(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 November 2014 (13.11.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/182789 A2

(51) International Patent Classification:
C07D 241/22 (2006.01) *A61K 31/496* (2006.01)
C07D 241/18 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/US2014/037110

(22) International Filing Date:
7 May 2014 (07.05.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/820,447 7 May 2013 (07.05.2013) US

(71) Applicant: **THE REGENTS OF THE UNIVERSITY OF CALIFORNIA** [US/US]; 1111 Franklin Street, 12th Floor, Oakland, CA 94607-5200 (US).

(72) Inventors: **MCBRD3E, William;** 7915 Naylor Avenue, Los Angeles, CA 90045 (US). **MICEWICZ, Ewa;** 1641 Veteran Avenue, #5, Los Angeles, CA 90024 (US).

(74) Agents: **HALSTEAD, David, P.** et al; Foley Hoag LLP, Seaport West, 155 Seaport Blvd., Boston, MA 02210-2600 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

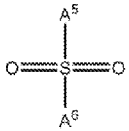
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

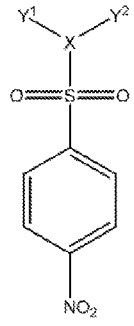
— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2014/182789 A2

(54) Title: RADIOMITIGATING PHARMACEUTICAL FORMULATIONS



(I)



(II)

(57) Abstract: The present disclosure relates to compounds of Formula (I) and (II), compositions containing the compounds (alone or in combination with other agents), and their use to prevent, mitigate or treat a) damage induced by ionizing radiation, b) inflammation or c) cancer.

RADIOMITIGATING PHARMACEUTICAL FORMULATIONS

Related Applications

This application claims the benefit of priority to U.S. Provisional Patent Application No. 61/820,447, filed May 7, 2013, which application is hereby incorporated by reference in its entirety.

Statement Regarding Federally Sponsored Research or Development

This invention was made with Government support under AI067769, awarded by the National Institutes of Health. The Government has certain rights in the invention.

Background

Radiomitigation

The tragic nuclear power plant accidents in Fukushima, Japan caused severe leaks of radioactive Iodine-131 and Cesium-137 and a subsequent widespread exposure scare of radiation. In addition, the global use and storage of radioactivity is increasing rapidly. Millions of radioactive sealed sources are used around the world for legitimate and beneficial commercial applications such as cancer treatment, food and blood sterilization, oil exploration, remote electricity generation, radiography, and scientific research. These applications use isotopes such as Cesium-137, Cobalt-60, Strontium-90, Americium-241, Iridium-192, Plutonium-238, Phrtonium-239, Curium-244, Radinm-226, and Californium-252. Many of these radiological sources at sites around the world are no longer needed and have been abandoned or orphaned; others are poorly guarded, making the risk of theft or sabotage significant. Currently, there are tens of thousands of civilian locations worldwide with radioacti ve material, about 5,000 of which contain sources of 1,000 curies or greater (Office of Global Threat Reduction (NA-21), GTRI Strategic Plan, release date January 2007. 955 L'Enfant Plaza, Washington, DC 20585. Iliopulos, loanna et ai. The Office of Global Threat Reduction: reducing the global threat from radiological dispersal devices.2007. JNMM Volume 35 Issue 3 PP 36-40), Beyond the public safety concerns are the clinical implications of radiation use.

Outside the radiation therapy clinic there is also significant relevance to identifying and characterizing novel compounds thai protect ceils from radiation induced cell death.

Fundamental to radiation exposure and injury is DNA strand breaks, resulting in genetic instability and DNA deletions wiiichare involved in cell death, cellular dysfunction, as well as Jong-term consequences such as birth defects ant! cancer.

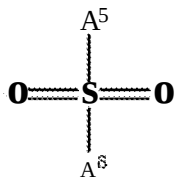
Discover}' of compounds that are capable of mitigating the process of normal tissue damage from radiation during radiotherapy, accidents, or terrorist attacks is of importance. Most currently available treatments for radiation exposure are free radical scavengers that reduce initial radiation-induced DNA damage and work best if added just before or at the time of irradiation. Because of this, these compounds are not practical eountermeasnres in a radiation incident. In that case, the search for radiomitigators - agents with robust, prolonged efficacy, broad specificity, and minimal toxicity that could protect a large population in the event of a radiological emergency is of importance.

Summary of the Invention

The present invention provides compounds having structures as disclosed herein. Preferred compounds are radiomiiigating, and thus can be used in the prevention, mitigation and treatment of radiation irjury, and oilier medical conditions related to exposure to ionizing radiation.

The subject compounds are also useful for treating or preventing inflammatory disease and for treating or preventing cancer or other hyperproliferative conditions.

In one aspect, the invention provides compounds represented by general formula **I** or a pharmaceutically acceptable salt, ester, or prodrug thereof:



Formula I

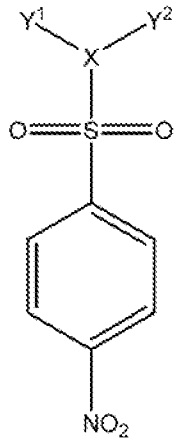
wherein:

A^5 is a secondary or tertiary amine (i.e., thereby forming a sulfonamide), and

A^6 is a substituted or unsubstituted aryl or heteroaryi group, preferably wherein the aryl or heteroaryi group bears at least one substituent including a nitro substitutent, e.g., disposed at a position distal o the sulfonyl.

In certain embodiments, A^5 is a heterocyciic **amine,,** such as a piperidine, **piperazine,** or **morpholine** ring, while in other embodiments, the amine **is** acyclic and/or the nitrogen atom **bound** to the sulfonyl is not **included in any** ring **that** may be present in A^5.

In certain embodiments, the invention provides compounds represented by general formula II or a pharmaceutically **acceptable** salt, ester or prodrug thereof:

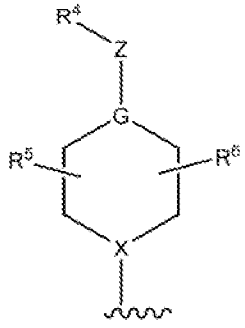


Formula II

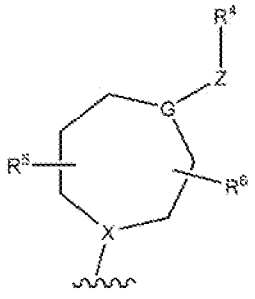
wherein:

X is N or -C(H)-, **preferably** N;

Y^5 and Y^6 are each **.independently** lower alkyl **or** Y^1 and Y^2 taken **together** with X **form a** heteroeyely! ring system, such as



or



wherein

X is N;

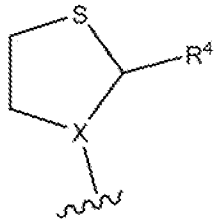
G is **selected** *from* **N or -C(H)-,** preferably **N;**

Z is absent or selected from **substituted** or unsubstituted alkyl, heteroalkyl, alkenyl, or alkynlyl; and

R^4 is hydrogen or selected from substituted or unsubstituted **aryl** (e.g., **phenyl)** and heteroaryl, **and**

R^5 and R^6 are each independently absent or **lower** aikyi.

In other **embodiments, X, Y**^{1} and Y^2 taken together form a ring system



wherein **X** is **-C(H)-, and**

R* is selected from **substituted** or **unsubstituted** aryl (e.g., **phenyl)** and **heteroaryl, such as** a **halogen-substituted** piienyi group, e.g., **4-fluorophenyi** or 3-cMorophertyS.

in certain embodiments, Y^1 and Y^2 are each ethyl.

In certain preferred embodiments, **Y**^{1} and Y^2 taken together form a piperazine ring.

In certain preferred embodiments, Z is absent.

In certain embodiments, the compound of Formula **i**I has a structure of one of compounds **1 - 7.** However, in certain preferred embodiments of the compounds, compositions, uses, **and methods** disclosed herein, compounds 1-12 (or even compounds 1-12 and compounds P1, P2, and P3) are excluded.

In certain embodiments, compounds of the invention may be prodrugs of the compounds **of formula I** or 0, e.g., wherein a **hydroxyl** in the parent compound is presented as an ester **or** a carbonate, or carboxylic acid present in the parent compound is presented as an ester. in certain **such** embodiments, the prodrug is **metabolized** to the **active** parent compound /« *vivo* (e.g., **the** ester is **hydrolyzed.** to the **corresponding** hydroxyl, or **carboxylic** acid).

In certain embodiments, compounds of the **invention** may be racemic. In certain embodiments, compounds of the invention may be enriched in one enantiomer. For example, a compound of the invention may have greater than **30%** ee, 40% ee, **50%** ee,

60% ee„ 70% ee, 80% ee, 90% ee, or even 95% or greater ee. In certain embodiments, compounds of the invention may have more than one stereoeenter. In certain such embodiments, compounds of the invention may be enriched in one or more diasiereorner. For example, a compound of the invention may have greater than 30% de, 40% de, 50% de, 60% de, 70% de, 80% de, 90% de, or even 95% or greater de.

In certain embodiments, the present invention relates to methods of treatment with a compound of formula 1or II, or a pharmaceutically acceptable salt thereof. In certain embodiments, the therapeutic preparation may he enriched to provide predominantly one enantiomer of a compound (e.g., of formula I or II). An cnaniiomerically enriched mixture may comprise, for example, at least 60 mol percent of one enantiomer, or more preferably at least 75, 90, 95, or even 99 mol percent. In certain embodiments, the compound enriched in one enantiomer is substantially free of the other enantiomer, wherein substaruiiaiiy free means that the substance in question makes up less than 10%, or less than 5%, or less than 4%, or less than 3%, or less than 2%, or less than i% as compared to the amount of the other enantiomer, *e.g.,* in the composition or compound mixture. For example, if a composition or compound mixture contains 98 grams of a first enantiomer and 2 grams of a second enantiomer, it would be said to contain 98 mo! percent of the first enantiomer and only *2%* of the second enantiomer.

In certain embodiments, the therapeutic preparation may be enriched to provide predominantly one diastereomer of a compound (e.g., of formula I or II). A diastereomerically enriched mixture may comprise, for example, at least 60 mol percent of one diastereomer, or more preferably at least 75, 90, 95, or even 99 mol percent.

In certain embodiments, the present invention relates to methods of treatment with a compound of formula 1or Is, or a pharmaceutically acceptable salt thereof. in certain embodiments, the therapeutic preparation may be enriched to provide predominantly one enantiomer of a compound (e.g., of formula 1or II). An enantiomerically enriched mixture may comprise, for example, at least 60 mol percent of one enantiomer, or more preferably at least 75, 90, 95, or even 99 mol percent. In certain embodiments, the compound enriched in one enantiomer is substantially free of the other enantiomer, wherein substantially free means that the substance in question makes up less than 10%, or less than 5%, or less than 4%, or less than 3%, or less than 2%, or less than 1% as compared to the amount of the other enantiomer, *e.g.,* in the composition or compound mixture. For example, if a composition or compound mixture contains 98 grams of a first enantiomer and 2 grams of a

second enantiomer, it would be said to contain 98 mol percent of the first enantiomer and only 2% of the second enantiomer.

In certain embodiments, the therapeutic preparation may be enriched to provide predominantly one diastereomer of a compound (e.g., of formula 1or 11). A diastereomerieaily enriched mixture may comprise; for example, at least 60 mol percent of one diastereomer, or more preferably at least 75, 90, 95, or even 99 mol percent.

