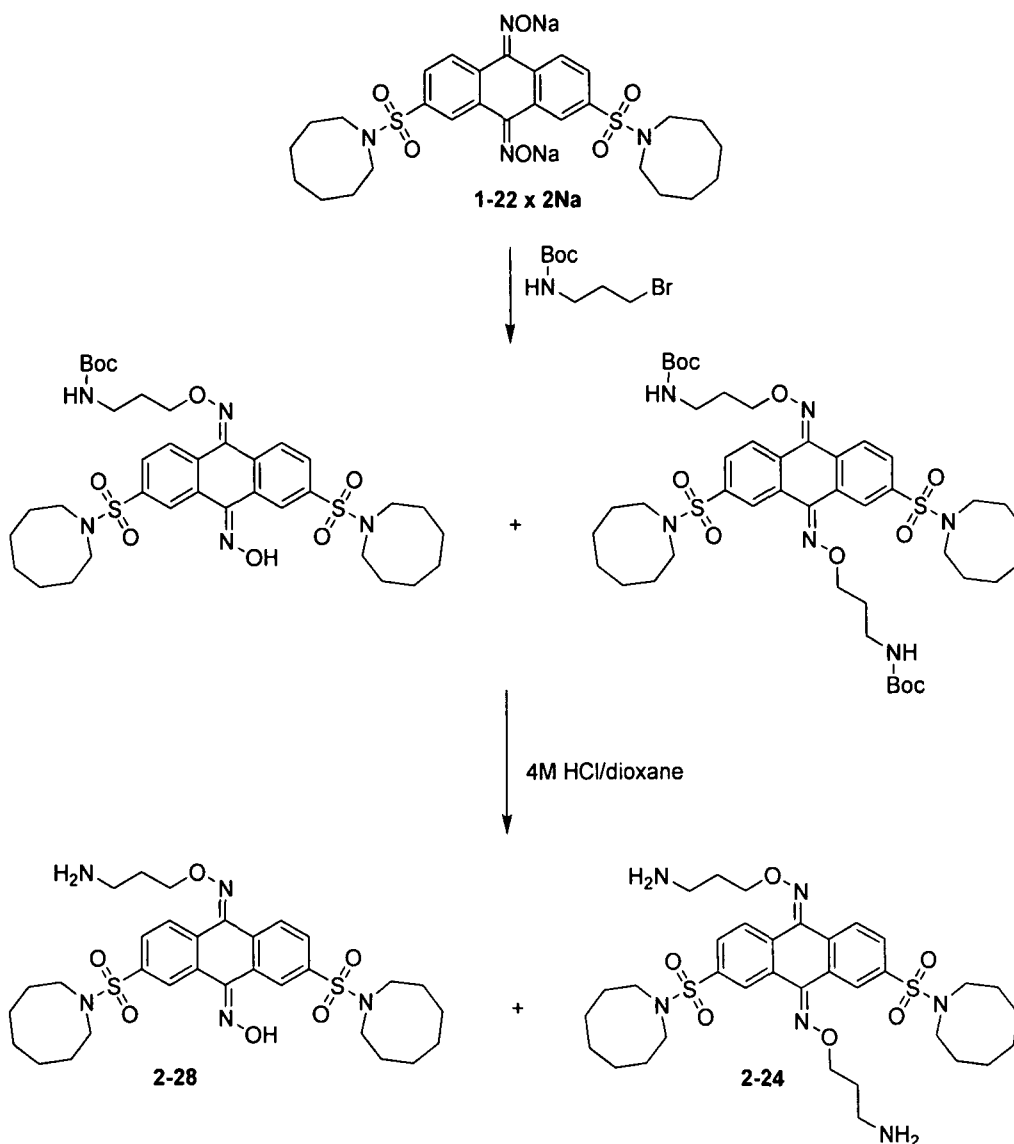
15

20

25

30

Scheme 3



EXAMPLE 5

5 **9,10-bis[(3-aminopropyl)oxyimino]-2,7-bis(azocan-1-ylsulfonyl)-9,10-dihydro-anthracene (2-24)**

To a solution of compound **1-22 x 2Na** (320 mg, 0.5 mmole) in DMSO (2 mL) tert-butyl 3-bromopropylcarbamate (180 mg, 0.75 mmole) was added and the mixture was stirred at room temperature for 1h. Water was added to the reaction mixture and precipitated products were extracted with ethyl acetate. The extract was dried with sodium sulfate, evaporated, and the residue was

