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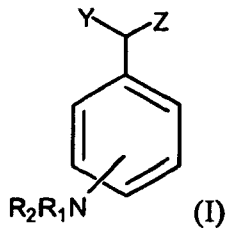
(54) **Title**: METHODS FOR PREVENTING OR REDUCING CARCINOGENESIS OR OXIDATIVE STRESS



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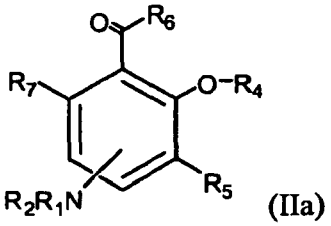

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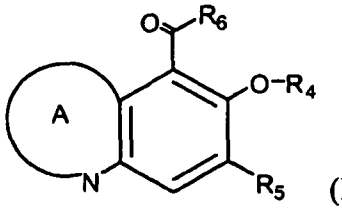


(IIb)

(57) **Abstract**: The present invention is directed in part to methods of preventing or reducing colon carcinogenesis comprising administering to a patient at risk of colorectal cancer, a pharmaceutical preparation comprising disclosed chemopreventive. In another aspect, the invention is directed to methods attenuation of oxygen free radicals comprising administrating to a patient in need thereof an antioxidant effective amount of a compound represented by formula (I), (IIa) or (IIb) as disclosed herein.

METHODS FOR PREVENTING OR REDUCING CARCINOGENESIS OR OXIDATIVE STRESS

RELATED APPLICATIONS

[0001] This application claims priority to EP08425775.7, filed December 5, 2008; U.S.S.N. 61/157674, filed March 5, 2009; and U.S.S.N. 61/222, 281 filed July 1, 2009, all of which are hereby incorporated by reference.

BACKGROUND

[0002] Colorectal cancer is a serious complication in patients with ulcerative colitis or Crohn's disease. Early age at diagnosis, the extent and severity of colonic disease, the presence of primary sclerosing cholangitis, and/or a family history of cancer represent independent risk factors for the development of colorectal cancer. Aspirin has been found to exert chemopreventive effects in colon cancer, but the mechanism by which it exerts these effects may be complex.

[0003] One target for activity of chemopreventive drugs against cancers such as colorectal cancer and solid tumor cancers and adenocarcinomas (such as breast, prostate, lung and heptocellular carcinoma) may be improvement of DNA replication. The fidelity of DNA replication is a product of polymerase accuracy, its proofreading activity, and/or the proficiency of the postreplicational mismatch repair system. Inefficiency of fidelity replication can be a key to the development of human cancer. Chemopreventive drugs that increase such efficiency in colorectal cells could significantly reduce the life-threatening manifestations of cancer and diminish cancer deaths.

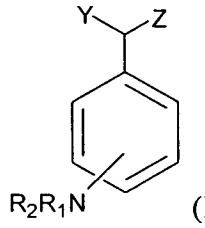
[0004] The overproduction of reactive oxygen species (ROS) is a common underlying mechanism of many pathologies, as they have been shown to damage various cellular components, including proteins, lipids and DNA. Free radicals, especially superoxide ($O_{(2)}^{*-}$), can be generated in quantities large enough to overwhelm endogenous protective enzyme systems, such as superoxide dismutase (SOD). Overproduction of ROS leads to a prooxidant state also known as oxidative stress. Increased levels of ROS and markers of oxidative stress have been consistently found in such cardiovascular diseases as atherosclerosis or hypertension, and studies involving animal models suggest that antioxidant superoxide dismutase mimetics

offer a potential new therapeutic approach to the prevention and treatment of chronic obstructive pulmonary disease as well.

[0005] The association between compromised antioxidant status, indices of oxidative damage, and other clinical conditions like diabetes mellitus, cardiac disorders such ischemia, various degenerative disorders (e.g. aging) and hair loss is also well documented. Free radicals such as superoxides have also been implicated in a number of skin conditions including photodamage, general aging of the skin, contact dermatitis, and wrinkling. However, there are limited medications available for treating e.g., oxidative damage.

SUMMARY

[0006] Also provided herein are methods for attenuating oxygen free radicals comprising administering compounds disclosed herein to a patient. For example, a method of treating fine lines, wrinkles or surface irregularities of the skin, protecting from and/or ameliorating free radical damage to the skin in a subject or patient in need thereof or suffering from same, or a method of treating a patient suffering from unwanted hair loss is provided, comprising administering a a pharmaceutical preparation comprising administering (e.g. topically), a chemopreventive agent having the formula I, IIa or IIb:



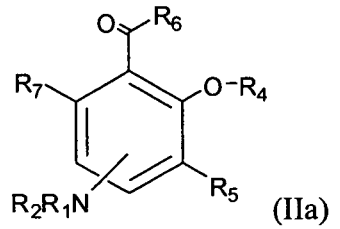
(I)

wherein:

R_1 and R_2, are each independently selected from the group consisting of H and C_{1-6} alkyl; or R_1 and R_2 together with the nitrogen atom they are bonded to form an aromatic or aliphatic ring with 5 or 6 atoms;

Y and Z are each independently selected from the group consisting of H, OH, COOH, $-OR_3$, $-CH(OR_3)COOH$; and

R_3 is selected from the group consisting of H, phenyl, benzyl, vinyl, allyl, C_{1-6} alkyl or C_{1-6} alkyl substituted by one or more halogens;



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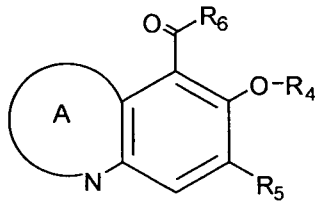


(IIb)

wherein:

R_1 and R_2 are each independently selected from the group consisting of H and C_{1-6} alkyl; or R_1 and R_2 together, with the nitrogen atom they are bonded to, form an aromatic or aliphatic ring with 5 or 6 atoms;

R_6 is selected from the group consisting of: $-NR_9OH$, OH, and $-OR_9$;

R_9 is C_{1-6} alkyl;

R_4 is selected from H, halo, phenyl, benzyl, vinyl, allyl, C_{1-6} alkyl or C_{1-6} alkyl substituted by one or more halogens;

R_5 and R_7 are each independently hydrogen or halo, or

R_4 and R_5, or R_4 and R_6 together, form a fused heterocyclic ring with 5 or 6 atoms, optionally substituted with halo or C_{1-6} alkyl; and A is a fused heterocyclic ring; or a pharmaceutically acceptable salt thereof.

[0007] In another embodiment, a method for attenuation of oxygen free radicals or treating hypoxia is provided, comprising administrating to a patient in need thereof an antioxidant effective amount of a compound represented by formula I, IIa or IIb, as defined above.

[0008] Also provided herein are methods of treating a vascular or cardiac disorder, comprising identifying a patient suffering from or at risk of developing said disorder and administering to said patient an effective amount of a compound represented by formula I, IIa, or IIb, as defined above. For example, a cardiac disorder being treated may be chosen from chronic

coronary ischemia, arteriosclerosis, congestive heart failure, ischemic or reperfusion related injury, angina, atherosclerosis, myocardial infarction, stroke and myocardial hypertrophy. In another embodiment, a method of treating an autoimmune disorder is provided, wherein the autoimmune disorder may be chosen from, for example, Addison's disease, chronic thyroiditis, dermatomyositis, Grave's disease, multiple sclerosis, systemic lupus erythematosis, psoriasis, or rheumatoid arthritis, and may comprise administering to a patient in need thereof an effective amount of a compound of formula I, IIa, or IIb, as defined above. For example, methods disclosed herein may include methods wherein the patient is human.

[0009] This disclosure is directed in part to methods of preventing and/or reducing colon, solid tumor, and/or adenocarcinoma carcinogenesis, e.g. minimizing or prolonging a manifestation of colon cancer comprising administering compounds disclosed herein to a patient, e.g. a human. Such a patient may or may not have, for example, detectable colorectal cancer. In some embodiments, upon or before administration, spontaneous mutation frequency of a colon carcinoma cells are present in the patient. In other embodiments, the patient has Crohn's disease, inflammatory bowel disease, or ulcerative colitis.

[0010] Also provided herein are methods for delaying clinical manifestation of a colorectal tumor (or, e.g., a solid tumor or adenocarcinoms) in a patient at risk of colorectal cancer, comprising administering to the patient an effective amount of a chemopreventive compound of a disclosed compound. For example, the delay is at least 1 year as compared to a patient who is not administered a chemopreventive compound. In another embodiment, a patient may have at least about a 30% reduction of the mutation rate of colon carcinoma cells present in the patient.

[0011] Also provided herein a methods of treating an age-related disorder selected from the group consisting of: diabetes, cataracts, Alzheimer's disease, Parkinson's disease, macular degeneration, retinal ulcers or retinal vasculitis, comprising administering an effective amount of a composition comprising a compound of formula I, IIa or IIb, as defined above.

[0012] These and other aspects and advantages of the invention will become apparent upon consideration of the following figures, detailed description, and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] The invention can be more completely understood with reference to the following drawings.

[0014] Figure 1 depicts superoxide scavenging properties of compounds disclosed herein.

[0015] Figure 2 depicts superoxide scavenging properties of compounds disclosed herein.

[0016] Figure 3 depicts the changes in mutations rate of HCT116 A2.1 cells upon incubation with various concentrations (mM) of compounds disclosed herein.