In certain embodiments, the present invention provides a pharmaceutical preparation suitable for use in a human patient, comprising any of the compounds shown above (e.g., a compound of the invention, such as a compound of formula 1or II), and one or more pharmaceutically acceptable excipients. In certain embodiments, the pharmaceutical preparations may be for use in treating or preventing a condition or disease as described herein. In certain embodiments, the pharmaceutical preparations have a low enough pyrogen activity to be suitable for use in a human patient.

Compounds of any of the above structures may be used in the manufacture of medicaments for the treatment of any diseases or conditions disclosed herein.

In certain embodiments, the compounds of Formula I or 1I mitigate tissue damage induced by exposure to ionizing radiation and/or inhibit inflammation.

In one aspect, the invention provides a pharmaceutical composition comprising a compound as disclosed herein and a pharmaceutiealiy acceptable excipient or solvent. In certain embodiments, a pharmaceutical composition may comprise a prodrug of a compound as disclosed herein.

In another aspect, the invention provides a method of mitigating the effect of ionizing radiation on a cell, organ, tissue, or organism by contacting the ceil, organ, tissue, or organism with at least one compound shown in Table 1. The cell, organ, tissue, or organism may be contacted with a compound shown in Table 1 before, during, or after exposure to ionizing radiation.

In some embodiments, the compound may be administered prophyiactieaiiy, i.e., before exposure to ionizing radiation, for example, prior to cancer radiation therapy or X-ray. In some embodiments, the compound may be administered during exposure, or upon repeated exposure to ionizing radiation. in some embodiments, the compound may be administered after exposure to
ionizing radiation, or after the initiation of exposure to radiation.

When administering a compound of Formula I or il to an organism:, the compound may be administered by any suitable means. In some embodiments, the compounds or formulations arc administered orally, lo some embodiments, the compounds or formulations are administered by injection, e.g. subcutaneous, parenteral, or intravenous, injections. In some embodiments., the compound may be administered in combination with other potential mitigators. In certain embodiments, compounds of Formula 1 or II are administered in conjunction with other therapies, such as radiation therapy, other anti¬inflammatory compounds, or other anticancer drugs.

In certain embodiments, a method of the invention may comprise contacting a cell with a prodrug of a compound as disclosed herein.

Definitions

The terms "a," "an," "the" and similar referents used in the context of describing the present invention are to be construed to cover both the singular and the plural,, unless otherwise indicated herein or clearly contradicted by context. Ali methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein is intended merely to better illuminate the present invention and does not pose a limitation on the scope of the invention otherwise claimed. No language in the present specification should be construed as indicating any unclaimed element is essential to the practice of the invention.

The term "acyi" is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)-, preferably alkylC(0)-.

The term "acyiamino" is art-recognized and refers to an amino group substituted with an aeyl group and may be represented, for example, by the formula hydrocarbylC(0)NH- .

The term "acyloxy" is art-recognized and refers to a group represented by the general formula hydrocarbyiC(0)0-, preferably alkylC(O)O-.

The term "alkoxy" refers to an alkyl group, preferably a lower alkyl group, having an oxygen attached thereto. Representative alkoxy groups include methoxy, ethoxy, propoxy, tert-butoxy and the like.

The term "alkoxyalky!" refers to an alkyl group substituted with an alkoxy group and may be represented by the genera! formula a!kyl-O-alkyl.

The term "alkenyl", as used herein, refers to an aliphatic group containing at least one double bond and is intended to include both "unsubstituted alkenyis" and "substituted alkenyis", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the alkenyl group. Such substituents may occur on one or more carbons that are included or not included in one or more double bonds. Moreover, such substituents include all those contemplated for aikyl groups, as discussed below, except where stability is prohibitive. For example, substitution of alkenyl groups by one or more aikyl, carbocyclyi, aryl, heterocyclyi or heteroaryl groups is contemplated.

An "aikyl" group or "alkane" is a straight chained or branched non-aromatic hydrocarbon which is completely saturated. Typically, a straight chained or branched aikyl group has from 1 to about 20 carbon atoms, preferably from 1 to about 10 unless otherwise defined. Examples of straight chained and branched alkyl groups include methyl,, ethyl, n-propyi, iso-propyl, n-butyk see-butyl, tert-butyk pentyl, hexyl, pentyl and ocryi. A C_1-C_6 straight chained or branched aikyl group is also referred to as a "lower aikyl" group. An aikyl group with two open valences is sometimes referred to as an alkylene group, such as methylene, ethylene, propylene and the like.

Moreover, the term "aikyl" (or "Sower aikyl") as used throughout the specification, examples, and claims is intended to include both "unsubstttuted alkyis" and "substituted alkyls", the latter of which refers to aikyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone . Such substituents, if not otherwise specified, can include, for example, a halogen, a hydroxy!, a carbonyl (such as a earboxyl, an alkoxyearbony!, a formyl, or an acyl), a thioearbonyl (such as a thioester, a thioacetate, or a tbioforraate), an alkoxyl, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkyiihio, a sulfate, a sulfonate, a suifamoyl, a sulfonamido, a sulfonyl, a heterocyciyl, 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 can themselves be substituted, if appropriate. For instance, the substituents of a substituted aikyl may include substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and siiyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, earboxylates, and esters), -CF$_3$, -CN and the like. Exemplary substituted alkyls are

described **below.** Cycloalkyls can be further substituted with **alkyls,,** alkenyis, aikoxys, alkyithios, **aminoalkyls,** carbonyl-substituted aikyls, -CF_3, ~CN, and the like.

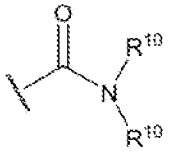
The term "C_{x-y}" when used **in conjunction** with a **chemical moiety,** such as, acyl, acyioxy, alkyi, alkenyl, alkynyl, or alkoxy is **meant** to include groups that **contain** from **x** to y carbons in the chain. For example, the term "C_{x-y}aikyi" refers **to** substituted **or unsubstituted** saturated hydrocarbon groups, **including** straight-chain **alkyi** and **branched-chain alkyl groups** that **contain** from x to **y carbons** in the chain, including rtaloalkyl groups such as **trifluoromethyl** and 2,2,2~tirtluoroethyl, etc. C_0 **alkyl** indicates a hydrogen where the group **is** in a terminal position, a bond if internal. **Hie** terras "C_{2-y}**alkenyl**" and "C_{2-y}**alkynyl**" refer **to substituted or unsubstituted unsaturated aliphatic groups** analogous **in** length and possible substitution to the alkyls described above, but that contain at least one double or **triple** bond respectively. As applied to heteroalkyls, "C_{x-y}" indicates that the group contains **from x to** y carbons and heteroatorns in the chain. As applied to earboeyclic **structures,** such as aryl and cyeloalkyl groups, "C_{x-y}" indicates that the ring comprises x to **y** carbon atoms. As applied to **heterocyclic** structures, such as heteroaryl and heteroeyclyl groups, "C_{x-y}" indicates that the ring contains from x to y carbons and **heteroatorns.** As applied **to** groups, such **as** aralkyl and **heterocyctylalkyl** groups, that have both ring and chain components, "C_{x-y}" indicates that the ring and the chain **together** contain from x to y carbon atoms and, as appropriate heteroatorns.

The term "**alkylamino**", as used herein, refers **to** an amino group substituted with **at** least one alkyl group.

The term "**alkylthio**", **as** used herein, refers **to** a **thiol group** substituted with an **alkyl** group and may be represented by the genera! formula aikyiS-.

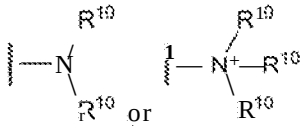
The term **"alkynyl",** as used herein, refers to an aliphatic group containing at !east one triple bond and is intended to include both **"unsubstituted** alkynyis" and "substituted **alkynyls", the** latter of which refers **to** alkynyl moieties having substituents **replacing** a hydrogen on one or more carbons of the **alkynyl** group. Such substituents may occur on one or more carbons that are included or not included in one or more triple bonds. Moreover, **such substituents include** all those **contemplated** for alkyi **groups,** as discussed above, except where stability is prohibitive. For example, substitution of alkynyl groups **by** one **or** more alkyl **carbocycty!,** atyi, **heteroeyclyl,** or heteroaryl **groups** is **contemplated.**

The term **"amide",** as used herein, refers to a group



wherein each $\mathbf{R}^{10}$ independently represent a hydrogen or hydrocarbyl group, or two $\mathbf{R}^{10}$ are taken together with the N atom to which they are attached complete a heterocycie having from 4 to 8 atoms in the ring structure.

The terms "amine'' and "amino" are art-recognized and refer to both unsubstituted and substituted amines and salts thereof, e.g., a moiety that can be represented by



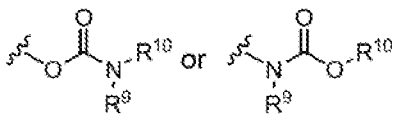
wherein each R^{10} independently represents a hydrogen or a hydrocarbyl group, or two $\mathbf{R}^{10}$ arc taken together with the N **atom** to which they are attached complete a heterocycie having from 4 to 8 atoms in the ring structure.

The term "**aminoalkyl**", as used herein, refers to an **alkyl** group **substituted** with **an** amino group.

The term "**aralkyi**", as used herein, **refers** to **an alkyl group** substituted with an **aryi** group.

The term "aryl" as used herein include substituted or **unsubstituted** single-ring aromatic groups in which each atom of the ring is carbon. **Preferably** the ring is a 5- to ?-membered ring, more preferably a **6-me-mbered** ring. The term "**aryl**" also includes polyeyelic ring systems having two or **more** cyclic rings in which two or more carbons are **common** to two adjoining rings wherein at least one of the rings **is** aromatic, e.g., **the** other cyclic rings can be **cycloalkyls, cycloalkenyls, cycloaOcynyls,** aryls, **heteroaryls,** and/or heterocyeiyis. Aryi groups include benzene, naphthalene, phenaiithrene, phenol, aniline, and the like.

The term "carbamate" is ail-recognized and refers to a group



wherein R^9 and $\mathbf{R}^{10}$ independently represent hydrogen or a hydrocarbyl group, such as an **alkyl** group, or R^9 and $\mathbf{R}^{10}$ taken together with the intervening atom(s) **complete** a **heterocycie** having **from 4** to 8 atoms in the ring **structure.**

The terms **"carboeycle"**, and "carbocyclic", as used herein, refers to a saturated **or** unsaturated ring in which each atom of the **ring** is carbon. The **term** carboeycle includes both aromatic carbocyeles and non-aromatic carbocyeles. **Non-aromatic** carbocyeles include both cycloaikane rings, in which all carbon atoms are saturated, and eyeioaikene rings, which contain at least one double bortd. "Carboeycle" includes 5-7 membered **monocyclic** and 8-*12* membered bicyciic rings. Each ring of a bicyciic **carboeycle may** be selected from saturated, unsaturated and aromatic rings. **Carboeycle includes tricyclic molecules** in which one, two or three or more atoms are shared between the two rings. The term "fused carboeycle" refers to a bicyciic carboeycle in which each of the rings shares two adjacent atoms with the other ring. Each ring of a **fused** carboeycle may be selected from saturated, unsaturated and aromatic rings. **In** an exemplary **embodiment,** an **aromatic** ring, **e.g., phenyl, may be fused** to a saturated **or** unsaturated ring, e.g., eyclohexane, **cyclopcntanc,** or **cyclohexenc.** Any combination of saturated, unsaturated and aromatic bicyciic rings, as **valence permits, is included in the** definition **of carbocyelic. Exemplary Carbocyeles"** include cyelopentane, eyclohexane, **bicyclop** .2. !]heptane, **1,5-cyclooctadiene,** 1,2,3,4-tetrahydrouaphihalene, **bicyclo{4 .2.0)oct-3-ene, naphthalene** and adamantane. **Exemplary** fused carbocyeles **include decalin, naphthalene,** 1,2,3,4-**tetrahydronaphthalene,** bicyelof4.2.0]octane, **4,5,6,?-tetrahydro-lH-i:ndene and** bicyclo[4.1.0]hept-3-ene. **"Carbocyeles"** may **be** substituted at any one **or** more positions capable of bearing a hydrogen atom.