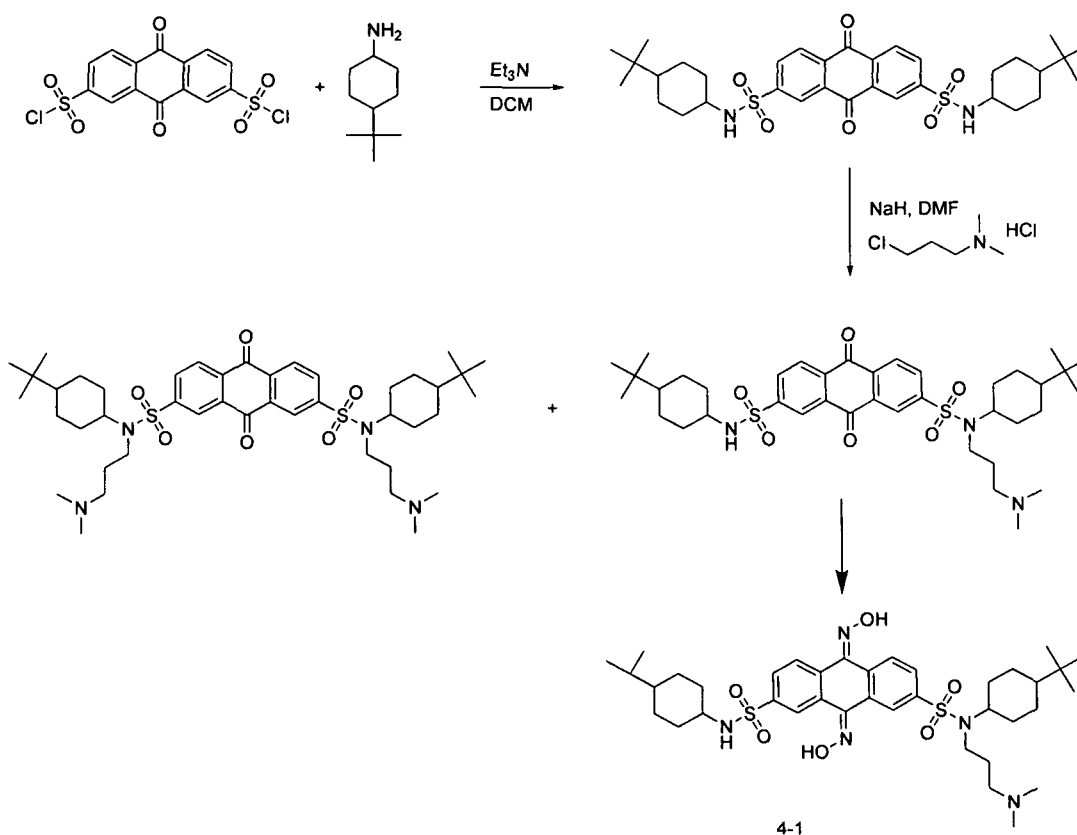
stirred with 4N HCl/dioxane (5 mL) for 1 hr. Solvent was evaporated and the residue was dissolved in methanol and purified by preparative HPLC. Fractions containing the major product were acidified with hydrochloric acid and evaporated. The residue was dissolved in water and lyophilized to provide the title compound as dihydrochloride salt (170 mg, 44% yield for 2 steps). MS 703 (MH⁺).

EXAMPLE 6

10-*(*3-aminopropyl*)*oxyimino-9-hydroxyimino-2,7-bis(azocan-1-ylsulfonyl)-9,10-dihydro-anthracene (2-28)

The title compound was isolated as a second major product from Example 5. Yield: 20% after 2 steps. MS 646 (MH⁺).

Scheme 4



EXAMPLE 7

***N*²,*N*⁷-bis(4-*tert*-butylcyclohexyl)-9,10-dioxo-9,10-dihydroanthracene-2,7-disulfonamide**

5 Anthraquinone-2,7-disulfonylchloride (10 g, 24.7 mmol)) was dissolved in 200 mL DCM. The solution was cooled to -50°C. To this solution was added 4-*tert*-butylcyclohexanamine (8.43 g, 54 mmol), followed by triethyl amine (8.6 ml, 61.7 mmol). The reaction mixture was stirred at room temperature for 4 hrs.
10 Solvent was evaporated and the residue was treated with MeOH, filtered off, and dried to obtain 15 g (95%) of the product as yellow powder.

EXAMPLE 8

***N*²,*N*⁷-bis(4-*tert*-butylcyclohexyl)-*N*²-(3-(dimethylamino)propyl)-9,10-dioxo-9,10-dihydroanthracene-2,7-disulfonamide**

and

***N*²,*N*⁷-bis(4-*tert*-butylcyclohexyl)-*N*²,*N*⁷-bis(3-(dimethylamino)propyl)-9,10-dioxo-9,10-dihydroanthracene-2,7-disulfonamide**

20 To an ice cold solution of the sulfonamide (product of Example 7, 6.82 g, 10.61 mmol) in anhydrous DMF (100 ml) under argon was added NaH (95.0%, 697 mg, 27.58 mmol). The solution was stirred for 5 min, and then 3-chloro-*N,N*-dimethylpropan-1-amine hydrochloride (2.18 g, 13.8 mmol) was
25 added. After 10 min, the reaction mixture was transferred to a pre heated oil bath at 40 °C and stirred for 3 days. LCMS showed the presence of monoalkylated and bisalkylated products (ratio, 65:25) together with unreacted starting material. After cooling, 1N NaOH was added to the reaction mixture and extracted with ethyl acetate. The organic phase was dried over
30 anhydrous magnesium sulfate and the filtrate was evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography. The unreacted starting material was recovered when the column was eluted with 40 % EtOAc in hexane. Pure monoalkylated product (LCMS, MS 728.0 (MH⁺)) was obtained when eluted using EtOAc alone and
35 the bisalkylated product (LCMS, MS 813.2 (MH⁺)) was isolated with 5%

triethylamine in EtOAc as the eluent. The fractions collected were evaporated under reduced pressure to dryness to get (3.02 g, 53 %) and (1.10 g, 17 %).