[0017] Figure 4 depicts the changes in mutations rate of HCT116 A2.1 cells upon incubation with various concentrations (mM) of a compound disclosed herein.

[0018] Figure 5 depicts the cell cycle changes in HCT116 and HT29 cells upon treatment with a compound disclosed herein.

[0019] Figure 6 depicts the effect on cell proliferation in HCT116, HCT 116+chr3, HT29 and Lovo cells using a compound disclosed herein.

DETAILED DESCRIPTION

[0020] The invention is based, in part, upon the discovery that certain compounds disclosed herein have superoxide scavenging potential and/or have the ability to improve the replication fidelity in cancer cells, for example, in colorectal cancer cells. In one aspect, the disclosure is directed to methods of preventing or reducing the incidence of cancer, e.g. colon cancer, in, for example, patients at risk of and/or having risk factors indicating a susceptibility of developing colon cancer. In another aspect, the disclosure is directed to methods of attenuating oxygen free radicals in a patient, and/or methods of treating diseases related to excess of such free radicals. The disclosed methods comprise administering a compound disclosed herein.

[0021] Before further description of the present invention, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

[0022] A "patient," "subject" or "host" to be treated by the subject method may mean either a human or non-human animal, e.g. a small mammal such as a mouse or rat, and including horse, cow, dog, cat, etc.

[0023] The term "therapeutic agent" is art-recognized and refers to any chemical moiety that is a biologically, physiologically, or pharmacologically active substance that acts locally and/or systemically in a subject. Examples of therapeutic agents, also referred to as "drugs", are described in well-known literature references such as the Merck Index, the Physicians Desk Reference, and The Pharmacological Basis of Therapeutics, and they include, without limitation, medicaments; vitamins; mineral supplements; substances used for the treatment, prevention, diagnosis, cure or mitigation of a disease or illness; substances which affect the structure or function of the body; or pro-drugs, which become biologically active or more active after they have been placed in a physiological environment.

[0024] The term "therapeutic effect" is art-recognized and refers to a local and/or systemic effect in animals, particularly mammals, and more particularly humans caused by a pharmacologically active substance. The term thus means any substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease or in the enhancement of desirable physical or mental development and/or conditions in an animal or human. The phrase "therapeutically-effective amount" means that amount of such a substance that produces some desired local or systemic effect at a reasonable benefit/risk ratio applicable to any treatment. The therapeutically effective amount of such substance will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. For example, certain compositions of the present invention may be administered in a sufficient amount to produce a at a reasonable benefit/risk ratio applicable to such treatment.

[0025] The term "treating" is art-recognized and refers to curing as well as ameliorating at least one symptom of any condition or disease.

[0026] The term "alkyl" is art-recognized, and includes saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl

substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In certain embodiments, a straight chain or branched chain alkyl has about 30 or fewer carbon atoms in its backbone (e.g., C_1-C_{30} for straight chain, C_3-C_{30} for branched chain), and alternatively, about 20 or fewer, e.g. from 1 to 6 carbons. Likewise, cycloalkyls have from about 3 to about 10 carbon atoms in their ring structure, and alternatively about 5, 6 or 7 carbons in the ring structure. The term "alkyl" is also defined to include halosubstituted alkyls.

[0027] Moreover, the term "alkyl" (or "lower alkyl") includes "substituted alkyls", which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents may include, for example, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain may themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), -CN and the like. Exemplary substituted alkyls are described below. Cycloalkyls may be further substituted with alkyls, alkenyls, alkoxys, alkylthios, aminoalkyls, carbonyl-substituted alkyls, -CN, and the like.

[0028] The terms ortho, meta and para are art-recognized and refer to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and ortho-dimethylbenzene are synonymous.

[0029] The definition of each expression, e.g. alkyl, m, n, and the like, when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

[0030] Certain compounds contained in compositions of the present invention may exist in particular geometric or stereoisomeric forms. In addition, compounds of the present invention may also be optically active. The present invention contemplates all such compounds, including

cis- and trans-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

[0031] It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction.

[0032] The term "substituted" is also contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein above. The permissible substituents may be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds.

[0033] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover. Also for purposes of this invention, the term "hydrocarbon" is contemplated to include all permissible compounds having at least one hydrogen and one carbon atom. In a broad aspect, the permissible hydrocarbons include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic organic compounds that may be substituted or unsubstituted.

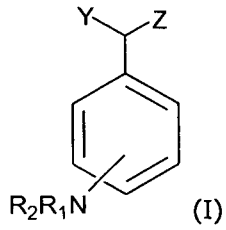
[0034] The term "pharmaceutically-acceptable salts" is art-recognized and refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds, including, for example, those contained in compositions of the present invention.

[0035] The term "pharmaceutically acceptable carrier" is art-recognized and refers to 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 any subject composition or component thereof from one organ, or 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 subject composition and its components and not injurious to the patient. Some examples of materials which may serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and 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) 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 substances employed in pharmaceutical formulations.

Compounds

[0036] Compounds contemplated for use in one or more of the disclosed methods include compounds represented by formula I, or a pharmaceutically acceptable salt, enantiomer or stereoisomer thereof:



(I)

wherein:

R_1 and R_2, are each independently selected from the group consisting of H and C_{1-6} alkyl; or R_1 and R_2 together with the nitrogen atom they are bonded to form an aromatic or aliphatic ring with 5 or 6 atoms which may be optionally substituted;

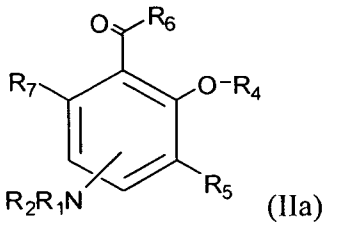
Y and Z are each independently selected from the group consisting of H, OH, COOH, $-OR_3$, $-CH(OR_3)COOH$; and

R_3 is selected from the group consisting of H, phenyl, benzyl, vinyl, allyl, C_{1-6} alkyl or C_{1-6} alkyl substituted by one or more halogens.

[0037] In an embodiment, Y may be H or COOH. For example, Y may be H and Z may be $CH(OR_3)COOH$, or Y may be COOH and Z maybe $-OR_3$. In some embodiments, R_3 may be methyl, ethyl, n-propyl, or isopropyl.

[0038] In other embodiments, the NR_1R_2 moiety may be in the 4' position or may be in the 3' position. In certain embodiments, R_1 and R_2 are H.

[0039] Exemplary compounds also include those represented by formulas IIa or IIb or a pharmaceutically acceptable salt, enantiomer or stereoisomer of:



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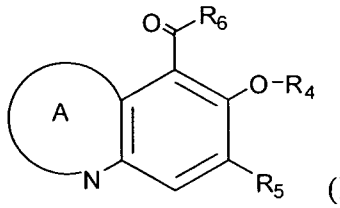


(IIb)

wherein:

R_1 and R_2 are each independently selected from the group consisting of H and C_{1-6} alkyl; or R_1 and R_2 together, with the nitrogen atom they are bonded to, form an aromatic or aliphatic ring with 5 or 6 atoms;

R_6 is selected from the group consisting of: $-NHOH$, OH, and $-OR_9$;

R_9 is C_{1-6} alkyl;

R_4 is selected from H, phenyl, benzyl, vinyl, allyl, C_{1-6} alkyl or C_{1-6} alkyl substituted by one or more halogens;

R_5 and R_7 are each independently hydrogen or halo, or ;

or

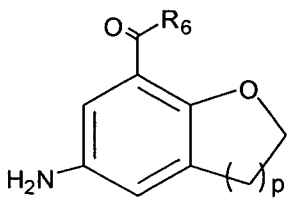
R_4 and R_5, or R_4 and R_6 together, form a fused heterocyclic ring with 5 or 6 atoms, optionally substituted with halo or C_{1-6} alkyl; and

[0040] A is a fused heterocyclic ring; or a pharmaceutically acceptable salt thereof.

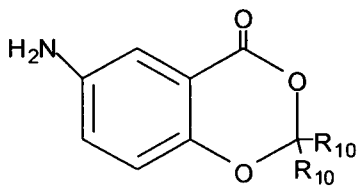
[0041] In certain embodiments, the NR_1R_2 moiety of formula IIa may be in the 4' position or may be in the 3' position. In certain embodiments, R_1 and R_2 are H.

[0042] R_9, in some embodiments, may be methyl, ethyl, n-propyl, or isopropyl.

[0043] In some embodiments a compound can be represented by

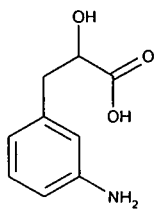


or



wherein p is 1 or 2, R_6 is OH or $-OR_9$, wherein R9 is defined above, and R_{10}, independently for each occurrence, is selected from the group consisting of H, halo, or C_{1-6} alkyl, e.g. methyl or ethyl.