A **"cycloalkyl"** group is **a** cyclic hydrocarbon which is completely saturated. **"Cycloalkyl"** includes **monocyclic** and bicyciic rings. Typically, a **monocyclic** cycloalkyl group has from 3 to about **10** carbon atoms, more typically 3 **to** S carbon atoms unless otherwise defined. The second ring of a bicyciic cycloalkyl may be selected from saturated, unsaturated **and aromatic rings. Cycloalkyl includes bicyciic molecules in which one, two** or three or more **atoms** are shared between the two rings. The term "fused **cycloalkyl"** refers to a bicyciic **cycloalkyl** in which each of the rings shares two adjacent atoms with **the other** ring. The second ring of a **fused** bicyciic **cycloalkyl** may be selected from saturated, **unsaturated** and aromatic rings. A "cycioalkenyi" group **is** a cyclic hydrocarbon containing one or more double bonds.

The term "earbocyclylalkyl' ', **as used** herein, **refers to an alky**l group substituted with **a** carboeycle group.

The term **"carbonate"** is art-recognized **and** refers to a group -OCOr R^{10}>wherein R^{10} represents a **hydrocarbyi** group.

The **term** "carboxy", as used herein, refers to **a group represented** by the formula -CO_2H.

The term:"ester", as used herein, refers to a group -C(O)OR^{10} wherein R^{10} represents a **hydrocarbyi group.**

The term "ether", as used herein, refers to a hydrocarbyi group linked through an oxygen to **another** hydrocarbyi **group. Accordingly,** an ether **substituent** of a hydrocarbyi group may be hydrocarbyl-O-, Ethers may be either **symmetrical** or **asymmetrical.** Examples of ethers include, but are not **iimited** to, heterocye!e-O-heterocycle ***m d*** aryi-G-heterocyele. **Ethers** include "aikoxyalkyi" groups, **which may be represented by the** general formula alkyl~0~alkyi.

The **terms** "halo" and **"halogen"** as used herein means halogen and **includes** chloro, fiitoro, **bromo,** and iodo.

The terms "hetaralkyi" and **"heieroaraikyr,** as used herein, refers to an alky! group substituted with a **hetaryt** group.

The term "heteroaikyi", as used herein, refers **to** a saturated or unsaturated chain of carbon atoms and at least one heferoatoin, wherein no **two** heteroatoms are adjacent. In analogy **with alkyl** groups, heteroaikyi groups **with two** open valences are sometimes referred to as heteroaikylene groups. Preferably, **the** heteroatoms in heteroaikyi groups are selected from O and N,

The terms "heteroaryl" and "hetaryi" include substituted or unsubstituted aromatic single **ring** structures, preferabiy 5- to 7-membered **rings,** more preferably 5- **to** 6~ **membered** rings, whose ring **structures** include at least one heteroatom, preferably one to four heteroatoms, more preferably one or **two** heteroatoms. The terms "heteroaiy P and **"hetaryl"** also **include** poiycyclic **ring** systems **having two or** more cyclic **rings in** which two or more carbons are common to **two** adjoining rings wherein at least one of the rings is **heteroaromatic, e.g.,** the other cyclic rings **can** be **cycloalkyis,** cyeioaikeiiyls, **cycioalkynyis,** aryis, **heteroaryls,** and/or heteroeyclyls, Heteroaryt **groups include,** for example, pyrrole, firran, thiophene, imidazole, **oxazole,** thiazole, pyrazole, pyridine, **pyrazine, pyridazine,** and pyrrolidine, and the like.

The **term "heteroatom"** as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, and sulfur.

The terms "heterocyclyl", "heteroeycle", and "heterocyclic" refer to substituted or unsubstituted non-aromatic ring structures, preferably 3- to 10-membered rings, more preferably 3- to 7-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms "heterocyclyl" and "heterocyclic" also include polyeyclie ring systems having two or more cyclic tings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heterocyclic, e.g., the other cyclic rings can be eycloalkyls, cyeJoaJkenyls. cyeloal.kynyls, aryls, heteroaryls, and/or heteroeyely ls. Heterocyclyl groups include, for example, piperidine, piperazine, pyrrolidine, rnorphoiine, lactones, lactams, and the like.

The term "heterocyclyl alkyl", as used herein, refers to an aikyl group substituted with a heierocycle group.

The term "hydrocarbyl", as used herein, refers to a group that is bonded through a carbon atom that does not have a =O or ~S subsiittsent, and typically has at least one carbon-hydrogen bond and a primarily carbon backbone, but may optionally include heteroatomS. Thus, groups like methyl ethoxyethyl, 2-pyridyL and trifiuororaethyl are considered to be hydrocarbyl for the purposes of this application, but substituents such as acetyl (which has a =O subsfiruenf on the linking carbon) and ethoxy (which is linked through oxygen, not carbon) are not. Hydrocarbyl groups include, but are not limited to aryl, heteroaryi, carbocycle, heterocyclyl, alkyi, alkenyi, alkynyl, and combinations thereof.

The term "hydroxyaikyl", as used herein, refers to an aikyl group substituted with a hydroxy group.

The term "lower" when used in conjunction with a chemical moiety, such as, acyl, acyloxy, aikyl, alkenyi, alkynyl, or alkoxy is meant to include groups where there are ten or fewer non-hydrogen atoms in the substituent, preferably six or fewer. A "lower alkyi", for example, refers to an alkyi group that contains ten or fewer carbon atoms, preferably six or fewer. In certain embodiments, acyl, acyloxy, alkyi, alkenyi, alkynyl, or alkoxy substituents defined herein are respectively lower acyl, lower acyloxy, lower aikyl, lower alkenyi, lower alkynyl, or lower alkoxy, whether they appear alone or in combination with other substituents, such as in the recitations hydroxyaikyl and aralkyl (in which case, for example, the atoms within the aryl group are not counted when counting the carbon atoms in the alkyi substituent).

The terms "**polycyd y**l", "**polycyde**'\, **and** "polycyclic" refer **to two** or more **rings** (e.g., **cycloalkyls,** cycloaikenyls, cydoalkynyis, aryls, heteroaryls, and/or **heierocydyls)** in which two or more **atoms** are **common** to two **adjoining** rings, e.g., the rings are "fused rings". Bach of the rings of the **polycycle** can he substituted or **unsubstituted. In** certain **embodiments,** each **ring** of the polycycle **contains** f om 3 to 10 atoms in the ring, preferably from 5 to 7. When a poly cyclic substituent is attached through an aryl or hcteroaryi ring, that **substituent** may be referred to herein as an ary! or heteroaryl group, while if the poly cyclic substituent is attached through a **cycioalkyl** or heteroeyelyl group, that **substituent** may be referred to herein **as** a cycloalkyl or heterocyciyl group. By way of example, a 1,2,3,4-tetrahydrortaphthaien- i-yi group would **be** a **cycioalkyl group,** while a **1**,2,3,4-tetrahydronaphthalen-5-yl group **would** be an aryl **group.**

The term: "**siiy**l" refers to a silicon moiety with **three** hydrocarbyl moieties attached thereto.

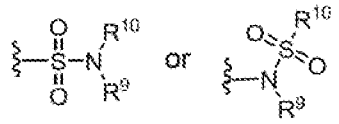
The term "substituted" refers to moieties having substituents replacing a hydrogen on one **or** more carbons or heteroatoms of the moiety. It will be understood that "**substitution**" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the **substituent,** and that the substitution results **in** a stable compound, e.g., which docs not **spontaneously** undergo transformation such as by rearrangement, eyclization, elimination, etc. As used herein, the term "substituted" is contemplated to include all permissible subsrituents of organic compounds.

In a broad aspect, the permissible **substituents** include **acyclic** and cyclic, **branched** and unbranched, carbocyciic and heterocyclic, aromatic and non-aromatic subsrituents of organic compounds. The permissible substifuents can be one or more and the same or different for appropriate organic compounds. For purposes **of** this invention, the **heteroaioras** such as nitrogen **may have hydrogen** substituents **and/or any** permissible substituents of organic compounds described herein which satisfy the valences **of the** heteroatoms. Substituents can include any substituents described herein, for example, **a** halogen, a hydroxy!, a **carbonyl** (such as a carboxy!, **an** aJkoxyearbom4, a **formyl,** or an **acyl),** a th.iocarbonyi (such as a thioester, a thioacetate. or a thioformate), an atkoxyl, a phosphoryi, a phosphate, a phosphonate, a phosphioate, an amino, an amido, an **amidine,** an imine, **a cyano,** a nitro, an azido, a sulfhydryi, an **a**!kylthio, a **sulfate,** a sulfonate, **a** sulfamoyl, a sulfonamide, a sul6 nyl, a heterocyciyl, an aralkyl, or an aromatic or

heteroaromatic moiety. it will be understood by those skilled in the art that substituents can themselves be substituted, **if appropriate. Unless** specifically stated as '^substituted," **references** to chemical **moieties** herein are **understood** to include **substituted variants.** For example, reference to an "ary!" group or moiety implicitly includes both substituted and unsubstituted variants.

The term "sulfate" is **art-recognized** and refers to the group -QSO$_3$H, or a pharmaceutically acceptable salt thereof.

The **term "sulfonamide"** is art-recognized and refers to the group **represented** by the genera! formulae



wherein R^y and **R**^{10} independently represents hydrogen or hydrocarbyi, such **as** alkyl, or R^9 and R^{10} taken **together** with the **intervening** atom(s) complete a heteroeycle having from 4 to S atoms in the ring structure.

The **term "sulfoxide" is art-recognized** and refers to the **group** -S(O)-R^{10}, wherein **R**^{10} **represents** a hydrocarbyi.

The term "sulfonate" is art-recognized **and refers** to **the group** SO$_3$H, **or** a pharmaceutically acceptable salt thereof.

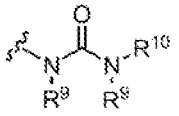
The **term** "sulfone" is art-recognized and refers to the group -S(O)$_2$-R^{10}, wherein **R**^{10} represents a hydrocarbyi.

The **term "thioalkyl",** as used **herein,** refers to **an** alkyl **group** substituted with **a** thiol group.

The term "**thioester**", as used herein, refers to a group **-C(0)SR** ^{10} or -SC(0)R ^{10} wherein R^{10} represents a hydrocarbyi.

The term: "diioether", as used herein, is equivalent to an **ether,** wherein the oxygen is replaced with a sulfur.

The term "urea" is art-recognized and may be represented by **the** general **formula**



wherein R^9 and R^{10} independently represent hydrogen or a hydrocarbyi, such **as** alkyl, or either occurrence **ofR*** taken together with **R**^{9} and the **intervening** aiom(s) complete a heteroeycle having from 4 to 8 atoms in the ring structure.