5

Example 9

***N*²,*N*⁷-bis(4-*tert*-butylcyclohexyl)-*N*²-(3-(dimethylamino)propyl)-9,10-bis(hydroxyimino)-9,10-dihydroanthracene-2,7-disulfonamide (4-1)**

The dioxime (4-1) was prepared following the general procedure using
10 monoalkylated sulfonamide (product of Example 8, 2g, 2.7 mmol), excess hydroxylamine hydrochloride (2.7 g, 27.5 mmol) and pyridine (50 ml) at 95 °C for 36 hrs. After cooling, excess hydroxylamine was removed by filtration, washed with pyridine and the filtrate was evaporated under reduced pressure to dryness. To this was added excess of aqueous 1N HCl, the oxime was
15 precipitated out, filtered to collect the colorless precipitate and dried. The oxime (4-1) was further purified by crystallization or HPLC to get it as a colorless HCl salt (1.42 g, 65%).

¹H NMR (400 MHz, DMSO-d₆) δ: 13.04-13.01 (m, 1H), 12.94-12.89 (m, 1H), 10.48 (br s, 1H), 9.18-9.07 (m, 1H), 8.87-8.78 (m, 1H), 8.40-7.78 (m, 4H),
20 3.75-3.05 (m, 16 H), 2.72 (s, 6H), 1.96-0.76 (m, 28H).

Example 10

HT-29 Growth Inhibition Activity

25

The APH (acid phosphatase) assay, which is based on quantification of cytosolic acid phosphatase activity, was utilized for determining cell viability in cell lines (Connolly et al., 1986; Friedrich et al., 2007; Martin & Clynes, 1993). Intracellular acid phosphatases in viable cells hydrolyze p-nitrophenyl
30 phosphate to p-nitrophenol. Its absorption at 405 nm is directly proportional to the cell number in the range of 10³-10⁵ monolayer cells. HT-29 cells were grown in standard flat-bottom 96-well microtiter plates and allowed to adhere for 24 hours prior to drug treatment. After 72 hours of drug treatment, the cells

were washed with PBS and 100 μ l of the assay buffer (0.1 M sodium acetate, 0.1% Triton X-100, supplemented with ImmunoPure p-nitrophenyl phosphate, Pierce Biotech. Inc., Rockford, IL USA) were added per well and incubated for 90 min at 37°C. Following incubation, 10 μ l of 1 N NaOH were supplemented to each well and absorption at 405 nm was measured within 10 minutes on a Fusion Universal Microplate Analyzer (Packard, Meriden, CT, USA). Results are shown in Table 6:

Table 6: *In vitro* cell growth inhibition

CPD#	Result		CPD#	Result		CPD#	Result
1-1	++		1-78	++		3-1	+++
1-2	+++		1-79	+++		3-2	+++
1-3	++		1-80	++		3-3	+++
1-4	+++		1-81	++		3-4	+++
1-5	+++		1-82	++		3-7	+++
1-6	+++		1-83	+++		3-8	++
1-9	+		1-84	+++		3-9	+++
1-10	++		1-85	+++		3-10	+++
1-13	++		1-86	+++		3-11	+++
1-14	+		1-87	+++		3-12	+++
1-15	++		1-88	+++		3-13	+++
1-16	++		1-89	++		3-14	+++
1-19	+		1-90	+++		3-15	+
1-26	+++		1-91	++		3-16	+++
1-27	+++		1-92	++		3-17	+++
1-28	+++		1-93	+++		3-18	+++
1-29	+++		1-95	+++		3-19	+++
1-31	+++		1-96	+++		3-20	+++
1-34	+		1-97	+++		3-21	+++
1-37	+++		1-98	+		3-22	+++
1-39	+++		1-99	+++		3-24	++

1-40	+++		2-1	++		3-26	++
1-41	+++		2-2	+++		3-28	+++
1-42	+++		2-3	+++		3-29	+++
1-43	+++		2-4	+++		3-32	+++
1-44	+++		2-5	++		3-33	+++
1-45	+++		2-6	+++		3-34	+++
1-46	+++		2-8	++		3-37	+++
1-48	+++		2-9	++		3-39	+++
1-49	+++		2-10	++		3-41	++
1-50	+++		2-11	++		3-42	+++
1-51	++		2-12	++		3-43	+++
1-52	++		2-13	+++		3-44	+++
1-55	++		2-14	+++		3-45	+++
1-56	+++		2-15	++		3-46	+++
1-57	++		2-16	+++		4-1	+++
1-59	++		2-17	++		4-2	+++
1-60	+++		2-18	+++		4-3	+++
1-62	++		2-20	++		4-4	+++
1-65	+++		2-21	++		4-5	+++
1-66	+++		2-22	+		4-6	+++
1-67	+++		2-23	+++		4-8	+
1-69	++		2-24	+++		4-9	++
1-71	+++		2-25	++		4-10	++
1-74	+++		2-26	+++		4-11	+++
1-75	+++		2-27	+++			
1-76	++		2-28	+++			
1-77	++						

Values in Table 6 indicate results as +++ (Good), ++ (Moderate) and + (Poor). The range values for these results are as follows: +++ (IC₅₀ 1 micromole or less), ++ (IC₅₀ between 1 and 5 micromole), and + (IC₅₀ greater than 5 micromole).

Example 11

In Vivo Protocol: Xenograft Efficacy Study.