[0044] Exemplary compounds contemplated herein include:



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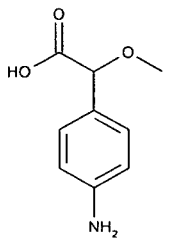

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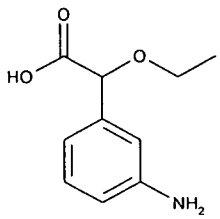

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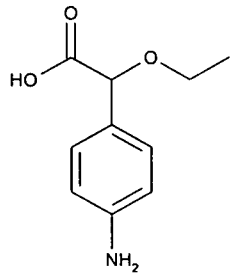
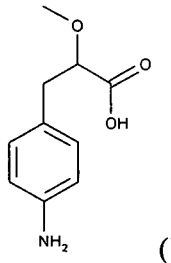
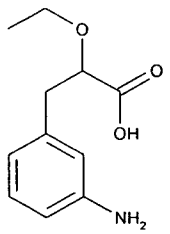


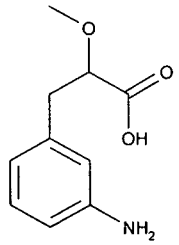
(V),



(VI),



(VIII), and

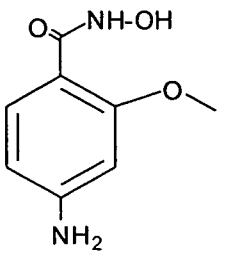
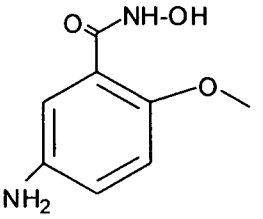


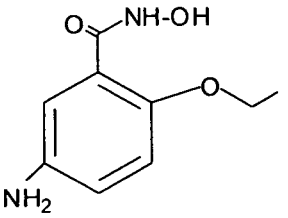
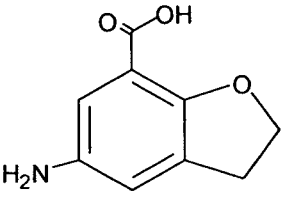
(IX), or a pharmaceutically acceptable salt thereof.

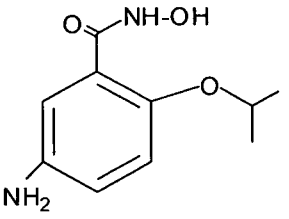
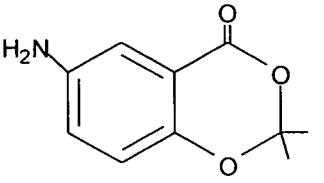
[0045] In some embodiments, contemplated compounds include: 4-amino-N-hydroxy-2-methoxybenzamide (compound 13); 6-methoxy quinoline-5-carboxylic acid (compound 36); 6-

methoxy-1,2,3,4-tetrahydroquinoline-5-carboxylic acid (compound 37); 5-diisopropylaminosalicylic acid (compound 38).

[0046] Other exemplary compounds include those represented by:

(compound 13):  ; (compound 14):  ;

(compound 26):  ; (compound 17): 

(compound 31):  ; (compound 28):  .

[0047] Compounds contemplated herein include racemic mixtures, and enantiomers of compounds, for example: (±)-2-hydroxy-3-(3'-aminophenyl) propionic acid (compound 20); (±)-2-methoxy-2-(4'-aminophenyl) acetic acid (compound 23); (±)-2-ethoxy-2-(3'-aminophenyl) acetic acid (compound 32); (±)-2-ethoxy-2-(4'-aminophenyl) acetic acid (compound 33); (±)-2-methoxy-3-(4'-aminophenyl) propionic acid (compound 34) "±34" (racemic form); (±)-2-ethoxy-3-(4'-aminophenyl) propionic acid (compound 39); (±)-2-ethoxy-3-(3'-aminophenyl) propionic acid (compound 40).

[0048] For example, the compounds used in the methods of the present invention can be enantiomers of the following racemic mixtures: (R,S)-2-hydroxy-2-(3-aminophenyl)acetic acid (compound 10); (R,S)-2-hydroxy-2-(4-aminophenyl)acetic acid (compound 11); (R,S)-2-hydroxy-3-(4'-aminophenyl)propionic acid (compound 21); (R,S)-2-methoxy-2-(3'-

aminophenyl)acetic acid (compound 22); (R,S)-2-methoxy-3-(3'-aminophenyl)propionic acid (compound 35); (R,S)-2-methoxy-3-(4-aminophenyl)propionic acid(compound 34), as well as enantiomers, e.g.: (+) 2-S-methoxy-3-(4-aminophenyl)propionic acid(compound 34); (-) 2-R-methoxy-3-(4-aminophenyl)propionic acid(compound 34).

[0049] Other racemic type mixtures of compounds contemplated include: e.g. (±)-2-hydroxy-2-(3'-aminophenyl)acetic acid (compound 10); (±)-2-hydroxy-2-(4'-aminophenyl)acetic acid (compound 11); (±)-2-hydroxy-3-(4'-aminophenyl)propionic acid (compound 21) and (±)-2-methoxy-2-(3'-aminophenyl)acetic acid (compound 22).

[0050] Further compounds contemplated for use in the disclosed methods: 5-aminosalicylo-hydroxamic acid (compound 5); 3-dimethylaminosalicylic acid (compound 6); 2-methoxy-4-aminobenzoic acid (compound 7); 2-methoxy-5-aminobenzoic acid (compound 8); 5-methylaminosalicylic acid (compound 9); 4-methylaminosalicylic acid (compound 12); 4-acetylaminosalicylic acid (compound 16); 2-ethoxy-4-aminobenzoic acid (compound 18); 2-ethoxy-5-aminobenzoic acid (compound 19); 4-dimethylaminosalicylic acid (compound 24); 2-ethoxy-4-aminobenzoylhydroxamic acid (compound 25); 6-hydroxyquinoline-5-carboxylic acid (compound 27); 2-(2-propyl)oxy-4-aminobenzoic acid (compound 30); 4-(1-piperazinyl)salicylic acid (compound 41); (R,S) 5-oxa-quinoline-6-carboxylic acid (compound 15); 6-methoxy quinoline-5-carboxylic acid (compound 36); 6-methoxy-1,2,3,4-tetrahydroquinoline-5-carboxylic acid (compound 37); 5-diisopropylaminosalicylic acid (compound 38); and 4-diisopropylaminosalicylic acid (compound 42).

[0051] Methods for making contemplated compounds may be found for example in WO2007/010516 and WO2007/010514, each hereby incorporated by reference in their entirety.

Therapeutic Applications

[0052] Methods of preventing or reducing colon carcinogenesis or colon cancer form part of this disclosure. Such methods may comprise administering to a patient, for example, a patient at risk of colorectal cancer, a pharmaceutical preparation comprising a chemopreventive agent such as those disclosed herein, e.g., compounds 17, 29, 39 or 34. A patient at risk of colon cancer or colon carcinogenesis may include those patients with ulcerative colitis, inflammatory bowel disease, or Crohn's disease. A patient at risk may also include those patients with an early age at

diagnosis of Crohn's or colitis, extensive and/or severe of colonic disease, patients with the presence of primary sclerosing cholangitis, and/or patient's having a family history of cancer.

[0053] Patients treated using the above method may or may not have detectable colorectal cancer. In an different embodiment, spontaneous mutation frequency of a colon carcinoma cells may or may not be present in the patient before initial administration, or during the administration of a course, of a compound disclosed herein. In some embodiments, the patient has at least about a 5%, 10%, 20%, 30%, 40% or even 50% or more reduction of the mutation rate of colon carcinoma cells present in the patient after administering a disclosed compound, after e.g. 1 day, 2 days, 1 week, 1 month or 6 months or more. Without being bound by any theory, compounds disclosed herein may reduce mutation rate by interacting with cellular machineries involved in progression through the cell cycle. Such a progression may result in slowing down processes such as DNA replication (S phase) and/or cell division (mitosis) through the onset of cell cycle checkpoints, which would give the cell the opportunity to either repair the damage that the DNA may have encountered or undergo apoptosis. In both cases, this would prevent accumulation of mutated or damaged cells and would lead to maintenance of DNA integrity.

[0054] Also contemplated herein is a method for delaying clinical manifestation of a colorectal tumor, or a solid tumor (e.g., a breast, prostate, lung or hepatocellular carcinoma) in a patient, for example, a patient at risk of colorectal cancer, comprising administering to the patient an effective amount of a chemopreventive compound disclosed herein, e.g. compounds 17, 29, 39 or 34. Administering such a compound may be on e.g., at least a daily basis. The delay of clinical manifestation of a colorectal tumor in a patient as a consequence of administering a compound disclosed here may be at least e.g., 6 months, 1 year, 18 months or even 2 years or more as compared to a patient who is not administered a chemopreventive compound such as one disclosed herein.

[0055] Also forming part of this disclosure are methods of preventing or reducing solid tumors or adenocarcinomas, such as breast, cervix, pancreas, prostate adenocarcinomas and/or hepatocellular carcinomas. Such methods may comprise administering to a patient, for example, a patient at risk of such cancers, a pharmaceutical preparation comprising a chemopreventive agent such as those disclosed herein, e.g., compounds 17, 29, 39 or 34 disclosed herein.

[0056] Methods of treating a patient that is suffering from a disease where attenuation of oxygen free radicals is useful, for example, autoimmune, cardiovascular, and skin and/or hair disorders, comprising administering a disclosed compound (e.g., Formulas I, IIa, or IIb) are also contemplated herein.