"'Protecting group" refers to a group of atoms that, when attached to a reactive functional group in a molecule, mask, reduce or prevent the reactivity of the functional group. Typically, a protecting group may be selectively removed as desired during the course of a synthesis. Examples of protecting groups can be found in Greene and Wuts, *Protective Groups in Organic Chemistry,* 3rd Ed., 1999, John Wiley & Sons, NY and Harrison et al., *Compendium of Synthetic Organic Methods,* Vols. 1-8, 1971-1996, John Wiley & Sons, NY. Representative nitrogen protecting groups include- but are not limited to, formyl, acetyl, trifiuoroaeety!, benzyl, benzyloxycarhonyl ("CBZ"), tert-butoxyearboiiy! ("Boc"), trimethylsilyi ("TMS"), 2-trimethylsilyl-ethanesulfonyl ("TES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-ffluoreny!meihyioxycarbonyi ("FMOC"), nitro-veratryloxyearbonyl ("NVOC") and the like. Representative hydroxylproteeting groups include, but are not limited to, those where the hydroxy! group is either acylated iesterified) or alkylated such as benzyl and trityl ethers, as well as alky! ethers, tetraliydropyranyl ethers, trialkylsilyl ethers (e.g., IMS or TIPS groups), glycol ethers, such as ethylene glycol *and* propylene glycol derivatives and ally! ethers.

As used herein, a therapeutic that "prevents" a disorder or condition refers to a compound that, in a statistical sample, reduces the occurrence of the disorder or condition in the treated sample relative to an untreated control sample, or delays the onset or reduces the severity of one or more symptoms of the disorder or condition relative to the untreated control sample.

The term "treating" includes prophylactic and/or therapeutic treatments. The term "prophylactic or therapeutic" treatment is art-recognized *and* includes administration to the host of one or more of the subject compositions. If it is administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the host animal) then the treatment is prophylactic (i.e., it protects the host against developing the unwanted condition), whereas if it is administered after manifestation of the unwanted condition, the treatment is therapeutic (i.e., it is intended to diminish, ameliorate, or stabilize the existing unwanted condition or side effects thereof).

The term "prodrug" is intended to encompass compounds which, under physiologic conditions, are converted into the therapeutically active agents of the present invention (e.g., a compound of formula I or II). A common method for making a prodrug is to include one or more selected moieties which are hydroiyzed under physiologic conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic

activity of the host **animal.** For example, esters or carbonates (e.g., esters or carbonates of alcohols or carboxylic acids) are preferred prodrugs of the present **invention.** In certain embodiments, sonic or all of the compounds **of** formula 1or ii in a formulation representee! above can be replaced with the corresponding suitable **prodrug,** e.g., wherein a hydroxy! in the parent compound is presented as an ester or a carbonate or **carboxylic** acid **present** in the parent **compound** is presented as an ester,

Pharmaceutical Compositions

The compositions and **methods of the** present invention may be utilized to treat an individual in need thereof, in certain embodiments, the individual is a mammal such as a human, **or** a non-human mammal. When administered to an animal, such as a human, the composition **or** the compound is preferably administered as **a pharmaceutical** composition **comprising,** for **example,** a compound of the invention and a pharmaceutically acceptable **carrier. Pharmaceutically** acceptable carriers are well known ***in*** **the** art and include, for **example,** aqueous **solutions** such as water or **physiologically** buffered saline or other solvents or vehicles such **as** glycols, **glycerol,** oils such as olive oil, or injectable organic-esters. In a preferred embodiment, when such **pharmaceutical** compositions are for human **administration, particularly** for invasive routes of administration (i.e., routes, such as injection **or** implantation, that circumvent transport or diffusion through an epithelial barrier), the aqueous solution is pyrogen-free, or **substantially** pyrogen-free. The exeipients **can be** chosen, for **example,** to effect delayed release of an agent or to selectively target one or more cells, tissues or organs. The pharmaceutical composition can be **in** dosage unit form such as tablet, capsule (including sprinkle capsule and gelatin capsule), granule, lyophile for reconsistation, powder, solution, syrup, suppository, injection or the like. The **composition** can also be present in a **transdermal** delivery system, eg;., a skin patch.

A pharmaceutical composition disclosed herein may comprise a therapeutic **compound in** an amount sufficient to allow **customary** administration to an **individual,** in certain **embodiments,** a pharmaceutical composition disclosed herein may comprise, e.g., at least 5 mg, at least 10 **mg,** at least 15 rag, at least 20 mg, at least 25 mg, at least 30 **mg,** at least 35 mg, at least 40 mg, **at** least 45 mg, at least **50** mg, **at** least 55 **mg,** at least 60 mg, at least 65 mg, at least 70 mg, at least 75 mg, at least SO mg, at least 85 mg, at least 90 mg, at least 95 mg, or at least 10**0** mg of a therapeutic **compound. In** certain embodiments, a pharmaceutical composition disclosed herein may comprise, e.g., at least 5 mg, at least 10

mg, at least 20 rag, at least 25 mg, at least 50 mg, at least 75 mg, at least 100 rng, at least 200 mg, at least 300 mg,, at least 400 mg, at least 500 mg, at least 600 mg, at least 700 mg, at least 800 mg, at least 900 mg, at least 1,000 mg, at least 1,100 mg, at least 1,200 mg, at least 1,300 mg, at least 1,400 mg, or at least 1,500 mg of a therapeutic compound. In yet other aspects of this embodiment, a pharmaceutical composition disclosed herein may comprise itr the range of, e.g., about 5 mg to about 100 mg, about 10 mg to about 100 mg, about 50 mg to about 150 mg, about 100 mg to about 250 mg, about 150 nig to about 350 mg, about 250 mg to about 500 mg, about 350 mg to about 600 mg, about 500 mg to about 750 mg, about 600 mg to about 900 mg, about 750 mg to about 1,000 mg, about 850 mg to about 1,200 mg, or aboitt 1,000 mg to about i,500 mg. In still certain embodiments, a pharmaceutical composition disclosed herein may comprise in the range of, e.g., about 10 mg to about 250 mg, about 10 mg to about 500 mg, about 10 mg to about 750 mg, about 10 mg to about 1,000 mg, about 10 rng to about 1,500 rng, about 50 tug to about 250 mg, about 50 mg to about 500 mg, about 50 mg to about 750 mg, about 50 mg to about 1,000 mg, about 50 mg to about 1,500 mg, about 100 mg to about 250 rng, about 100 mg to about 500 mg, about 100 mg to about 750 mg, about 100 mg to about 1,000 .mg, aboist 100 mg to about 1,500 mg, aboist 200 mg to about 500 .mg, aboist 200 rag to about 750 mg, about 200 mg to aboist. 1,000 mg, about 200 tug to about 1,500 mg, about 5 mg to aboist 1,500 mg, about 5 mg to about 1,000 mg, or about 5 mg to about 250 mg.

A pharmaceutical composition disclosed herein may comprise a solvent, emulsion or other diluent in an amount sufficient to dissolve a therapeutic compound disclosed herein. In certain embodiments, a pharmaceutical composition disclosed herein may comprise a solvent, emulsion or a diluent in an amount of, e.g., less than about 90% (v/v), less than about 80% (v/v), less than about 70% (v/v), less than aboitt 65% (v/v), !ess than about 60% (v/v), less than about 55% (v/v), less than aboist 50% (v/v), less than about 45% (v/v), less than about 40% (v/v), less than about 35% (v/v), less than about 30% (v/v), less than about 25% (v/v), less than about 20% (v/v), less than about 15% (v/v), less than about 10% (v/v), less than about 5% (v/v), or less than about 1% (v/v). In certain embodiments, a pharmaceutical composition disclosed herein may comprise a solvent, etnuistion or other diluent in an amount in a range of, e.g., about 1% (v/v) to 90% (v/v), about 1% (v/v) to 70% (v/v), about 1% (v/v) to 60% (v/v), about 1% (v/v) to 50% (v/v), about 1% (v/v) to 40% (v/v), about 1% (v/v) to 30% (v/v), about 1% (v/v) to 20% (v/v), about 1% (v/v) to 10% (v/v), about 2% (v/v) to 50% (v/v), about 2% (v/v) to 40% (v/v), about 2% (v/v) to 30%

(v/v), about 2% (v/v) to 20% (v/v), about 2% (v/v) to 10% (v/v), about 4% (v/v) to 50% (v/v), about 4% (v/v) to 40% (v/v), about 4% (v/v) to 30% (v/v), about 4% (v/v) to 20% (v/v), about 4% (v/v) to 10% (v/v), about 6% (v/v) to 50% (v/v), about 6% (v/v) to 40% (v/v), about 6% (v/v) to 30% (v/v), about 6% (v/v) to 20% (v/v), about 6% (v/v) to 10% (v/v), about 8% (v/v) to 50% (v/v), about 8% (v/v) to 40% (v/v), about 8% (v/v) to 30% (v/v), about 8% (v/v) to 20% (v/v), about 8% (v/v) to 15% (v/v), or about 8% (v/v) to 12% (v/v).

The final concentration of a therapeutic compound disclosed herein in a pharmaceutical composition disclosed herein may be of any suitable concentration. In certain embodiments, the final concentration of a therapeutic compound in a pharmaceutical composition may be a therapeutically effective amount. In certain embodiments, the final concentration of a therapeutic compound in a pharmaceutical composition may be, e.g., at least 0.00001 mg/mL, at least 0.0001 mg/mL, at least 0.001 mg/mL, at least 0,01 mg/mL, at least 0.1 mg/niL, at least 1 mg/mL, at least 10 mg/mL, at least 25 mg/mL, at least 50 mg/mL, at least 100 mg/mL, at least 200 mg/mL, at least 500 mg/mL, at least 700 mg/mL, at least 1,000 mg/mL, or at least 1,200 mg/mL. In certain embodiments, the concentration of a therapeutic compound disclosed herein in the solution may be, e.g., at most 1,000 mg/niL, at most 1,100 mg/mL, al most 1,200 mg/mL, at most 1,300 mg/mL, at most 1,400 mg/mL, at most 1,500 mg/mL. at most 2,000 mg/mL. at most 2,000 mg/mL, or at most 3,000 mg/mL. In certain embodiments, the final concentration of a therapeutic compound in a pharmaceutical composition may be in a range of, e.g,, about 0.00001 mg/mL to about 3,000 mg/mL, about 0.0001 mg/mL to about 3,000 mg/mL, about 0.01 mg/mL to about 3,000 mg/mL, about 0.1 mg/mL to about 3,000 mg/mL, about I mg/mL to about 3,000 mg/mL, about 250 mg/mL to about 3,000 mg/mL, about 500 mg/mL to about 3,000 mg/mL, about 750 mg/mL to about 3,000 mg/mL, about 1,000 mg/mL to about 3,000 mg/mL, about 100 mg/mL to about 2,000 mg/mL, about 250 mg/mL to about 2,000 mg/mL, about 500 mg/mL to about 2,000 mg/mL, about 750 mg/mL to about 2,000 mg/mL, about 1,000 mg/mL to about 2,000 mg/mL, about 100 mg/mL to about 1,500 mg/mL, about 250 mg/mL to about 1,500 mg/mL, about 500 mg/mL to about 1,500 mg/mL, about 750 .mg/mL to about 1,500 mg/mL, about 1,000 mg/mL to about 1,500 mg/mL, about .100 mg/mL to about 1,200 mg/niL, about 250 mg/mL to about 1,200 mg/mL, about 500 mg/mL to about 1,200 mg/mL, about 750 mg/mL to about 1,200 mg/mL, about 1,000 mg/mL to about 1,200 mg/mL, about 100 mg/mL to about 1,000

mg/mL, about 250 rag/raL ɒ about !„000 mg/mL, about 500 mg/mL to about 1,000 mg/mL, about 750 rag/raL ɒ about ₁,000 mg/mL, about 100 mg/mL to about 750 mg/mL, about 250 mg/mL ɒ about 750 mg/mL, about 500 -mg/mL to about 750 mg/mL, about 100 mg/mL to about 500 mg/mL, about 250 mg/mL to about 500 mg/mL, about 0.00001 mg/mL to about 0.0001 mg/mL, about 0.00001. rag/raL to about 0.00.1 mg/mL, about 0.00001 mg/mL to about 0.01 mg/mL, about 0.00001 mg/mL to about 0.1 mg/mL, about 0.00001. mg/mL to about 1 mg/mL, about 0.00! mg/mL to about 0.01 mg/mL, about 0.00! mg/mL to about 0.1 mg/mL, about 0.001 mg/mL to about 1 mg/mL, about 0.001 mg/mL to about 10 mg/mL, or about 0.001 mg/mL to about 100 mg/mL.