5 Female nu/nu mice (20-30 g, 7-9 weeks old) were housed in ventilated racks and maintained with filtered acidified water and sterile lab chow ad libitum. Mice were allowed to acclimate for 1 week prior to testing. Before treating tumor-bearing animals with test compounds, a dose-ranging study of compound was performed in naive mice to determine the highest dose for the
10 5-week schedule. For this purpose, mice were dosed IP or ORAL once a day for one week and their body weight was monitored twice weekly for two weeks. The loss of 20% body weight or greater was considered lethal, and the highest dose was defined as that dose which caused sufficient morbidity as determined by body weight loss. [See: Emerson et al, Cancer Research, 15 (1995) 55, 603-609; Morton et al, Nature Protocols, (2007) 2(2) 247-250]

Tumors were established by injecting harvested tumor cells in a single subcutaneous site, on the flank of the mice in the left auxiliary region. The mice were then sorted according to body weight, grouped 5 mice/cage, and
20 micro-chipped for permanent identification. Within a treatment group, a narrow range in body weight ± 1 g and tumor size was established. Efficacy studies were performed over a dose range which included the highest dose. The tumor volume for each mouse was determined by measuring two dimensions with vernier calipers and calculated using the formula

25 Tumor volume = $\frac{\text{length} \times (\text{width})^2}{2}$

30 The overall growth of tumors was expressed as a ratio of T/C where the tumor volume at the end of treatment for test compounds (T) was divided by the tumor volume at the end of treatment for the vehicle (C). Compounds in Table 7 showed tumor growth inhibition compared to the control used in the study.

35

Table 7.

Cell line	Compound No.	dose	vehicle	route
Colo-205	1-10	10	PVP/glucose	IV
Colo-205	1-10	75	PVP/glucose	PO
Colo-205	1-26	15	PVP/glucose	IV
Colo-205	3-2	40	PVP/glucose	IP
Colo-205	3-2	40	PVP/glucose	IV
Colo-205	3-2	30	PVP/glucose	IP
Colo-205	3-2	40	PVP/glucose	IV
Colo-205	1-10	15	PVP/glucose	IV
Colo-205	3-2	30	PVP/glucose	PO
H460	3-2	40	PVP/glucose	IV
H460	3-2	30	PVP/glucose	IP
HT-29	1-22	75	glucose	PO
HT-29	1-6	50	glucose	PO
HT-29	1-8	25	glucose	IP
HT-29	1-22	75	glucose	PO
HT-29	1-6	25	glucose	PO
HT-29	1-22	50	glucose	PO
HT-29	2-14	5	glucose	IP
HT-29	1-22	75	glucose	PO
HT-29	1-28	75	glucose	PO
HT-29	1-6	50	glucose	PO
HT-29	1-8	50	glucose	IP
HT-29	1-6	50	glucose	PO
HT-29	3-2	40	PVP/glucose	IV
HT-29	3-2	30	PVP/glucose	PO
HT-29	1-5	75	glucose	PO
HT-29	1-6	75	glucose	PO
HT-29	1-8	25	glucose	IP
HT-29	3-4	50	glucose	PO

5

Example 12

Combination Chemotherapy

A panel of chemotherapeutics was assessed in colon cancer cell models (HT29 and SW480) to determine if the combination of these drugs with **compound 3-2** were synergistic in terms of cell death induction. Utilizing the statistical models developed by Chou and Talay (1981) ("Generalized equations for the analysis of inhibitors of Michaelis-Menten and higher order

kinetic systems with two or more mutually exclusive and non-exclusive inhibitors" in European Journal of Biochemistry, 115:207-216) we determined 4 drugs to exhibit synergy with **compound 3-2** (Table 8). Combination indices were calculated for each drug combination and values less than 1.09 for the
5 Combination Index indicate synergy and values less than 0.5 indicate strong synergy. The combination treatments for lovastatin, fluvastatin, oxaliplatin, and 5-FU are all synergistic for induction of cell death.

Table 8

10

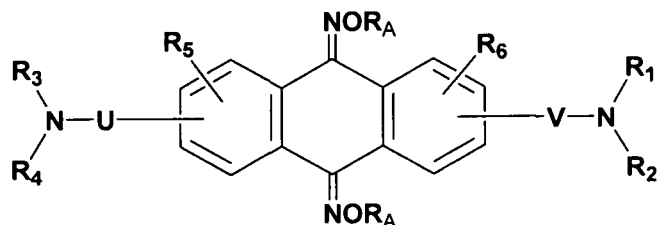
Drug	Combination Index	Result
Lovastatin	0.62	Synergy
Fluvastatin	0.72	Moderate synergy
Oxaliplatin	0.25	Strong synergy
5-FU	0.24	Strong synergy

15

20

What is claimed is:

1. A compound having the structure of Formula I

**Formula I**

Wherein each R_A is independently selected from H, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, $-C(=O)R_B$, $-C(=O)OR_B$, $-C(=O)NR_BR_C$, $-C(=NR_B)R_C$, $-NR_BR_C$, heterocycloalkyl, aryl or polyaromatic, heteroaryl, arylalkyl and alkylaryl

wherein each of said R_B and R_C is independently H, alkyl, or heteroalkyl,

U and V are each independently selected from C=O, and O=S=O and wherein when U is C=O, V is not C=O,

R_1 , R_2 , R_3 , and R_4 are each independently selected from H, alkyl, heteroalkyl, cycloalkyl, arylcycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, and each of said R_1 , R_2 and said R_3 , R_4 can independently combine to form heterocycloalkyl,

R_5 and R_6 are each independently selected from H, OH, SH, alkoxy, thioalkoxy, alkyl, halogen, CN, CF_3 , NO_2 , $COOR_D$, $CONR_DR_E$, NR_DR_E , NR_DCOR_E , $NR_DSO_2R_E$, and $NR_FCONR_DR_E$;

wherein R_D , R_E and R_F are independently H, alkyl, heteroalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or heterocycloalkyl;

and wherein when each R_A is NOH, and U and V are each O=S=O and one of R_1 or R_2 and one of R_3 or R_4 is phenyl or substituted phenyl, then the other of R_1 or R_2 and R_3 or R_4 is not H or alkyl,

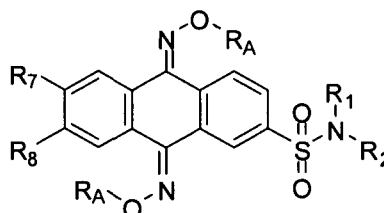
including all pharmaceutically acceptable salts, esters, amides,
5 stereoisomers, geometric isomers, solvates or prodrugs thereof.