[0057] For example, a method of treating hair loss in a patient suffering from unwanted hair loss, is contemplated, wherein the method comprises administering an effective amount of a composition comprising a disclosed compound, e.g. a compound of formula I, IIa or IIb (for example, compounds 17, 28, 29 34 or 14. Such a composition may be administered topically. Superoxide dismutase has been used as a treatment for hair loss, and in an embodiment, disclosed compounds having superoxide dismutase properties are contemplated for use in methods of treating hair growth and/or decreasing hair loss, e.g. such compounds when administered to a patient, e.g. topically, may increase the size of hair follicles and/or increase the rate of hair growth. Methods of treating alopecia areata, androgenetic alopecia and/or telogenic defluvium are contemplated.

[0058] Methods of protecting from and/or ameliorating free radical damage to the skin, comprising administering, e.g. administering topically, an effective amount of a composition comprising a compound disclosed herein, .e.g., a compound of formula I, IIa or IIb is disclosed, e.g. compounds 17, 28, 29 34 or 14. Superoxide dismutase, for example, is known for such treatments (see e.g., J. Cell. Mol. Med. 8 (1): 109-116, (2007): "Topical superoxide dismutase reduces post-irradiation breast cancer fibrosis"; J. Derm Sci. Suppl 2(1) S65-S74, (2006)).

[0059] For example, the disclosed compounds may be used to reduce or ameliorate scar tissue of the skin, heal wounds and burns, protect skin against UV rays, and/or heal skin damaged from exposure to UV light. For example, disclosed compounds may be used to reduce fibrosis following radiation. Also contemplated are methods of treating fine lines, wrinkles or surface irregularities of the skin, comprising administering, e.g. administering topically, an effective amount of a composition comprising a compound disclosed herein, .e.g., a compound of formula I, IIa or IIb (e.g., compounds 17, 28, 29 34 or 14).

[0060] Methods of treating dermatological conditions are also provided, such as the treatment of at least one of: acne vulgaris, comedo-type acne, polymorphic acne, acne rosacea, nodulocystic acne, acne conglobata, senile acne, secondary acne, solar acne, acne

medicamentosa or occupational acne, ichthyosis, Darrier's disease, keratosis palmaris or plantaris, cutaneous, mucosal or ungual psoriasis, skin disorders due to exposure to UV radiation, of skin aging, photoinduced or chronological or actinic pigmentations and keratoses, acne hyperseborrhoea, simple seborrhoea or seborrhoeic dermatitis, cicatrization disorders or stretch marks, comprising administering an effective amount of a disclosed compound. Method of treating atopic dermatitis is also contemplated. The composition may be administered orally or topically.

[0061] Superoxide has been implicated in age-related diseases such as diabetes, cataracts, neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, macular degeneration, retinal ulcers and/or retinal vasculitis, and prostate cancer. (See e.g., "Antioxidants, diabetes and endothelial dysfunction." Cardiovascular Research, 47(3) 457-464, 2000; Role of anti-oxidant enzymes superoxide dismutase and catalase in the development of cataract: study of serum levels in patients with senile and diabetic cataracts", J Indian med Assoc. 104(7): 394, 396-7, 2006; "Oxidative stress hypothesis in Alzheimer's disease", Free Radical Biology and Medicine, 23(1): 134-147, 1997; "Oxidative mechanisms in nigral cell death in Parkinson's disease." Mov Disord. 1998; "Involvement of oxidative and nitrosative stress in promoting retinal vasculitis in patients with Eales' disease" Clinical Biochemistry, 36(5): 377-385, 2003; Contemplated herein are methods of treating such age-related disorders such as diabetes, cataracts, neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, macular degeneration, retinal ulcers and/or retinal vasculitis, comprising disclosed compounds. For example, methods of ameliorating, reducing the effects of, or preventing macular degeneration are provided herein comprising administering a compound represented by Formula I, IIa or IIb (for example, compounds 17, 28, 29, or 34).

[0062] In an embodiment, methods are provided for treating oxidative stress in patients in need thereof, comprising administering compounds disclosed herein. For example, a method of treating hypoxia is provided comprising administering to a patient in need thereof a compound disclosed herein.

[0063] Oxidative stress may result, for example, from the metabolic reactions that use oxygen, and in some embodiments, can describe a disturbance in the equilibrium status of pro-oxidant/anti-oxidant systems in intact cells. Oxidative stress has been implicated, for example, in cardiac and vascular disorders and diseases such as chronic coronary ischemia, arteriosclerosis,

congestive heart failure, angina, atherosclerosis, myocardial infarction, stroke and myocardial hypertrophy. For example, a method of treating or inhibiting an ischemic or reperfusion related injury in a patient in need thereof is provided, comprising administering to the patient a composition comprising an effective amount of compound of formula I, IIa, or IIb. Methods are provided herein for treating such cardiac and/or vascular disorders in a patient in need thereof comprising administering a disclosed compound, e.g. a compound represented by formula I, IIa or IIb. A method for treating chronic obstructive pulmonary disorder is also provided, comprising administering a disclosed compound, e.g. a compound represented by formula I, IIa or IIb, e.g., compounds 17, 28, 29 34 or 14

[0064] Methods for treating autoimmune disorders are also contemplated, for example, methods of treating Addison's disease, chronic thyroiditis, dermatomyositis, Grave's disease, multiple sclerosis, systemic lupus erythematosis, psoriasis, or rheumatoid arthritis, comprising administering to a patient in need thereof an effective amount of a compound of formula I, or e.g. compounds 17, 28, 29 34 or 14.

[0065] Generally, a therapeutically effective amount of active component will be in the range of from about 0.1 mg/kg to about 100 mg/kg, optionally from about 1 mg/kg to about 100 mg/kg, optionally from about 1 mg/kg to 10 mg/kg. The amount administered will depend on variables such as the type and extent of disease or indication to be treated, the overall health status of the particular patient, the relative biological efficacy of the binding protein delivered, the formulation of the binding protein, the presence and types of excipients in the formulation, and the route of administration. The initial dosage administered may be increased beyond the upper level in order to rapidly achieve the desired blood-level or tissue level, or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. Human dosage can be optimized, e.g., in a conventional Phase I dose escalation study designed to run from 0.5 mg/kg to 20 mg/kg. Dosing frequency can vary, depending on factors such as route of administration, dosage amount and the disease condition being treated. Exemplary dosing frequencies are once per day, once per week and once every two weeks.

[0066] Contemplated formulations or compositions comprise a disclosed compound and typically include a compound a pharmaceutically acceptable carrier.

[0067] Compositions of the present invention may be administered by various means, depending on their intended use, as is well known in the art. For example, if compositions of the present invention are to be administered orally, they may be formulated as tablets, capsules, granules, powders or syrups. Alternatively, formulations of the present invention may be administered parenterally as injections (intravenous, intramuscular or subcutaneous), drop infusion preparations or suppositories. For application by the ophthalmic mucous membrane route, compositions of the present invention may be formulated as eyedrops or eye ointments. These formulations may be prepared by conventional means, and, if desired, the compositions may be mixed with any conventional additive, such as an excipient, a binder, a disintegrating agent, a lubricant, a corrigent, a solubilizing agent, a suspension aid, an emulsifying agent or a coating agent.

[0068] In formulations of the subject invention, wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants may be present in the formulated agents.

[0069] Subject compositions may be suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal, aerosol and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of composition that may be combined with a carrier material to produce a single dose vary depending upon the subject being treated, and the particular mode of administration.

[0070] Methods of preparing these formulations include the step of bringing into association compositions of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association agents with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0071] Formulations suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base,

such as gelatin and glycerin, or sucrose and acacia), each containing a predetermined amount of a subject composition thereof as an active ingredient. Compositions of the present invention may also be administered as a bolus, electuary, or paste.

[0072] In solid dosage forms for oral administration (capsules, tablets, pills, film-coated tablets, sugar-coated tablets, powders, granules and the like), the subject composition is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[0073] Formulations and compositions may include micronized crystals of the disclosed compounds. Micronization may be performed on crystals of the compounds alone, or on a mixture of crystals and a part or whole of pharmaceutical excipients or carriers. Mean particle size of micronized crystals of a disclosed compound may be for example about 5 to about 200 microns, or about 10 to about 110 microns.

[0074] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. Tablets, and other solid dosage

forms, such as film coated tablets or sugar coated tablets, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art.

[0075] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the subject composition, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, cyclodextrins and mixtures thereof.

[0076] Suspensions, in addition to the subject composition, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[0077] Formulations for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing a subject composition with one or more suitable non-irritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the body cavity and release the active agent. Formulations which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

[0078] Dosage forms for transdermal or topical administration of a subject composition include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active component may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

[0079] The ointments, pastes, creams and gels may contain, in addition to a subject composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[0080] Powders and sprays may contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays may additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[0081] Compositions and compounds of the present invention may alternatively be administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (e.g., fluorocarbon propellant) suspension could be used. Sonic nebulizers may be used because they minimize exposing the agent to shear, which may result in degradation of the compounds contained in the subject compositions.

[0082] Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

[0083] Pharmaceutical compositions of this invention suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[0084] Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate and cyclodextrins. Proper fluidity may be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and

by the use of surfactants. The efficacy of treatment with the subject compositions may be determined in a number of fashions known to those of skill in the art.

[0085] Throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated that compositions also consist essentially of, or consist of, the recited components. Similarly, where processes are described as having, including, or comprising specific process steps, the processes also consist essentially of, or consist of, the recited processing steps. Except where indicated otherwise, the order of steps or order for performing certain actions are immaterial so long as the invention remains operable. Moreover, unless otherwise noted, two or more steps or actions may be conducted simultaneously.