In certain embodiments, a therapeutically effective amount of a therapeutic compound disclosed herein generally is in the range of about 0.001 mg/kg/day to about 100 mg/kg/day. ɪn certain embodiments, an effective amount of a therapeutic compound disclosed herein may bc, e.g., at least 0,001 mg/kg/day, at least 0,01 mg/kg/day, at least 0.1 mg/kg/day, at least 1.0 mg/kg/day, at least 5.0 mg/kg/day, at least 10 mg/kg/day, at least 15 mg/kg/day, at least 20 mg/kg/day, at least 25 mg/kg/day, at least 30 mg/kg/day, at least 35 mg/kg/day, at least 40 mg/kg/day, at least 45 mg/kg/day, or at least 50 mg/kg/day. In certain embodiments, an effective amount of a therapeutic compound disclosed herein may be in the range of, e.g., about 0.001. mg/kg/day ɒ about 10 mg/kg/day, about 0.001 mg/kg/day to about 15 mg/kg/day, about 0.001 mg/kg/day to about 20 mg/kg/day, about 0.001. mg/kg/day to about 25 mg/kg/day, about 0.00! mg/kg/day to about 30 mg/kg/day, about 0.001 mg/kg/day to about 35 mg/kg/day, about 0.001 mg/kg/day to about 40 mg/kg/day, about 0.001 mg/kg/day to about 45 mg/kg/day, about 0.001 mg/kg/day to about 50 mg/kg/day, about 0.001 mg/kg/day to about 75 mg/kg/day, or about 0.001 mg/kg/day to about 100 mg/kg/day. In yet other aspects of this embodiment, an effective amount of a therapeutic compound disclosed herein may be in the range of, e.g., about 0.01 mg/kg/day to about 10 mg/kg/day, about 0.01 mg/kg/day to about 15 mg/kg/day, about 0.01 mg/kg/day to about 20 mg/kg/day, about 0.01 mg/kg/day to about 25 mg/kg/day, about 0.0.1 mg/kg/day to about 30 mg/kg/day, about 0.01. mg/kg/day ɒ about 35 mg/kg/day, aboitt 0.01 mg/kg/day to about 40 mg/kg/day, about 0.01. mg/kg/day ɒ about 45 mg/kg/day, aboitt 0.01 mg/kg/day to about 50 mg/kg/day, about 0.0 i mg/kg/day to about 75 mg/kg/day, or about 0.01 mg/kg/day to about 100 mg/kg/day. In certain embodiments, an effective amount of a therapeutic compound disclosed herein may be in the range of, e.g., about 0.1 mg/kg/day to about 10 mg/kg/day, about 0.1 mg/kg/day ɒ about 15 mg/kg/day, about 0.1 mg/kg/day to

about 20 mg/kg/day, about OJ mg/kg/day to about 25 mg/kg/day, about OJ mg/kg/day to about 30 mg/kg/day, about OJ mg/kg/day to about 35 mg/kg/day, about OJ mg/kg/day to about 40 mg/kg/day, about 0.1 mg/kg/day to about 45 mg/kg/day, about 0.1 mg/kg/day to about 50 mg/kg/day, about 0.1 mg/kg/day to about 75 mg/kg/day, or about 0.1 mg/kg/day to about 100 mg/kg/day.

In other aspects of this embodiment, an effective amount of a therapeutic compound disclosed herein may be in the range of, e.g., about i mg/kg/day to about 10 mg/kg/day, about . mg/kg/day to about 15 mg/kg/day, about 1 mg/kg/day to about 20 mg/kg/day, about 1 mg/kg/day to about 25 mg/kg/day, about 1 mg/kg/day to about 30 mg/kg/day, about 1 mg/kg/day to about 35 mg/kg/day, about 1 mg/kg/day to about 40 mg/kg/day, about 1 mg/kg/day to about 45 mg/kg/day, about 1 mg/kg/day to about 50 mg/kg/day, about i mg/kg/day to about 75 mg/kg/day, or about 1 mg/kg/day to about 100 mg/kg/day. In certain embodiments, an effective amount of a therapeutic compound disclosed herein may be in the range of, e.g., about 5 mg/kg/day to about 10 mg/kg/day, about 5 mg/kg/day to about 15 mg/kg/day, about 5 mg/kg/day to about 20 mg/kg/day, about 5 mg/kg/day to about 25 mg/kg/day, about 5 mg/kg/day to about 30 mg/kg/day, about 5 mg/kg/day to about 35 mg/kg/day, about 5 mg/kg/day to about 40 mg/kg/day, about 5 mg/kg/day to about 45 mg/kg/day, about 5 mg/kg/day to about 50 mg/kg/day, about 5 mg/kg/day to about 75 mg/kg/day, or about 5 mg/kg/day to about 100 mg/kg/day.

In liquid and semi-solid formulations, a concentration of a therapeutic compound disclosed herein typically may be between about 50 mg/mL to about 1,000 mg/mL. In certain embodiments, a therapeutically effective amount of a therapeutic disclosed herein may be from, *e.g.*, about 50 mg/mL to about 100 mg/mL, about 50 mg/mL to about 200 mg/mL, about 50 mg/mL to about 300 mg/mL, about 50 mg/mL to about 400 mg/mL, about 50 mg/mL to about 500 mg/mL, about 50 mg/mL to about 600 mg/mL, about 50 mg/mL to about 700 mg/mL, about 50 mg/mL to about 800 mg/mL, about 50 mg/mL to about 900 mg/mL, about 50 mg/mL to about 1,000 mg/mL, about 100 rag/raL to about 200 mg/mL, about 100 mg/mL to about 300 mg/mL, about 100 mg/mL to about 400 mg/niL, about 100 mg/mL to about 500 mg/mL, about 100 mg/mL to about 600 mg/mL, about 100 mg/mL to about 700 mg/mL, about 100 mg/mL to about 800 mg/mL, about 100 mg/mL to about 900 mg/mL, about 100 mg/mL to about 1,000 mg/mL, about 200 mg/mL to about 300 mg/mL, about 200 mg/mL to about 400 mg/mL, about 200 mg/mL to about 500 mg/mL, about 200 mg/mL to about 600 mg/mL, about 200 mg/mL to about 700 mg/mL, about 200 mg/mL to

about 800 mg/mL, about 200 mg/mL to about 900 mg/mL, about 200 mg/mL to about 1,000 mg/mL, about 300 mg/mL to about 400 mg/mL, about 300 mg/mL to about 500 mg/mL, about 300 mg/mL to about 600 mg/mL, about 300 mg/mL to about 700 mg/mL, about 300 mg/mL to about 800 mg/mL, about 300 mg/mL to about 900 mg/mL, about 300 mg/mL to about 1,000 mg/mL, about 400 mg/mL to about 500 mg/mL, about 400 mg/mL to about 600 mg/mL, about 400 mg/mL to about 700 mg/mL, about 400 mg/mL to about 800 mg/mL, about 400 mg/mL to about 900 mg/mL, about 400 mg/mL to about 1,000 mg/mL, about 500 mg/mL to about 600 mg/mL, about 500 mg/mL to about 700 mg/mL, about 500 mg/mL to about 800 mg/mL, about 500 mg/mL to about 900 mg/mL, about 500 mg/mL to about 1,000 mg/mL, about 600 mg/mL to about 700 mg/mL, about 600 mg/mL to about 800 mg/mL, about 600 mg/mL to about 900 mg/mL, or about 600 mg/mL to about 1,000 mg/mL.

Brief Description of the Figures

Figure 1 shows the ability of certain compounds of the invention to mitigate radiation induced apoptosis *in vitro* relative to control values.

Figure 2 shows the mitigation against whole body radiation lethality *in vivo* by compound 1 (Figure 2A), compound 2 (Figure 2B), compound 3 (Figure 2C), compound 4 (Figure 2D), compound 5 (Figure 2E).

Figure 3 shows the dose response experiments for compounds 2 (5355512) and 3 (5346360) in C3H male mice and C57BL/6 female mice.

Figure 4 shows the dose response experiments for compounds 2 (5355512) and 3 (5346360) when increased to 25 mg/kg (Figure 4A and 4B) and if dosing of compound 2 (5355512) was given after 24 hours (D1), 48 hours (D2), and 72 hours (D3) (Figure 4C).

Figure 5 shows the dose response when compounds 2 (5355512) and 3 (5346360) are given orally by gavage.

Figure 6 shows the Probit analysis of the effect of varying the radiation dose with compounds 2 (5355512), 3 (5346360), and 5 (5163119).

Figure 7 shows the mitigation against whole body radiation lethality *in vivo* by analogs of Compound 2 (5355512).

Figure 8 shows the reduction in radiation induced apoptosis with the administration of certain compounds of the invention.

Figure 9 shows flow cytometric assay results demonstrating the ability of active compounds to mitigate radiation-induced apoptosis relative to inactive compounds.

Figure 10 shows that compounds 2 (5355512) and 3 (5346360) inhibit TNF-a production when added to stimulated peritonea! macrophages 1 hour after LPS measured by ELISA (Figure **10A)** and other compounds of the invention that were able to inhibit TNF-a production (Figure 10B)

Figure 11 shows that compounds 2 (5355512) and 3 (5346360) inhibit expression of TNF-a mRNA, and other cytokines, when added to bone marrow-derived macrophages 1 hour after LPS measured by RT-PCR.

Figure 12 shows how compound 2 (5355512) induces peritoneal macrophages to produce TKF- a in response to lipopolysaecharide (LPS).

Figure 13 shows that compound 2 (5355512) increases the total endogenous CFU in spleens (Figure 13A) and average endogenous CPU per spleen (Figure 13B) at 10 days after various doses of whole body irradiation (WBI).

Figure 14 shows the results of the ***in vivo*** assay with compound 2 (5355512) in C57B1/6 mice who were irradiated with 16 and 18 Gy abdominally.

Figure 15 shows the mitigation of radiation pneumonitis and fibrosis after local thoracic irradiation in C3H mice with pneumonitis (Figure 15A) and C57B1/6 mice with fibrosis (Figure 1SB).

Figure 16 shows the effects of the certain compounds of the invention on the growth of tumor lung colonies ***in vivo*** and on radiation response.

Detailed Description

Compounds shown in Table 1 mitigate the effects of ionizing radiation, inhibit inflammation, and are useful for treating cancer and other hyperproliferative disorders. Pharmaceutical formulations using compounds shown in Table 1 have potential to improve the outcome of radiation exposure, and therefore they may be useful in the cancer radiotherapy, as well as in the situation of a radiological emergency.