2. The compounds of claim 1, wherein U and V are each O=S=O.

3. The compounds of claim 2, wherein NOR_A is NOH.

10

4. The compounds of claim 1 having the structure of Formula II



Formula II

15

wherein R_7 and R_8 are independently selected from H and $SO_2NR_3R_4$, wherein one of R_7 and R_8 is hydrogen and the other substituents have the meanings as defined in claim 1.

20

5. The compounds of claim 4, wherein R_1 , R_2 , R_3 , and R_4 are each independently selected from H, alkyl, cycloalkyl, alkenyl, or alkynyl.

6. The compounds of claim 4, wherein R_A is hydrogen and R_1 , R_2 , R_3 , and R_4 are each independently selected from H, alkyl, cycloalkyl, alkenyl, or alkynyl.

25

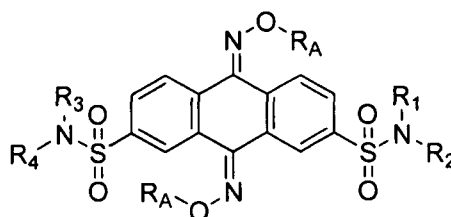
7. The compounds of claim 4, wherein NR_1R_2 and NR_3R_4 are independently 6- to 15-membered heterocycloalkyl containing one nitrogen in the ring.

30

8. The compounds of claim 7, wherein said ring is a 8-membered ring.

9. The compounds of claim 7, wherein said ring is a 9-membered ring.

5 10. The compounds of claim 4 having formula III

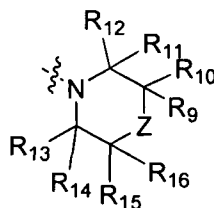


Formula III

10 wherein NR_1R_2 and NR_3R_4 are independently 6- to 12-membered heterocycloalkyl containing one nitrogen in the ring.

11. The compounds of claim 10, wherein R_A is H

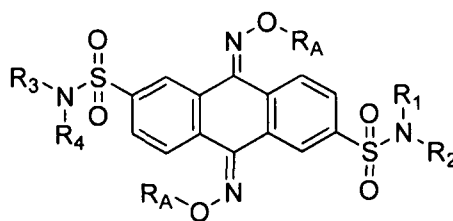
15 12. The compounds of claim 10, wherein NR_1R_2 and NR_3R_4 are independently from formula IV



Formula IV

20 wherein Z is $(\text{CR}_{17}\text{R}_{18})_m$ and $m = 1-4$, R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{15} , R_{16} , R_{17} , and R_{18} are independently H, methyl, ethyl, propyl, butyl, methoxy or ethoxy.

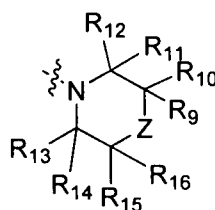
13. The compounds of claim 4 having formula V

**Formula V**

wherein NR_1R_2 and NR_3R_4 are independently 6- to 12-membered
 5 heterocycloalkyl containing one nitrogen in the ring.

14. The compounds of claim 13, wherein R_A is H

15. The compounds of claim 13, wherein NR_1R_2 and NR_3R_4 are
 10 independently from formula VI

**Formula VI**

wherein Z is $(\text{CR}_{17}\text{R}_{18})_m$ and $m = 1-4$, R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{15} ,
 15 R_{16} , R_{17} , and R_{18} are independently H, methyl, ethyl, propyl, butyl,
 methoxy or ethoxy.

16. A compound, including pharmaceutically acceptable salts thereof,
 having a structure shown in table 1.

20 17. A compound, including pharmaceutically acceptable salts thereof,
 selected from compounds 1-1, 1-2, 1-3, 1-4, 1-5, 1-6, 1-22, 1-26, 1-37, 1-
 44, 1-45, 1-46, 1-49, 1-51, 1-56, 1-77, 1-95 of table 1.

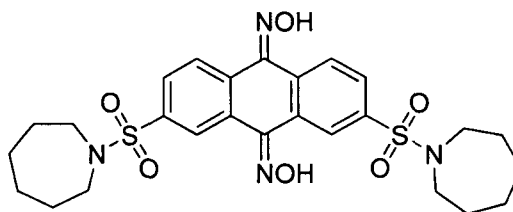
18. A compound, including pharmaceutically acceptable salts thereof,
 25 having a structure shown in Table 2.