EXAMPLES

Example 1 Superoxide Scavenging

[0086] Compounds 17 and 39 were tested for their potential to scavenge superoxide (O_2^-) released by activated neutrophils (PMN) using a standardized O_2^- assay. Briefly, $1x10^6$ freshly isolated neutrophils were activated with phorbol-myristate-acetate (PMA) in absence or presence of the compounds (each 5mM). 30 min after activation the O_2^- release was measured by lucigenin amplified chemiluminescence on a luminometer. 5-ASA (5-aminosalicylic acid) and superoxide dismutase (SOD) was used as a control. Experiments were done in triplicates.

[0087] At 5mM, compound 17 acts as a strong scavenger of superoxide (5% of control), being as active as a mixture of superoxide dismutase and catalase. Compound 39 has similar scavenging properties to 5-ASA, as shown in Figure 1.

Example 2 Superoxide Scavenging

[0088] Compounds 14 and 34 were tested for their potential to scavenge superoxide (O_2^-) released by activated neutrophils (PMN) using a standardized O_2^- assay, similar to Example 1. Activated neutrophils (PMN) were used as O_2^- donors. Briefly, $1x10^6$ freshly isolated neutrophils were activated with 100nM phorbol-myristate-acetate (PMA). The O_2^- release was measured every 15 min for a 90 min period by lucigenin amplified chemiluminescence on a luminometer. Either non-activated PMNs or activated PMNs incubated with superoxide dismutase (2000 U/ml, SOD) was used as a control. Experiments were carried out in triplicates

[0089] At the investigated concentrations both compounds exhibited significant scavenging properties. Figure 2A represents the results for compound 14, and Figure 2B represents the results for compound 34.

Example 3 Replication Fidelity

[0090] A EGFP-based assay to determine the changes in mutation rate upon incubation with various concentrations of the compounds was used to test whether compounds improve the replication fidelity. Briefly, $1x10^3$ EGFP negative HCT116 A2.1 cells were sorted into 24-well plates on a FACS Aria. 24 hours later cells were treated with the compounds for a period of 7 days and the mutant fraction was measured by flow cytometry.

[0091] Compound 17 affects cell growth already at low concentrations starting from 1.25mM. Surprisingly, compound 17 leads to a 50% reduction of the intermediate mutant cells (M1 population) at a concentration of 5mM. Furthermore compound 17 led to about a 30% reduction of definitive mutant cells (M2 population) at concentrations between 2.5 and 5mM (Fig. 3A)

[0092] Figure 3B indicates that compound 28 does not appear to cause significant changes at concentrations up to 1mM. Compound 39 reduced cell growth at 20mM but did not reduce the mutant fraction M1 or M2. Instead, treatment with 20mM compound 39 leads to an increase of M1 (Fig. 3C), comparable to the effect of aspirin.

[0093] Among the tested compounds 17, 28 and 39, compound 17 exhibits positive effects on the replication fidelity in HCT116 cells harboring a (CA)13 repeat. This effect is not only seen in the intermediate mutant fraction M1 but also in the definite mutants M2. Compound 17 is also the strongest scavenger. This reduction of M1 or M2 does not seem to depend on an S-phase arrest (as it was seen with 5-ASA; Luciani G, Gastroenterology 2007).

Example 4

[0094] A EGFP-based assay similar to Example 3 was used to determine the changes in mutation rate upon incubation with various concentrations of disclosed compounds and to test whether the compounds improve the replication fidelity. A EGFP based assay was used to determine the changes in mutation rate at a (CA)13 repeat upon incubation with various

concentrations of the compounds. Briefly, $1x10^3$ EGFP negative HCT116 A2.1 cells were sorted into 24-well plates on a FACS Aria. 24 hours later cells were treated with the compounds for a period of 7 days. The total cell number (c) and the EGFP-positive fraction (mutant fraction (MF)) were analyzed by flow cytometry. The mutation rate (m/(CA)13/generation (gen) was estimated by m=MF/(gen+1) and gen=log2(c/1000 x cloning efficiency). The transient mutant (M1) and definitive mutant (M2) cells were distinguished.

[0095] As shown in Figure 4, compound 39 significantly lowered the number of M1 cells, which reflects a population of cells immediate after the polymerase error in MMR deficient HCT116 cells starting at a concentration of 10mM up to 40mM ($p<0.05$). There was also a significant reduction in the permanent mutant M2 population at 40mM.

Example 5 Cell cycle analysis

[0096] BrdU staining was used to analyze cell cycle changes in HCT116 and HT29 cells upon 72 hour treatment with compound 39. Data represent the mean values of 3 independent experiments (* indicates a $p < 0.05$ compared to control)

[0097] Compound 39 (10mM – 40mM) did not induce a significant change in the cell cycle distribution of HCT116 cells. HT29 cells revealed a mild increase in the G2 phase (ranging from 6.7% to 13.6%, $p<0.05$) which was paralleled by a decrease in the G1 population (ranging from 52.7% to 44.9%, $p<0.05$) (Figures 5A and 5B).

Example 6 Cell Proliferation

[0098] The inhibitory effect on cell proliferation of compound 34 using MTT assay was investigated. Briefly, $5x10^3$ HCT116, HCT116+chr3, HT29 and Lovo cells were incubated for 72 hours in 96-well plates with various concentrations. Compound 34 is soluble in IMDM. Stocks of 100mM were prepared and the pH was adjusted to 7.4.

[0099] Figure 6 indicates that compound 34 has an IC_{50} at 30-40mM dependent on the cell type.

INCORPORATION BY REFERENCE

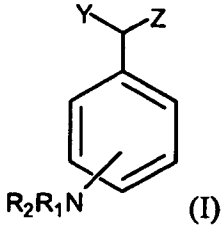
[00100] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

[00101] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

We claim:

1. A method for attenuation of oxygen free radicals, or treating a condition associated with oxygen free radicals, comprising administering to a patient in need thereof an antioxidant effective amount of a compound represented by the formula I, IIa or IIb:



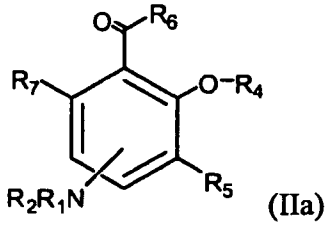
(I)

wherein:

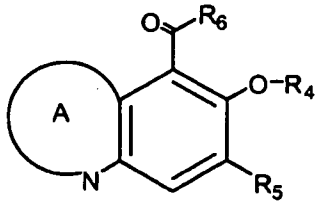
R_1 and R_2, are each independently selected from the group consisting of H and C_{1-6} alkyl; or R_1 and R_2 together with the nitrogen atom they are bonded to form an aromatic or aliphatic ring with 5 or 6 atoms;

Y and Z are each independently selected from the group consisting of H, OH, COOH, $-OR_3$, $-CH(OR_3)COOH$; and

R_3 is selected from the group consisting of H, phenyl, benzyl, vinyl, allyl, C_{1-6} alkyl or C_{1-6} alkyl substituted by one or more halogens;



(IIa)



(IIb)

wherein:

R_1 and R_2 are each independently selected from the group consisting of H and C_{1-6} alkyl; or R_1 and R_2 together, with the nitrogen atom they are bonded to, form an aromatic or aliphatic ring with 5 or 6 atoms;

R_6 is selected from the group consisting of: $-NR_9OH$, OH, and $-OR_9$;

R_9 is C_{1-6} alkyl;

R_4 is selected from H, halo, phenyl, benzyl, vinyl, allyl, C_{1-6} alkyl or C_{1-6} alkyl substituted by one or more halogens;

R_5 and R_7 are each independently hydrogen or halo;

or

R_4 and R_5, or R_4 and R_6 together, form a fused heterocyclic ring with 5 or 6 atoms, optionally substituted with halo or C_{1-6} alkyl; and

A is a fused heterocyclic ring; or a pharmaceutically acceptable salt or stereoisomer thereof.

2. A method of treating fine lines, wrinkles or surface irregularities of the skin, or protecting from and/or ameliorating free radical damage to the skin, comprising topically administering to a patient in need thereof an effective amount of a composition comprising a compound of formula I, IIa or IIb, as defined in claim 1.

3. A method of treating hair loss in a patient suffering from unwanted hair loss, comprising administering an effective amount of a composition comprising a compound of formula I, IIa, or IIb, as defined in claim 1.

4. The method of claim 2 or 3, wherein the composition is administered topically.

5. A method of treating an age-related disorder selected from the group consisting of: diabetes, cataracts, Alzheimer's disease, Parkinson's disease, macular degeneration, retinal ulcers or retinal vasculitis, comprising administering an effective amount of a composition comprising a compound of formula I, IIa or IIb, as defined in claim 1, to a patient in need thereof.

6. A method of treating hypoxia comprising administrating to a patient in need thereof an antioxidant effective amount of a compound represented by formula I, IIa or IIb, as defined in claim 1.

7. A method of treating a vascular or cardiac disorder, comprising identifying a patient suffering from or at risk of developing said disorder and administering to said patient an effective amount of a compound represented by formula I, IIa, or IIb, as defined in claim 1.

8. The method of claim 7, wherein the cardiac disorder is chosen from chronic coronary ischemia, arteriosclerosis, congestive heart failure, ischemic or reperfusion related injury, angina, atherosclerosis, myocardial infarction, stroke and myocardial hypertrophy.