Radiomitigation

Without wishing to be bound by theory, the compounds shown in Table 1 may protect against deleterious effects of ionizing radiation by promoting repair of DNA

damage caused by exposure to radiation. The compounds also inhibit inflammation as vveli as protect bone marrow and other organs from radiation damage. As disclosed herein, after *in vitro* screening, the chosen compounds were applied in mice 24 hours after TBI and provided greatly elevated animals' survival level, compared to a control group. They also mitigated lethal normal gut and lung radiation damage, as well as having anti-tumor activity with and without therapeutic doses of ionizing radiation.

Embodiments of the invention include pharmaceutical formulations having a compound shown in Table 1, or pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or diluent.

Embodiments of the invention include methods of mitigating the effect of ionizing radiation on a cell, organ, tissue, or organism by contacting the cell, organ, tissue, or organism with at least one compound shown in Table 1.

As used herein, "mitigating" means reducing the negative effects caused fay exposure to ionizing radiation, relative to a cell, organ, tissue, or organism exposed to the same level of radiation for the same amount of time, but untreated.

In some embodiments, contacting the cell, organ, tissue, or organism with a compound in Table 1 may comprise administering a therapeutically effective amount of the compound to a subject.

As used herein, a "therapeutically effective amount" is an amount sufficient to mitigate the effects of the ionizing radiation.

The subject may be any organism that has been exposed to ionizing radiation, or which may be exposed to ionizing radiation. In one embodiment, the invention provides a method wherein the subject is a human, rat, mouse, cat, dog, horse, sheep, cow, monkey, avian, or amphibian. in another embodiment, the cell is *in vivo* or *in vitro*. Typical subjects to which compounds of the invention may be administered will be mammals, particularly primates, especially humans. For veterinary applications, a wide variety of subjects will be suitable, e.g. livestock such as cattle, sheep, goats, cows, swine and the like; poultry such as chickens, ducks, geese, turkeys, and the like; and domesticated animals particularly pets such as dogs and cats. For diagnostic or research applications, a wide variety of mammals will be suitable subjects including rodents (e.g. mice, rats, hamsters), rabbits, primates, and swine such as inbred pigs and the like. Additionally, for *in vitro* applications, such as *in vitro* diagnostic and research applications, body fluids and ceil samples of the above subjects will be suitable for use such as mammalian, particularly primate such as human,

blood, urine or tissue samples, or blood urine or tissue samples of the animals mentioned for veterinary applications.

The cell, organ, tissue, or organism may be contacted with a **compound** shown in Table 1 before, during, or after **exposure** to ionizing radiation. In some **embodiments,** the compound may be **administered** prophylacticaliy, i.e. before exposure to ionizing radiation, for example, prior to **cancer** radiation therapy or X-ray. **In** some embodiments, the compound may be administered during exposure, or upon repeated exposure to ionizing radiation. In some embodiments, the compound may be administered after exposure to ionizing radiation, or after the initiation of exposure to radiation.

When **administering** to an organism, the compound may be administered by any suitable means. In some embodiments, the compounds or formulations are administered orally. In some **embodiments,** the compounds or formulations are administered **by** injection, e.g. subcutaneous, parenteral, or intravenous, injections. **In** some embodiments *the* compound may be administered in combination with other potential roitigators or with other toxic agents such as ehemotherapeutic drugs.

Ionizing **radiation** may **refer** to radiation **with** a photon **energy greater** than 10 eV, according to the U.S. Federal **Communications** Commission, but for biological purposes may be considered o be radiation **having** energy greater than the first ionization potential of oxygen or the ionization potential of hydrogen, and may have other meanings according to practitioners.

Inflammatory Diseases

Compounds of the **current** invention may also be used for the treatment or prevention **of inflammation** and **inflammatory** diseases,

.Examples of **inflammatory** conditions, which may be treated or prevented by the administration of a compound of the invention include, but are not limited to, inflammation of the lungs, joints, connective tissue, eyes, nose, bowel, kidney, liver, skin, central nervous system, **vascular** system and heart. **In** certain embodiments, **inflammatory** conditions which **may** be treated by the current **invention** include inflammation due to the **infiltration** of leukocytes or other **immune** effector cells **into** affected tissue. Other relevant **examples** of **inflammatory** conditions which **may** be treated by the present invention **include inflammation** caused by infectious agents, including, but not limited to, viruses, bacteria fungi and parasites.

.Inflammatory lung conditions **include,** but are not **limited to**, asthma, **adult** respiratory distress syndrome, bronchitis, pulmonary inflammation, pulmonary fibrosis, and cystic fibrosis **(which may additionally** or **alternatively** involve the **gastro-intestinal** tract or other **tissue(s)).** Inflammatory joint conditions include rheumatoid **arthritis,** rheumatoid spondylitis, **juvenile rheumatoid** arthritis, osteoarthritis, gouty arthritis and other arthritic conditions. Eye diseases with **an inflammatory component** include, but are not limited to, uveitis (including iritis), **conjunctivitis,** seleritis, **keratoconjunctivitis** sicca, **and retinal** diseases, including, but not limited to, diabetic retinopathy, retinopathy of prematurity, retinitis pigmentosa, **and** dry and wet age-related macular degeneration. **Inflammatory** bowel conditions **include** Crohn's disease, ulcerative colitis and distal proctitis.

Inflammatory skin diseases include, but are not limited to, conditions associated with cell proliferation, **such** as psoriasis, eczema and dermatitis, (e.g., eczematous **dermatttides,** topic and **seborrheic dermatitis, allergic** or **irritant** contact dermatitis, **eczema craquelee, photoallergic dermatitis, phototoxic dermatitis,** phytophotodermatitis, radiation dermatitis, and stasis **dermatitis). Other inflammatory** skin diseases include, but are not **limited** to, scleroderma, ulcers and erosions resulting **from** trauma, bums, bullous disorders, or **ischemia** of the skirt er roneous membranes, several forms of ichthyoses, **epidermoiysis bullosae, hypertrophic** sears, keloids, **cutaneous** changes **of** intrinsic aging, photoaging, **fiictional** blistering caused by mechanical shearing of the skin **and** cutaneous atrophy resulting from the topical use of corticosteroids. Additional inflammatory skin conditions **include** inflammation of mucous **membranes,** such as cheilitis, chapped lips, nasal irritation, mucositis and vulvovaginitis.

Inflammatory disorders of the endocrine system include, but are not limited to, **autoimmune** thyroiditis (Hashimoto's disease), Type I diabetes, and acute and chronic inflammation of the adrenal **cortex. inflammatory** conditions **of the** cardiovascular system include, but are not limited to, coronary infarct damage, peripheral vascular disease, myocarditis, vasculitis, revascularization of stenosis, artheroscierosis, and vascular disease associated with Type **II** diabetes.

Inflammatory condition of the kidney include, but are not limited to, glomerulonephritis, interstitial nephritis, lupus nephritis, nephritis **secondary** to Wegener's disease, acute renal failure secondary to acute **nephritis,** Goodpasture's **syndrome, post-obstructive syndrome** and **tubular ischemia.**

Inflammatory conditions of the liver include, but are not limited to, hepatitis (arising

from viral infection, autoimmune responses, drug treatments, toxins, environmental agents, or as a secondary consequence of a primary disorder), biliary atresia, primary biliary cirrhosis and primary sclerosing cholangitis.

Inflammatory conditions of the central nervous system include, but are not limited to, multiple sclerosis and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, or dementia associated with HIV infection.

Other inflammatory conditions include periodontal disease, tissue necrosis in chronic inflammation, endotoxin shock, smooth muscle proliferation disorders, graft versus host disease, tissue damage following ischemia reperfusion injury, and tissue rejection following transplant surgery.

The present invention further provides a method of treating or preventing inflammation associated with post-surgical wound healing in a patient comprising administering to said patient a compound of the invention.

It should be noted that compounds of the current invention may be used to treat or prevent any disease which has an inflammatory component, such as those diseases cited above. Further, the inflammatory conditions cited above are meant to be exemplary rather than exhaustive.

Those skilled in the art would recognize that additional inflammatory conditions (e.g., systemic or local immune imbalance or dysfunction due to an injury, an insult, infection, inherited disorder, or an environmental intoxicant or perturbant to the subject's physiology) may be treated or prevented by compounds of the current invention. Thus, the methods of the current invention may be used to treat or prevent any disease which has an inflammatory component, including, but not limited to, those diseases cited above.

The present invention also provides methods for treating or preventing arthritis, inflammatory bowel disease, uveitis, ocular inflammation, asthma, pulmonary inflammation, cystic fibrosis, psoriasis, arterial inflammation, cardiovascular diseases, multiple sclerosis, or neurodegenerative disease by administering an effective amount of a compound of the invention.

The present invention also provides methods for treating ischemia by administering an effective amount of a compound of the invention. In certain embodiments, the ischemia is cardiac ischemia, cerebral ischemia, bowel ischemia (e.g., ischemic colitis or mesenteric ischemia), or cutaneous ischemia.

Cancer

Compounds of die **current** invention may also **be** used for the treatment of **cancer.** The actual symptoms associated with cancer are **well** knowo and cao **be determined** by a person of ordinary **skill** in the art **by** taking into **account** one or **more factors,** including, without limitation, die **location of the** cancer, the cause of **the cancer,** the severity of the cancer, and'or the tissue or organ affected by the cancer. Those **of skill in** the **art will** know the appropriate symptoms or **indicators** associated with a specific **type** of cancer and wili know how to determine if an individual is a candidate for **treatment** as disclosed herein.

Exemplary forms **of** cancer which may be treated **by** the subject methods include, but are not limited to, **leukemia, non-Hodgkin's** lymphoma, prostate cancer, bladder cancer, lung cancer (including either small cell or **non-small** cell **cancer),** colon cancer, kidney cancer, liver cancer, breast cancer, cervical cancer, endometrial or other **uterine** cancer, ovarian cancer, skin cancer (e.g., **melanoma), testicular cancer,** cancer of die penis, cancer of the vagina, cancer of the urethra, gall bladder cancer, esophageal cancer, or pancreatic cancer. Additional **exemplary** forms of cancer which may be treated by the subject methods include, but are not limited to, cancer of skeletal or **smooth muscle,** stomach cancer, **cancer** of the small intestine, cancer of the salivary gland, anal cancer, rectal **cancer,** thyroid cancer, parathyroid cancer, pituitary cancer, and **nasopharyngeal** cancer.

In certain embodiments, a therapeutic compound disclosed herein reduces the size of a tumor by, **e.g.,** at least 10%, at least 15%, at least 20%, at least **25%,** at least 30%, at least 35%, **at** least 40%, at least **45%,** at least 50%, at least 55%, at least 60%, **at** least **65%,** at least 70%, at least 75%, at least 80%, at least 85%, **at** least 90% or at least **95%.** In yet other aspects of this embodiment, a therapeutic compound disclosed herein reduces the size **of a tumor from,** e.g., about **5%** to about **100%, about** 10% to **about** 100%, about **20% to** about 100%, about 30% to about 100%., about 40% to about 100%, about 50% to about **100%, about 60% to** about 100%, about 70% to about 100%, about **80%** to about 100%, about **10%** to about 90%, about **20%** to about **90%,** about **30%** to about **90%,** about 40% **to** about 90%, about 50% to about 90%, about **60%** to about **90%,** about 70% to about 90%, about 10% to about 80%, about 20% to about 80%, about **30%** to about **80%,** about 40% **to** about 80%, about **50%** to about 80%, or about 60% to about 80%, about **10%** to about 70%, about 20% to about **70%,** about 30% to about **70%,** about **40%** to about **70%,** or about 50% to about 70%.