19. A compound, including pharmaceutically acceptable salts thereof, having structure shown in table 3.

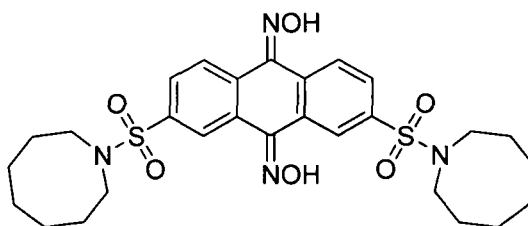
20. A compound, including pharmaceutically acceptable salts thereof, selected from compounds 3-1, 3-2, 3-3, 3-4, 3-7, 3-8, 3-11, 3-13, 3-14, 3-16, 3-21, 3-28, 3-38, 3-39 and 3-40 of table 3.

21. A compound, including pharmaceutically acceptable salts thereof, having a structure shown in Table 4.

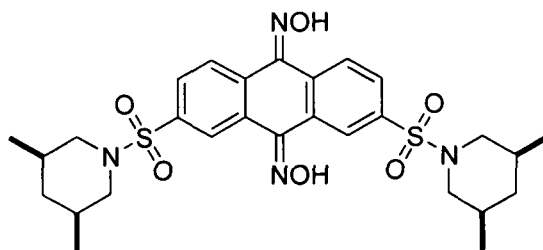
22. A compound, including pharmaceutically acceptable salts thereof, having the structure



23. A compound, including pharmaceutically acceptable salts thereof, having the structure

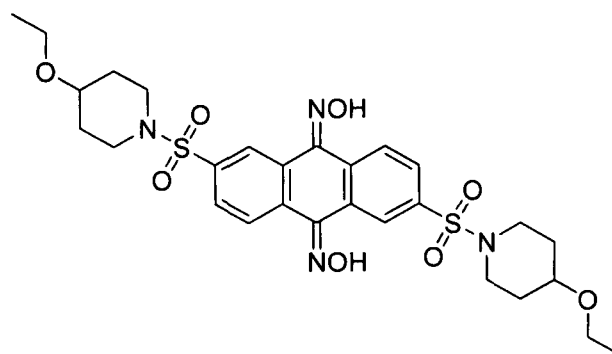


24. A compound, including pharmaceutically acceptable salts thereof, having the structure



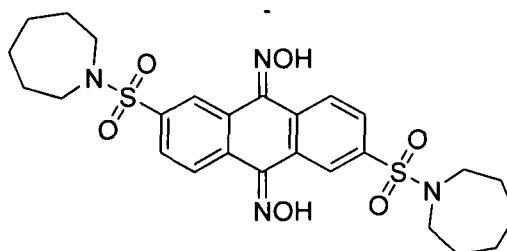
25. A compound, including pharmaceutically acceptable salts thereof, having the structure

5



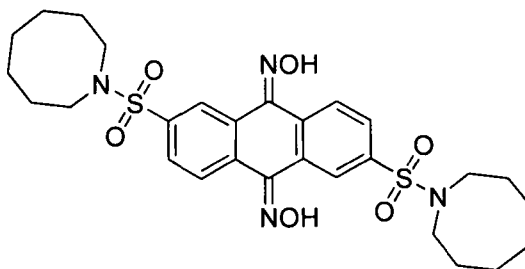
26. A compound, including pharmaceutically acceptable salts thereof, having the structure

10



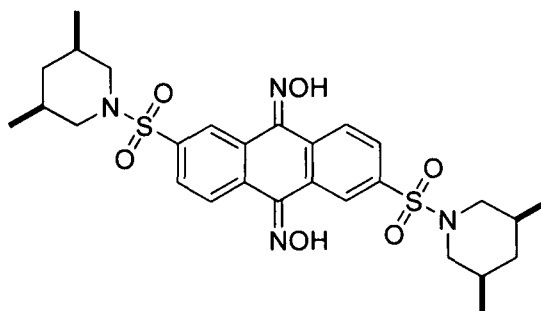
27. A compound, including pharmaceutically acceptable salts thereof, having the structure

15



28. A compound, including pharmaceutically acceptable salts thereof, having the structure

5



29. A composition comprising a therapeutically effective amount of a compound, including pharmaceutically acceptable salts thereof, of claim 1, 4, 10, 13, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28, in a pharmaceutically acceptable carrier.

10

30. The composition of claim 29, further comprising a therapeutically effective amount of at least one additional therapeutic agent wherein said additional agent is an anticancer agent.

15

31. A second compound formed by one or more *in vivo* metabolic reactions on a first compound following administration of said first compound to a mammal wherein said first compound is a compound of claim 1 and said second compound has activity in preventing, treating or ameliorating cancer or tumor metastasis in said mammal.

20

32. The second compound of claim 31, wherein said first compound is a compound of claim 4.

33. The second compound of claim 31, wherein said first compound is a compound of claim 10.

5 34. The second compound of claim 31, wherein said first compound is a compound of claim 13.

35. The second compound of claim 31, wherein said first compound is a compound of Table 1, 2, 3 or 4, including a pharmaceutically acceptable salt thereof.

10

36. The second compound of claim 31, wherein said first compound is a compound of claim 16-28.

15 37. A method of preventing, treating or ameliorating cancer or tumor metastasis in a mammal comprising administering to said mammal an effective amount of a compound of Claim 1.

20 38. The method of claim 37, wherein said cancer is a member selected from the group consisting of colon cancer, adenocarcinoma, rectal cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, adenomatous polyposis, and hepatocellular carcinoma.

39. The method of claim 38, wherein said cancer is colon cancer or colorectal cancer.

25

40. The method of claim 37, wherein said compound is administered in combination with a second therapeutic agent.

30 41. A method of preventing, treating or ameliorating cancer or tumor metastasis in a mammal comprising administering to said mammal an effective amount of the compound of claim 4.