9. A method of treating an autoimmune disorder chosen from Addison's disease, chronic thyroiditis, dermatomyositis, Grave's disease, multiple sclerosis, systemic lupus erythematosis, psoriasis, or rheumatoid arthritis, comprising administering to a patient in need thereof an effective amount of a compound of formula I, IIa, or IIb, as defined in claim 1.

10. The method of any one of claims 1-9, wherein the compound is represented by formula I.

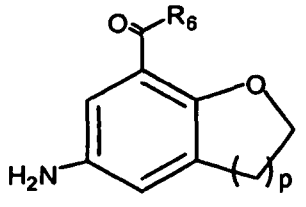
11. The method of claim 10, wherein Y is H and Z is $-CH(OR_3)COOH$;

12. The method of claim 11, wherein Y is COOH and Z is $-OR_3$.

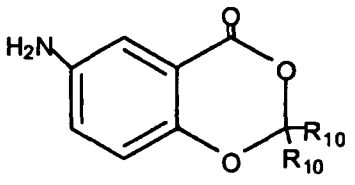
13. The method of any one of claims 10-12 wherein R_3 is methyl, ethyl, propyl, or isopropyl.

14. The method of any one of claims 1-9, wherein the compound is represented by formula IIa.

15. The method of claim 14, wherein the compound is represented by



or



wherein p is 1 or 2, R_6 is OH, and R_{10}, independently for each occurrence, selected from the group consisting of H, halo, or C_{1-6} alkyl.

16. The method of any one of claims 1-9, wherein the compound is selected from the group consisting of: 2-methoxy-3-(4'-aminophenyl) propionic acid (compound 34); 2-ethoxy-3-(4'-aminophenyl) propionic acid (compound 39); 6-amino-2,2-dimethyl-4H-benzo[1,3]dioxin-4-one (compound 28); 5-amino-N-hydroxy-2-

methoxybenzamide (compound 14); and 5-amino-2,3-dihydrobenzofuran-7-carboxylic acid (compound 17).

17. A method of preventing or reducing colon carcinogenesis comprising: administering to a patient at risk of colorectal cancer, a pharmaceutical preparation comprising a chemopreventive agent selected from the group consisting of: 2-methoxy-3-(4'-aminophenyl) propionic acid (compound 34); 2-ethoxy-3-(4'-aminophenyl) propionic acid (compound 39); 6-amino-2,2-dimethyl-4H-benzo[1,3]dioxin-4-one (compound 28); and 5-amino-2,3-dihydrobenzofuran-7-carboxylic acid (compound 17).

18. The method of claim 17, wherein the patient is human.

19. The method of claim 17 or 18, wherein the patient does not have detectable colorectal cancer.

20. The method of any one of claims 17-19, wherein upon or before administration, spontaneous mutation frequency of colon carcinoma cells are present in the patient.

21. The method of any one of claims 17-20, wherein the patient has Crohn's disease, inflammatory bowel disease, or ulcerative colitis.

22. A method for delaying clinical manifestation of a colorectal tumor in a patient at risk of colorectal cancer, comprising administering to the patient an effective amount of a chemopreventive compound selected from the group consisting of 2-methoxy-3-(4'-aminophenyl) propionic acid (compound 34); 2-ethoxy-3-(4'-aminophenyl) propionic acid (compound 39); 6-amino-2,2-dimethyl-4H-benzo[1,3]dioxin-4-one (compound 28); and 5-amino-2,3-dihydrobenzofuran-7-carboxylic acid (compound 17).

23. The method of claim 22, wherein the delay is at least 1 year as compared to a patient who is not administered a chemopreventive compound.

24. The method of claim 22 or 23, wherein the patient has at least about a 30% reduction of the mutation rate of colon carcinoma cells present in the patient.

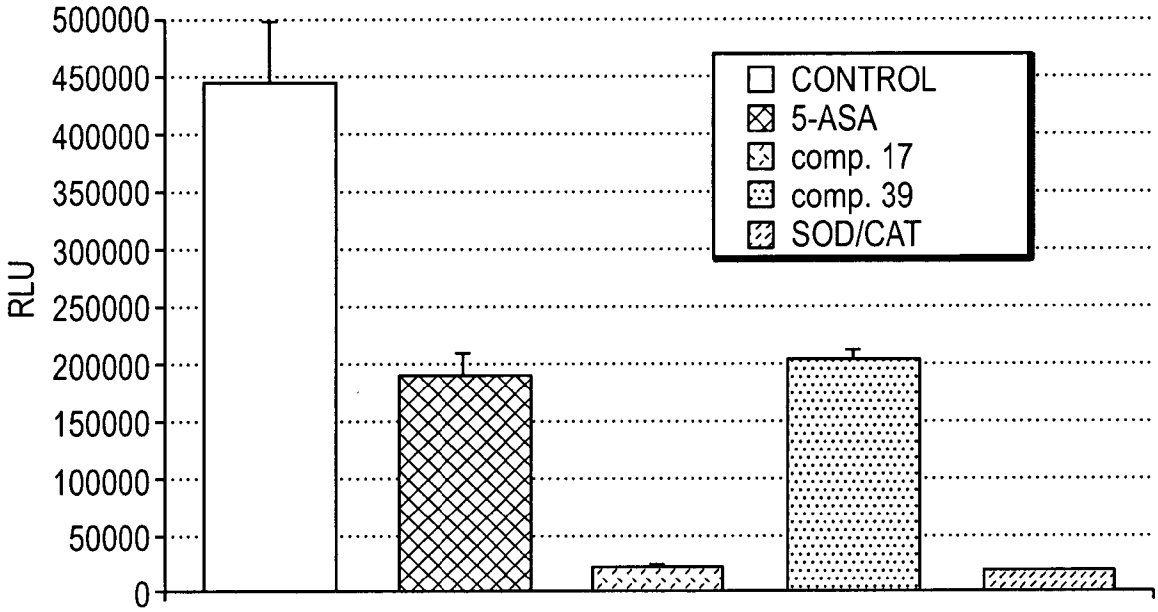

500000
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
RLU
CONTROL
5-ASA
comp. 17
comp. 39
SOD/CAT

FIG. 1

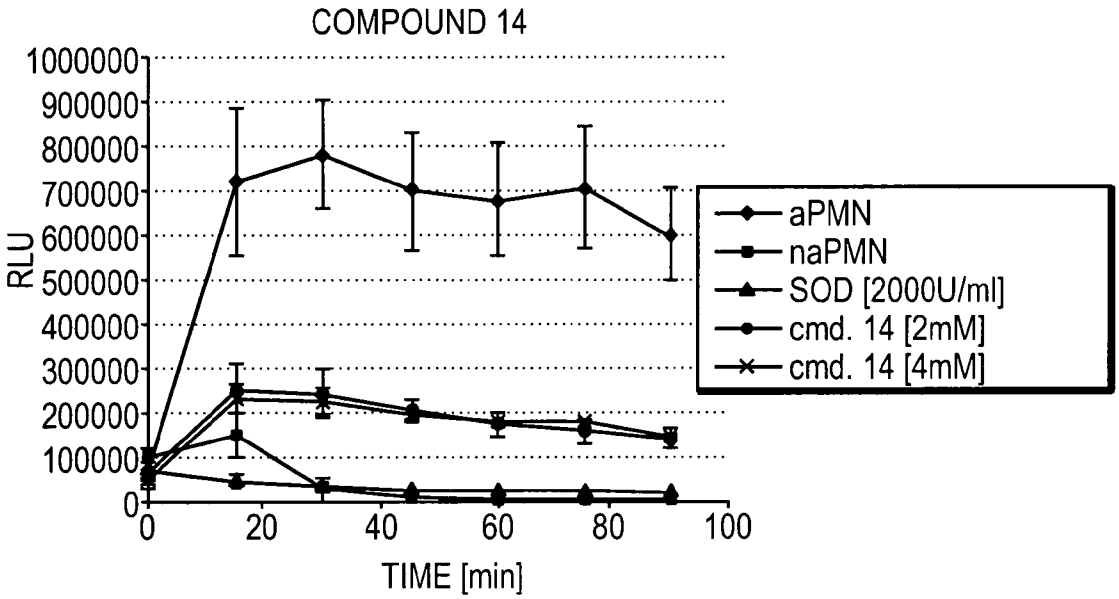

COMPOUND 14
RLU
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
0
20
40
60
80
100
TIME [min]
aPMN
naPMN
SOD [2000U/ml]
cmd. 14 [2mM]
cmd. 14 [4mM]