In certain embodiments, a cancer therapeutic disclosed herein is capable of reducing the number of cancer cells in an individual suffering from a cancer by, *e.g.*, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90% or at least 95% as compared to a patient not receiving the same treatment. In other aspects of this embodiment, a cancer therapeutic is capable of reducing the number of cancer cells in an individual suffering from a cancer fay, *e.g.*, about 10% to about 100%, about 20% to about 100%, about 30% to about 100%, about 40% to about 100%, about 50% to about 100%, about 60% to about 1.00%, about 70% to about 100%, about 80% to about 100%, about 10% to about 90%, about 20% to about 90%-, about 30% to about 90%, about 40% to about 90%, about 50% to about 90%, about 60% to about 90%, about 70% to about 90%, about 10% to about 80%, about 20% to about 80%, about 30% to about 80%, about 40% to about 80%, about 50% to about 80%, or about 60% to about 80%, about 10% to about 70%, about 20% to about 70%, about 30% to about 70%, about 40% to about 70%, or about 50% to about 70% as compared to a patient not receiving the same treatment.

In certain embodiments, a therapeutically effective amount of a cancer therapeutic disclosed herein reduces or maintains a cancer cell population and/or tumor cell size in an individual by, *e.g.*-, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 100%. In other aspects of this embodiment, a therapeutically effective amount of a cancer therapeutic disclosed herein reduces or maintains a cancer cell population and/or tumor cell size in an individual by, *e.g.*, at most 10%, at most 15%, at most 20%, at most 25%, at most 30%, at most 35%, at most 40%, at most 45%, at most 50%, at most 55%, at most 60%, at most 65%, at most 70%, at most 75%, at most 80%, at most 85%, at most 90%, at most 95% or at most 100%. In yet other aspects of this embodiment, a therapeutically effective amount of a cancer therapeutic disclosed herein reduces or maintains a cancer cell population and/or tumor cell size in an individual fay, *e.g.*, about 10% to about 100%, about 10% to about 90%, about 10% to about 80%, about 10% to about 70%, about 10% to about 60%, about 10% to about 50%, about 10% to about 40%, about 20% to about 100%, about 20% to about 90%, about 20% to about 80%, about 20% to about 20%, about 20% to about 60%, about 20% to about 50%, about 20% to about 40%, about 30% to about 100%, about

30% to about 90%, about 30% to about 80%, about 30% to about 70%, about 30% to about 60%, or about 30% to about 50%.

Compounds

The compounds herein described may have one or more asymmetric centers or planes. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms (racemates), by asymmetric synthesis, or by synthesis from optically active starting materials. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral (enantiomeric and diastereomeric), and racemic forms, as well as all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

The compounds herein described may have one or more charged atoms. For example, the compounds may be zwitterionic, but may be neutral overall. Other embodiments may have one or more charged groups, depending on the pH and other factors. In these embodiments, the compound may be associated with a suitable counter-ion. It is well known in the art how to prepare salts or exchange counter-ions. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate, or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Counter-ions may be changed, for example, by ion-exchange techniques such as ion-exchange chromatography. All zwitterions, salts and counter-ions are intended, unless the counter-ion or salt is specifically indicated. In certain embodiments, the salt or counter-ion may be pharmaceutically acceptable, for administration to a subject. Pharmaceutically acceptable salts are discussed later.

Pharmaceutical compositions

Embodiments of the invention include pharmaceutical compositions of compounds shown in Table 1 and at least one pharmaceutically acceptable carrier or diluent. As used herein, pharmaceutical compositions include compositions suitable for administration to a subject or patient. As such, compositions do not include chemical reaction solutions or solutions used for screening assays, as these are not suitable for administration to a subject or patient. In some embodiments the compositions may include one or more than one compound from Table I, one or more other pharmaceutically active agent, and may further contain other suitable substances and excipients, including but not limited to physiologically acceptable buffering agents, stabilizers (e.g. antioxidants), flavoring agents, agents to effect the solubilization of the compound, and the like.

In other embodiments, the composition may be in any suitable form such as a solution, a suspension, an emulsion, an infusion device, or a delivery device for implantation or it may be presented as a dry powder to be reconstituted with water or another suitable vehicle before use. The composition may include suitable pharmaceutically acceptable carriers and/or excipients.

In other embodiments, the compositions may comprise an effective amount of a modulator and/or other pharmaceutically active agent in a physiologically-acceptable earner. The carrier may take a wide variety of forms depending on the form of preparation desired for a particular route of administration. Suitable carriers and their formulation are described, for example, in Remington's Pharmaceutical Sciences by E. W. Martin.

In some embodiments, the compound may be contained in any appropriate amount in any suitable carrier substance, and is generally present in an amount of 1-95% by weight of the total weight of the composition. The composition may be provided in a dosage form that is suitable for parenteral (e.g., subcutaneously, intravenously, intramuscularly, or intraperitoneal!y) or oral administration route. The pharmaceutical compositions may be formulated according to conventional pharmaceutical practice (see, e.g.. Remington: The Science and Practice of Pharmacy (20th ed.}, ed, A. R. Gennaro, Lippmeott Williams & Wilkins, 2000 and Encyclopedia of Pharmaceutical Technology, eds. J. Swarfarick and J. C. Soylan, 1988-1999, Marcel Dekker, New York).

In some embodiments, the compositions may be in a form suitable for administration by sterile injection, in one example, to prepare such a composition, the

compositionsis) are dissolved or suspended **in** a parenterally aceeptable liquid vehicle. Among aceeptable vehicles and solvents that may be employed are water, water **adjusted** to a suitable **pH** by addition **of an** appropriate amount of hydrochloric acid, sodium hydroxide or a suitable buffer, i,3-hutanediol, Ringer's solution, and **isotonic** sodium chloride solution and dextrose solution. The aqueous formuiaiicm may also contain one or more preservatives (e.g., **methyl,** ethyl or n-propyl **p-hydroxybenzoate).** For parenteral **formulations,** the carrier will usually comprise sterile water, though other ingredients, for example, ingredients that aid solubility or for preservation, may be included. **Injectable** solutions **may** also be prepared in which case appropriate stabilizing agents may be **employed.**

Formulations suitable for parenteral administration usually comprise a sterile aqueous preparation **of the compound,** which may be isotonic with the blood of the recipient (e.g., physiological saline solution). Such formulations may **include** suspending agents and thickening agents **and** liposomes or other nheroparticulate systems which are designed to target the compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose form.

Parenteral **administration may** comprise any suitable **form** of **systemic** delivery or localized delivery. Administration may for example be intravenous, infra-arterial, **intrathecal, intramuscular, subcutaneous, intramuscular,** intra-abdominal (e.g., intraperitoneal), etc., and may be **effected** by infusion pumps (external or implantable) or any other suitable means appropriate to the desired **administration** modality.

In some **embodiments,** the compositions may be in **a** form suitable for oral administration. In compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as, for example, suspensions, elixirs and solutions, **suitable** carriers **and** additives **include** water, glycols, oils, **alcohols,** flavoring agents, **preservatives,** coloring agents and the like. For solid oral preparations such as, for example, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, **lubricants,,** binders, disintegrating agents and the like. If **desired,** tablets may be sugar coated or enteric coated by standard techniques.

Compositions suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets, **or** lozenges, each **containing** a predetermined amount of the active ingredient as a powder or granules. Optionally, a suspension in **an aqueous** liquor or a non-aqueous liquid may be employed, such as a syrup, an elixir, an emulsion, or a

draught Formulations **for oral** use include tablets containing active ingredients) in a mixture with pharmaceutically acceptable excipients. Such formulations are known to the **skilled** artisan. Excipients may be, **for example, inert diluents or fillers (e.g., sucrose,** sorbitol, sugar, **mannitol,** microcrystalline **cellulose,** starches **including** potato starch, calcium carbonate, sodium **chloride,** lactose, **calcium** phospha te, calcium: sulfate, or **sodium** phosphate); granulating and **disintegrating** agents **(e.g., cellulose** derivatives including microcrystallme cellulose, starches including potato starch, eroscarnieilose sodium, **alginates,** or alginic acid); **binding** agents (e.g., sucrose, glucose, sorbitol, acacia, alginic acid, sodium alginate, gelatin, starch, **ore-gelatinized** starch, **macrocrystalline** cellulose, **magnesium aluminum** silicate, **carboxymetaylcellulose sodium, methylcellulose, hydroxypropyi methylcellulose,** ethyicellulose, **polyvinylpyrrolidone,** or polyethylene **glycol);** and **lubricating** agents, glidants, and antiadhesives (e.g., **magnesium** stearate, **zinc** stearate, **stearic** acid, silicas, **hydrogenated** vegetable **oils,** or talc). Other **pharmaceutically** acceptable excipients can be colorants, flavoring agents, plasticizers, kimectatits, **buffering** agents, and the like.

A syrup may be made by adding the **compound to** a **concentrated aqueous solution of a** sugar, **for example sucrose,** to **which may also** be **added any accessory** ingredient **(s).** Such **accessory ingredients) may include flavorings, suitable** preservative, agents **to** retard **crystallization** of the **sugar,** and **agents to increase** the solubility of any **other** ingredient, such as a polyhydroxy alcohol, for example glycerol or sorbitol.

In some **embodiments-** the composition may be in a form of nasal or other mucosal spray formulations (e.g. inhalable forms). These formulations can include **purified** aqueous solutions **of the** active compounds with preservative agents and isotonic agents. Such formulations can be adjusted to **a** pH and isotonic state compatible with the nasal or other **mucous membranes.** Alternatively, **they can be in the form** of finely **divided** solid **powders** suspended **in** a **gas** carrier. **Such formulations may** be delivered **by** any suitable **means** or method, e.g., **by** nebulizer, atomizer, metered dose **inhaler,** or the **like.**

In some **embodiments**, the composition may be in a form suitable for rectal **administration.** These formulations **may** be **presented** as a **suppository with** a suitable carrier such as cocoa butter, hydrogenated fats, or hydrogenated fatty carboxylie acids.

In some embodiments, the **composition** may be **in** a **form** suitable for **transdermal administration.** These **formulations may be** prepared, for **example, by incorporating** the active compound in a thixotropie or gelatinous carrier such as a cellulosic medium, e.g..

methyl cellulose or hydroxyethyl cellulose, with the resulting formulation then being packed in a transdermal device adapted to be secured in dermal contact with the skin of a wearer.

In addition to the aforementioned ingredients, compositions of the invention may further include one or more accessory ingredients) selected from encapsulants, diluents, buffers, flavoring agents, binders, disintegrants, surface active agents, thickeners, lubricants, preservatives (including antioxidants), and the like.

In some embodiments, compositions may be formulated for immediate release, sustained release, delayed-onset release or any other reiease profile known to one skilled in the art.

In some embodiments, the pharmaceutical composition may be formulated to release the active compound substantially immediately upon administration or at any predetermined time or time period after administration. The latter types of compositions are generally known as controlled release formulations, which include (t) formulations that create a substantially constant concentration of the drug within the body over an extended period of time; (ii) formulations that after a predetermined lag time create a substantially constant concentration of the drug within the body over an extended period of time; (iii) formulations that sustain action during a predetermined time period by maintaining a relatively constant, effective level in the body with concomitant minimization of undesirable side effects associated with fluctuations in the plasma level of the active substance (sawtooth kinetic pattern); (iv) formulations that localize action by, e.g., spatial placement of a controlled release composition adjacent to or in the central nervous system or cerebrospinal fluid; (v) formulations that allow for convenient dosing, such that doses are administered, for example, once every one or two weeks; and (vi) formulations that target the site of a pathology. For some applications, controlled release formulations obviate the need for frequent dosing to sustain activity at a medically advantageous level.