42. The method of claim 41, wherein said cancer is a member selected from the group consisting of colon cancer, adenocarcinoma, rectal cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, adenomatous polyposis, and hepatocellular carcinoma.

5

43. The method of claim 42, wherein said cancer is colon cancer or colorectal cancer.

10

44. The method of claim 41, wherein said compound is administered in combination with a second therapeutic agent.

45. A method of preventing, treating or ameliorating cancer or tumor metastasis in a mammal comprising administering to said mammal an effective amount of the compound of claim 10.

15

46. The method of claim 45, wherein said cancer is a member selected from the group consisting of colon cancer, adenocarcinoma, rectal cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, adenomatous polyposis, and hepatocellular carcinoma.

20

47. The method of claim 46, wherein said cancer is colon cancer or colorectal cancer.

25

48. The method of claim 45, wherein said compound is administered in combination with a second therapeutic agent.

49. A method of preventing, treating or ameliorating cancer or tumor metastasis in a mammal comprising administering to said mammal an effective amount of the compound of claim 13.

30

50. The method of claim 49, wherein said cancer is a member selected from the group consisting of colon cancer, adenocarcinoma, rectal cancer,

colorectal cancer, breast cancer, lung cancer, ovarian cancer, adenomatous polyposis, and hepatocellular carcinoma.

5 51. The method of claim 50, wherein said cancer is colon cancer or colorectal cancer.

52. The method of claim 49, wherein said compound is administered in combination with a second therapeutic agent.

10 53. A method of preventing, treating or ameliorating cancer or tumor metastasis in a mammal comprising administering to said mammal an effective amount of the compound of claim 16.

15 54. The method of claim 53, wherein said cancer is a member selected from the group consisting of colon cancer, adenocarcinoma, rectal cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, adenomatous polyposis, and hepatocellular carcinoma.

20 55. The method of claim 54, wherein said cancer is colon cancer or colorectal cancer.

56. The method of claim 53, wherein said compound is administered in combination with a second therapeutic agent.

25 57. A method of preventing, treating or ameliorating cancer or tumor metastasis in a mammal comprising administering to said mammal an effective amount of the compound of claim 17.

30 58. The method of claim 57, wherein said cancer is a member selected from the group consisting of colon cancer, adenocarcinoma, rectal cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, adenomatous polyposis, and hepatocellular carcinoma.

59. The method of claim 58, wherein said cancer is colon cancer or colorectal cancer.

5 60. The method of claim 57, wherein said compound is administered in combination with a second therapeutic agent.

61. A method of preventing, treating or ameliorating cancer or tumor metastasis in a mammal comprising administering to said mammal an effective amount of the compound of claim 18.

10

62. The method of claim 61, wherein said cancer is a member selected from the group consisting of colon cancer, adenocarcinoma, rectal cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, adenomatous polyposis, and hepatocellular carcinoma.

15

63. The method of claim 62, wherein said cancer is colon cancer or colorectal cancer.

20 64. The method of claim 61, wherein said compound is administered in combination with a second therapeutic agent.

65. A method of preventing, treating or ameliorating cancer or tumor metastasis in a mammal comprising administering to said mammal an effective amount of the compound of claim 19.

25

66. The method of claim 65, wherein said cancer is a member selected from the group consisting of colon cancer, adenocarcinoma, rectal cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, adenomatous polyposis, and hepatocellular carcinoma.

30

67. The method of claim 66, wherein said cancer is colon cancer or colorectal cancer.

68. The method of claim 65, wherein said compound is administered in combination with a second therapeutic agent.

5 69. A method of preventing, treating or ameliorating cancer or tumor metastasis in a mammal comprising administering to said mammal an effective amount of a compound of claim 20.

10 70. The method of claim 69, wherein said cancer is a member selected from the group consisting of colon cancer, adenocarcinoma, rectal cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, adenomatous polyposis, and hepatocellular carcinoma.

15 71. The method of claim 70, wherein said cancer is colon cancer or colorectal cancer.

72. The method of claim 69, wherein said compound is administered in combination with a second therapeutic agent.

20 73. A method of preventing, treating or ameliorating cancer or tumor metastasis in a mammal comprising administering to said mammal an effective amount of a compound of claim 21.

25 74. The method of claim 73, wherein said cancer is a member selected from the group consisting of colon cancer, adenocarcinoma, rectal cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, adenomatous polyposis, and hepatocellular carcinoma.

30 75. The method of claim 74, wherein said cancer is colon cancer or colorectal cancer.

76. The method of claim 73, wherein said compound is administered in combination with a second therapeutic agent.

77. A method of preventing, treating or ameliorating cancer or tumor metastasis in a mammal comprising administering to said mammal an effective amount of a compound of claim 22.

5 78. The method of claim 77, wherein said cancer is a member selected from the group consisting of colon cancer, adenocarcinoma, rectal cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, adenomatous polyposis, and hepatocellular carcinoma.

10 79. The method of claim 78, wherein said cancer is colon cancer or colorectal cancer.

80. The method of claim 77, wherein said compound is administered in combination with a second therapeutic agent.

15

81. A method of preventing, treating or ameliorating cancer or tumor metastasis in a mammal comprising administering to said mammal an effective amount of a compound of claim 23.

20 82. The method of claim 81, wherein said cancer is a member selected from the group consisting of colon cancer, adenocarcinoma, rectal cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, adenomatous polyposis, and hepatocellular carcinoma.