FIG. 2A

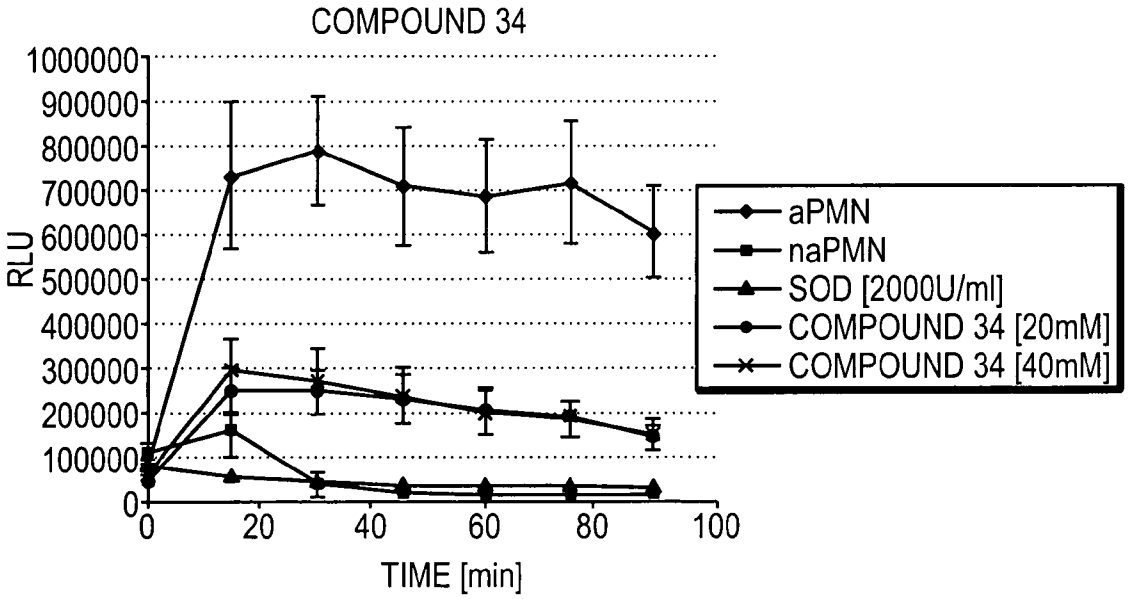

COMPOUND 34
RLU
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
0
20
40
60
80
100
TIME [min]
aPMN
naPMN
SOD [2000U/ml]
COMPOUND 34 [20mM]
COMPOUND 34 [40mM]

FIG. 2B

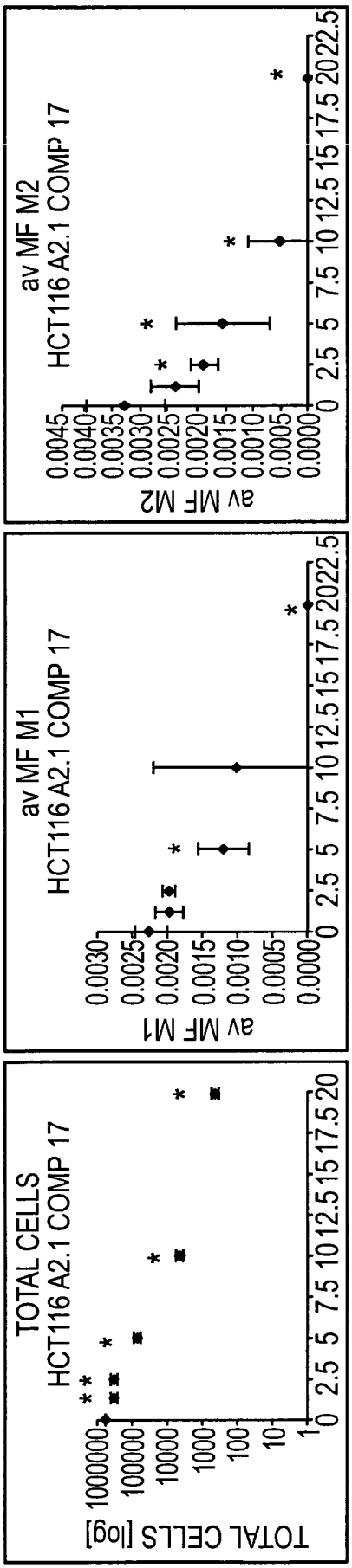

TOTAL CELLS
HCT116 A2.1 COMP 17
TOTAL CELLS [log]
av MF M1
HCT116 A2.1 COMP 17
av MF M1
av MF M2
HCT116 A2.1 COMP 17
av MF M2

FIG. 3A

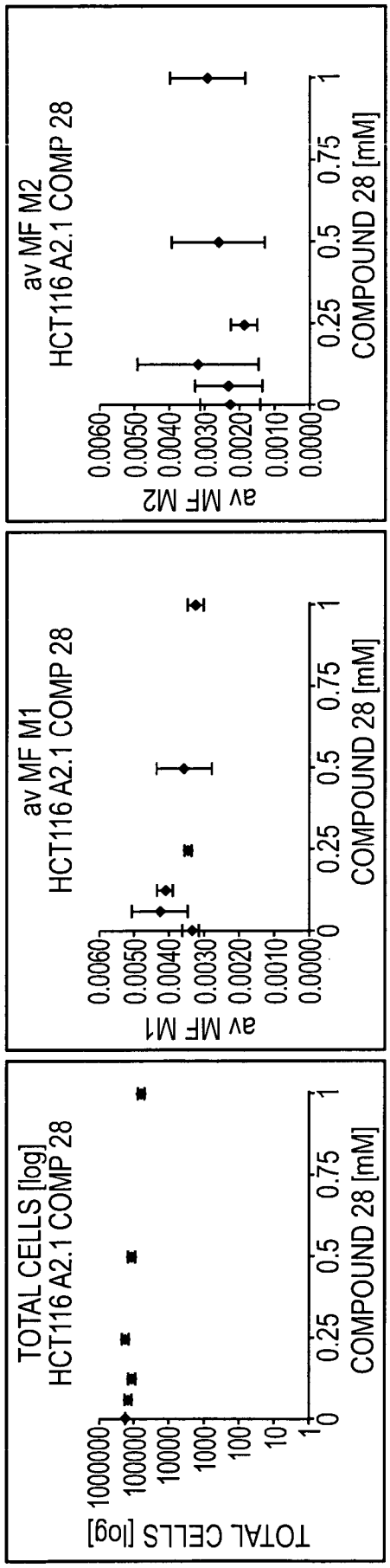

TOTAL CELLS [log]
HCT116 A2.1 COMP 28
COMPOUND 28 [mM]
av MF M1
HCT116 A2.1 COMP 28
COMPOUND 28 [mM]
av MF M2
HCT116 A2.1 COMP 28
COMPOUND 28 [mM]
av MF M2

FIG. 3B

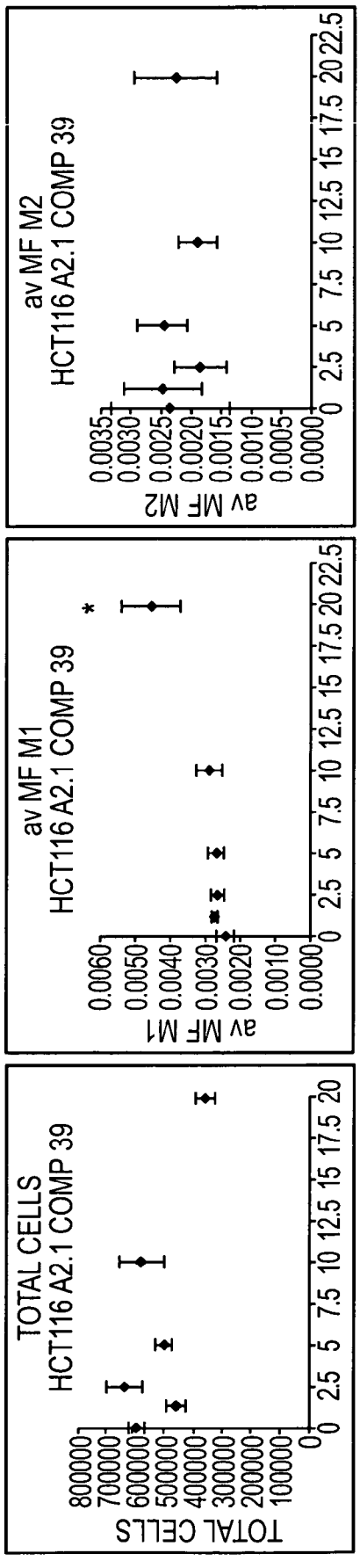

TOTAL CELLS
HCT116 A2.1 COMP 39
TOTAL CELLS
800000
700000
600000
500000
400000
300000
200000
100000
0
0 2.5 5 7.5 10 12.5 15 17.5 20
av MF M1
HCT116 A2.1 COMP 39
av MF M1
0.0060
0.0050
0.0040
0.0030
0.0020
0.0010
0.0000
0 2.5 5 7.5 10 12.5 15 17.5 20 22.5
av MF M2
HCT116 A2.1 COMP 39
av MF M2
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
0 2.5 5 7.5 10 12.5 15 17.5 20 22.5

FIG. 3C

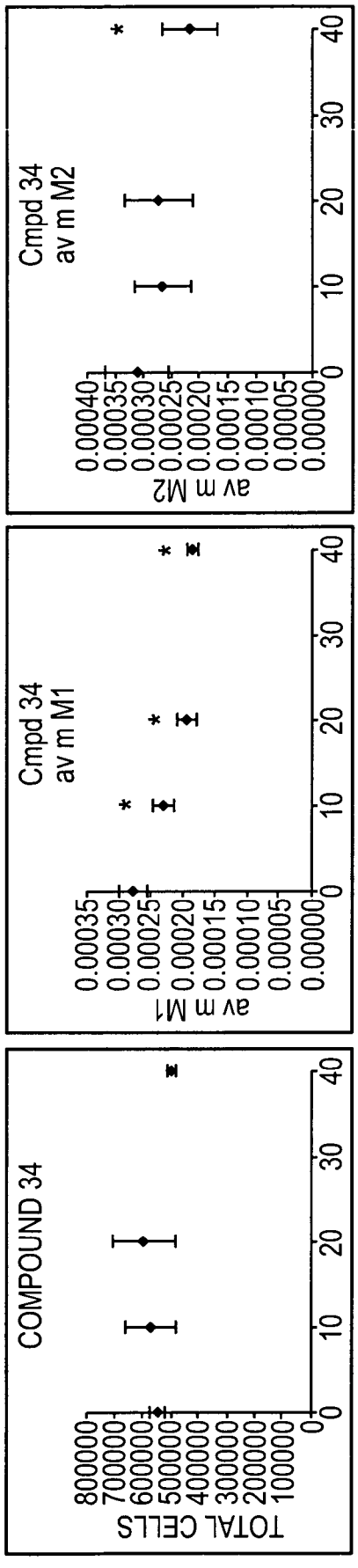

COMPOUND 34
TOTAL CELLS
800000
700000
600000
500000
400000
300000
200000
100000
0
0
10
20
30
40
Cmpd 34
av m M1
av m M1
0.00035
0.00030
0.00025
0.00020
0.00015
0.00010
0.00005
0.00000
Cmpd 34
av m M2
av m M2
0.00040
0.00035
0.00030
0.00025
0.00020
0.00015
0.00010
0.00005
0.00000

FIG. 4

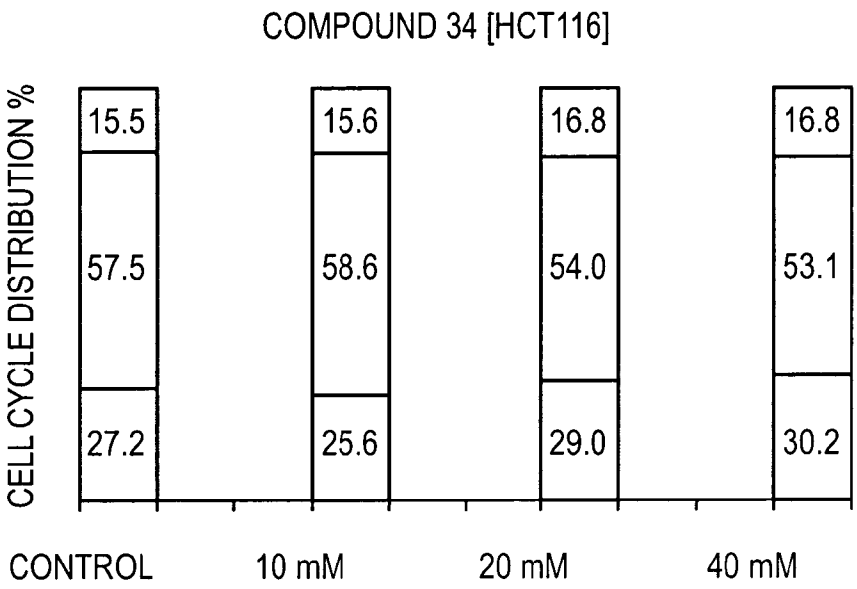

COMPOUND 34 [HCT116]
CELL CYCLE DISTRIBUTION %
15.5
57.5
27.2
15.6
58.6
25.6
16.8
54.0
29.0
16.8
53.1
30.2
CONTROL
10 mM
20 mM
40 mM

FIG. 5A

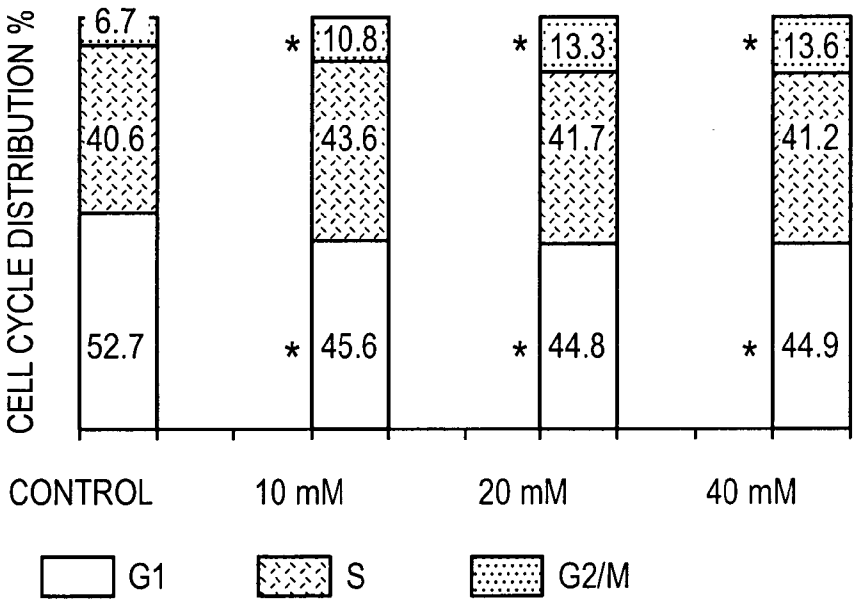

CELL CYCLE DISTRIBUTION %
6.7
40.6
52.7
* 10.8
43.6
* 45.6
* 13.3
41.7
* 44.8
* 13.6
41.2
* 44.9
CONTROL
10 mM
20 mM
40 mM
G1
S
G2/M

FIG. 5B

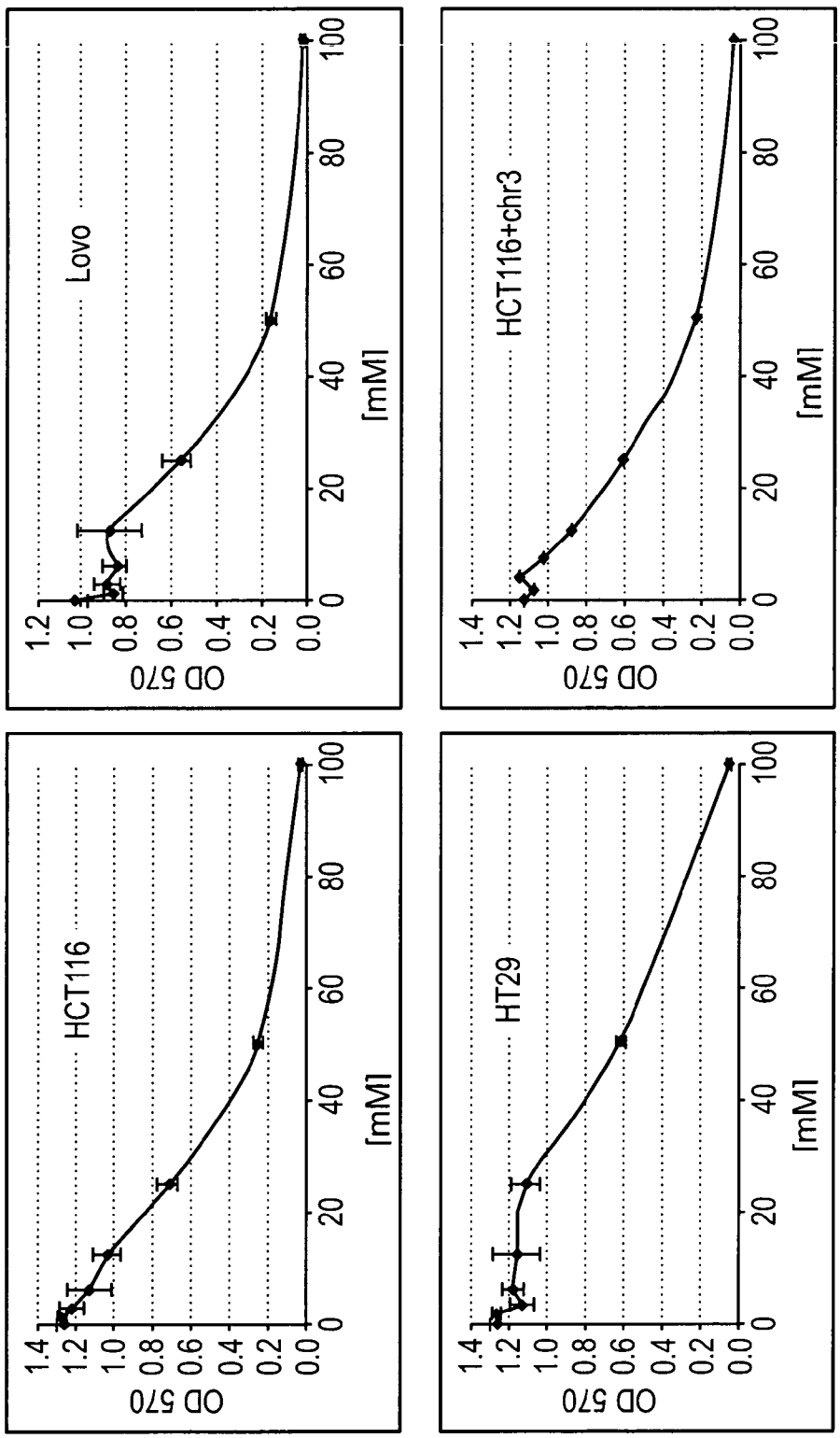

Lovo
HCT116+chr3
HCT116
HT29
OD 570
[mM]
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
0
20
40
60
80
100

FIG. 6