25 83. The method of claim 82, wherein said cancer is colon cancer or colorectal cancer.

84. The method of claim 81, wherein said compound is administered in combination with a second therapeutic agent.

30

85. A method of preventing, treating or ameliorating cancer or tumor metastasis in a mammal comprising administering to said mammal an effective amount of a compound of 24.

86. The method of claim 85, wherein said cancer is a member selected from the group consisting of colon cancer, adenocarcinoma, rectal cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, adenomatous polyposis, and hepatocellular carcinoma.

5

87. The method of claim 86, wherein said cancer is colon cancer or colorectal cancer.

88. The method of claim 85, wherein said compound is administered in combination with a second therapeutic agent.

10

89. A method of preventing, treating or ameliorating cancer or tumor metastasis in a mammal comprising administering to said mammal an effective amount of a compound of claim 25.

15

90. The method of claim 89, wherein said cancer is a member selected from the group consisting of colon cancer, adenocarcinoma, rectal cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, adenomatous polyposis, and hepatocellular carcinoma.

20

91. The method of claim 90, wherein said cancer is colon cancer or colorectal cancer.

92. The method of claim 89, wherein said compound is administered in combination with a second therapeutic agent.

25

93. A method of preventing, treating or ameliorating cancer or tumor metastasis in a mammal comprising administering to said mammal an effective amount of a compound of claim 26.

30

94. The method of claim 93, wherein said cancer is a member selected from the group consisting of colon cancer, adenocarcinoma, rectal cancer,

colorectal cancer, breast cancer, lung cancer, ovarian cancer, adenomatous polyposis, and hepatocellular carcinoma.

5 95. The method of claim 94, wherein said cancer is colon cancer or colorectal cancer.

96. The method of claim 93, wherein said compound is administered in combination with a second therapeutic agent.

10 97. A method of preventing, treating or ameliorating cancer or tumor metastasis in a mammal comprising administering to said mammal an effective amount of a compound of claim 27.

15 98. The method of claim 97, wherein said cancer is a member selected from the group consisting of colon cancer, adenocarcinoma, rectal cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, adenomatous polyposis, and hepatocellular carcinoma.

20 99. The method of claim 98, wherein said cancer is colon cancer or colorectal cancer.

100. The method of claim 97, wherein said compound is administered in combination with a second therapeutic agent.

25 101. A method of preventing, treating or ameliorating cancer or tumor metastasis in a mammal comprising administering to said mammal an effective amount of a compound of claim 28.

30 102. The method of claim 101, wherein said cancer is a member selected from the group consisting of colon cancer, adenocarcinoma, rectal cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, adenomatous polyposis, and hepatocellular carcinoma.

103. The method of claim 102, wherein said cancer is colon cancer or colorectal cancer.

5 104. The method of claim 101, wherein said compound is administered in combination with a second therapeutic agent.

105. A method of preventing, treating or ameliorating cancer or tumor metastasis in a mammal comprising administering to said mammal an effective amount of a compound that modulates expression of one or more genes of Table 5.

10

106. The method of claim 105, wherein said modulation is a decrease in expression.

15 107. The method of claim 105, wherein said compound is a compound of claim 1, 4, 10 or 13.

108. The method of claim 105, wherein said compound, including a pharmaceutically acceptable salt thereof, is a compound of Table 1, 2, 3 or 4.

20

109. The method of claim 108, wherein said compound is administered in combination with a second therapeutic agent.

25 110. The method of claim 108, wherein said cancer is a member selected from the group consisting of colon cancer, adenocarcinoma, rectal cancer, colorectal cancer, breast cancer, lung cancer, ovarian cancer, adenomatous polyposis, and hepatocellular carcinoma.

30 111. The method of claim 110, wherein said cancer is colon cancer or colorectal cancer.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/12995

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/54 (2009.01)

USPC - 514/224.8

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

USPC: 514/224.8

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

USPC: 514/224.8; 544/37

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubWEST (USPT, PGPB, EPAB, JPAB); Google Scholar

Search terms: anthraquinone, dioximes, dione, anthracene, cancer, tumor, pyridin, heterocyclic, beta-catenin, antitumor, azepan, sulfonyl, cycloalkyl

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US 2004/0019042 A1 (LEE et al) 29 January 2004 (29.01.2004); entire document, especially abstract, para [0011]-[0017]	1-4 — 5-36
Y	US 2004/0110756 A1 (EMIG et al) 10 June 2004 (10.06.2004); entire document, especially para [0010]	5-30, 33-36
Y	US 2004/0220197 A1 (BANERJEE et al) 04 November 2004 (04.11.2004); entire document, especially para [0121]	30-36

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

07 April 2009 (07.04.2009)

Date of mailing of the international search report

16 APR 2009

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

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PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/12995

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Group I: claims 1-36, a compound having the structure of Formula I and its metabolized derivatives.

Group II: claims 37-111, methods of use for the compound of Group I.

The technical feature shared between the inventions of Groups I-II is the compound of Group I. However, this shared technical feature is not a shared special technical feature, which is required to demonstrate unity of inventions. A shared technical feature is not a shared special technical feature because the noted feature fails to provide a contribution over the prior art, as evidenced by Lee (US 2004/0019042 A1).

Lee teaches/suggests the composition of Group I. In view of Lee, the compound of Group I does not provide a contribution over the prior art. In the absence of a contribution over the prior art, the noted shared technical feature is not a shared special technical feature. Without a shared special technical feature, the inventions lack unity with one another.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-36

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.