Any of a number of strategies can be pursued in order to obtain controlled release in whteh the rate of release outweighs the rate of metabolism of the compound in question. In one example, controlled release is obtained by appropriate selection of various formulation parameters and ingredients, including, e.g., various types of controlled release compositions and coatings. Thus, the compound is formulated with appropriate excipients into a pharmaceutical composition that, upon administration, releases the compound in a controlled manner. Examples include single or multiple unit tablet: or capsule compositions,

oil solutions, suspensions, emulsions, microcapsules, microspheres, **molecular** complexes, nanopartieles, patches, and liposomes.

In some embodiments, the composition may comprise **a** "vectorized" form, such as by encapsulation of the **compound** in a **liposome** or other encapsulate medium, or by fixation of the compound, e.g., by covalent bonding, chelation, or associative coordination, **on** a suitable biomoJeeitie, such as those selected from proteins, **lipoproteins, glycoproteins,** and polysaccharides.

In some **embodiments, the** composition can be incorporated into **microspheres,** microcapsules, nanopartieles, liposomes, **or the** like **for controlled release.** Furthermore, the composition may **include** suspending, solubiSzing, **stabilizing, pH-adjusting** agents, tonicity adjusting agents, and/or **dispersing,** agents. **Alternatively,** the **compound** may be incorporated in **biocompatible** carriers, **implants,** or infusion devices.

Materials for use in the preparation of microspheres and/or microcapsules arc, e.g., biodegradable/bioerodible polymers **such** as polygalactia, **po1y-(isobutyl cyanoacrylate), poly(2-hydroxyemyl-L-glutamine)** and, poly(laetie **acid).** Biocompatible carriers that may be used when **.formulating** a controlled release parenteral formulation are carbohydrates (e.g., **dextrans),** proteins (e.g., albumin), lipoproteins, or antibodies. Materials for use in implants can be non-biodegradable (e.g., polydmiethyi siloxane) or biodegradable (e.g., poiy(eaproiactone), poly(lactic **acid),** poly(giycolic **acid) or** poly(ortho esters) or combinations thereof).

In all embodiments, the **compound** or oilier active **compounds** may **be** present as pharmaceutically acceptable salts **or** other derivatives, such as ether derivatives, ester derivatives, acid derivatives, and aqueous **solubility** altering derivatives of the active compound. Derivatives include all individual enantiomers, diasiereomers, racemates, and other isomers of the compounds. Derivatives also include **all** polymorphs and solvates, such as hydrates and those formed with organic solvents, of the compounds. Such isomers, polymorphs, and solvates may be prepared **by** methods known in the art, such as by regiospectfic and/or **enantioselective** synthesis and resolution.

The ability to prepare salts depends on the acidity or basicity of the compounds. Suitable salts of the compounds include, but are not Hmited to, acid addition salts, such as those made with **hydrochloric, hydrobromic, hydroiodic,** perchloric, sulfuric, nitric, phosphoric, **acetic,** propionic, glycolic, lactic pyruvic, rnalonic, succinic, maleic, **fumaric, malic, tartaric,** citric, benzoic, carbonic, einnamic, mandelic, **methanesulfonic.**

eihanesulfbmc, hydroxyethanesulfonic, benezenesulfonic, p-toluene sulfonic, cyclohexanesulfamic, salicyclic, ^aminosalicylic, 2-phenoxybenz:oic, and 2-aeetoxyhenzoic acid; salts made with saccharin; alkali metal salts, such as sodium and potassium salts; alkaline earth metal salts, such as calcium and magnesium salts; and salts formed with organic or inorganic ligands, such as quaternary ammonium salts.

Additional suitable salts include, but are no. limited to, acetate, benzenesitlfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochSoride, ede-tate, edísylate, estolate, esyiate, fumarate, glueeptate, gluconate, glutamate, glyeo!lylarsaniiate, hexylresoreinate, hydrabamine, hydrobrornide, hydrochloride, hydroxynaphttioate, iodide, isothionate, lactate, lactobionate, laitrate, ma!ate, maleate, manddate, mesylate, raethylbromkfe, methySitrate, methyisulfate, mucate, napsylatc, nitrate, N-methylglucainine ammonium salt, oleate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonase, salicylate, stearate, sulfate, suhacetate, succinate, tannate, tartrate, teoelare, rosyiate, iriethtodide and valerate salts of the compounds.

The pharmaceutically acceptable acid addition salts can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

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 can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include; (!) water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as aseorbyl palmitate, butySated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal-ehelating agents, such as citric acid, ethylenediamme tetraacetie acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Unless the context clearly indicates otherwise, compositions of all embodiments can comprise various pharmaceutically acceptable salts, or other derivatives described above.

The formulation and preparation of such compositions are well known to those skilled in the art of pharmaceutical formulation. Formulations can be found in Remington: The Science and Practice of Pharmacy.

The amount of the compound employed in the present invention to be used varies according to the degree of the exposure to ionizing radiation encountered, and the stages of any radiation-induced damage. A suitable dosage is that which will result in concentration of the compound (in biood and/or tissues) sufficient to mitigate the damage of the ionizing radiation. The preferred dosage is that amount sufficient to render a subject asymptomatic after exposure to ionizing radiation.

The contents of all cited references (including literature references, issued patents, published patent applications) as cited throughout this application are hereby expressly incorporated by reference. The invention and the manner and process of making and using *it* are described in such M L clear, concise and exact terras as to enable any person skilled in the art to which it pertains, to make and use the same.

The term "unit dosage form" or "unit" as used herein refers to physically discrete units suitable as unitary dosages for human and animal subjects, each unit containing a predetermined quantity of the compound calculated in an amount sufficient to produce the desired effect in association with a pharmaceutically acceptable- diluent, carrier or vehicle. The specifications for the novel unit dosage forms of the present invention depend on the particular compound employed and the effect to be achieved, and the pharmacodynamics associated with each compound in the subject.

Actual dosage levels of the active ingredients in the pharmaceutical compositions may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound or combination of compounds employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound(s) being employed, the duration of the treatment.

other drugs, compounds and/or materials used in combination with the particular compound(s) employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the therapeutically effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the pharmaceutical composition or compound at levels lower than that reqoired in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. By "therapeutically effective amount" is meant the concentration of a compound that is sufficient to elicit the desired therapeutic effect. It is generally itnderstood that the effective amount of the compound will vary according to the weight, sex, age, and medical history of the subject. Other factors which influence the effective amount may include, but are not limited to, the severity of the patient's condition, the disorder being treated, the stability of the compound, and, if desired, another type of therapeutic agent being administered with the compound of the invention. A larger total dose can be delivered by multiple administrations of the agent. Methods to determine efficacy and dosage are known to those skilled in the art (Isselbacher *et al*. (1996) Harrison's Principles of Internal Medicine 13 ed., 1814-1882, herein incorporated by reference).

In general, a suitable daily dose of an active compound used in the compositions and. methods of the invention will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above.

Dosing can be single dosage or cumulative (serial dosing), and. can be readily determined by one skilled in the art. For instance, treatment may comprise a one-time administration of an effective dose of a pharmaceutical composition disclosed herein. Alternatively, treatment may comprise multiple administrations of an effective dose of a pharmaceutical composition earned out over a range of time periods, such as, e.g., once daily, twice daily, thrice daily, once every few days, or once weekly. The timing of administration can vary from individual to individual, depending upon such factors as the severity of an individual's symptoms. For example, an effective dose of a pharmaceutical composition disclosed herein can be administered to an individual once daily for an indefinite period of time, or until the individual no longer requires therapy. A person of ordinary skill in the art will recognize that the condition of the individual can be monitored.

throughout the course of treatment and that the effective amount of a pharmaceutical composition disclosed herein that is administered can be adjusted accordingly.

If desired, the effective daily dose of the active compound may be administered as one, two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In certain embodiments of the present invention, the active compound may be administered two or three times daily. In preferred embodiments, the active compound will be administered once daily.

In certain embodiments, the period of administration of a therapeutic compound is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more. In certain embodiments, a treatment regimen may comprise a period during which administration is stopped for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more.

The patient receiving mis treatment is any animal in need, including primates, in particular humans, and other mammals such as equines, cattle, swine and sheep; and poultry and pets in general

in other embodiments, the compound of Formula I or 0 may be provided with the one or more additional therapeutic agents in a kit, e.g., as separate pharmaceutical formulations capable of being used together in a conjoint therapy as discussed herein, either together in a single container or in separate containers. In certain such embodiments, the kit may further include instructions for the conjoint administration of the pharmaceutical formulations, e.g., for treating or preventing any of the conditions discussed above.

Such combination products may employ compounds of this invention, or pharmaceutically acceptable salts thereof, within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

The invention now being generally described, it will be more readily understood by reference to the following examples which are included merely for purposes of illustration

of certain aspects and **embodiments of the** present invention, and are **not** intended to limit **the invention.**

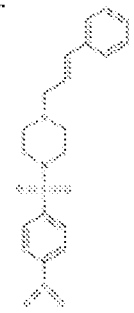
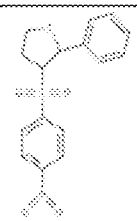
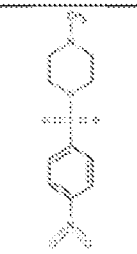
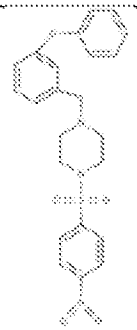
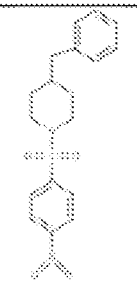
Examples

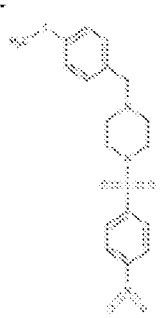
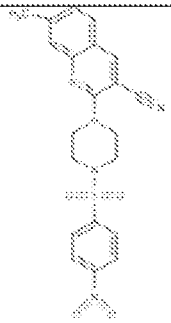
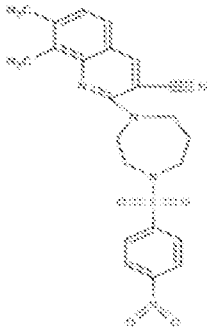
Example 1

The **structures** of 12 4-nitrophenylsuiftmyipiperazines **(NPSPs)** or 4-nitrophenylsulfonamides (NPSs) are shown. See Table 1

Table I: The **structures** of 12 NPSPs **or NPSs** of the invention

Compound	Compound ID	Compound Structure	Compound Name
1	5348300		1-(4-fluorophenyl)-4-[(4-nitrobenzene) sulfonyl]piperazine
2	5355512		1-[(4-nitrobenzene)sulfonyl]-4-phenylpiperazine
3	5346360		1-(3-chlorophenyl)-4-(4-nitrobenzene)sulfonyl]piperazine

4	5347486		1-[(4-nitrobenzene) Sulfonyl]-4-[(2E)-3-phenylprop-2-en-1-yl]piperazine
5	5116319		N,N-diethyl-4-nitrophenyl-1-sulfonamide
6	5475972		3-((4-nitrophenyl)sulfonyl)-2-phenyltetrahydrothiophene
7	5344400		1-methyl-4-((4-nitrophenyl)sulfonyl)piperazine
8	6561181		1-((4-nitrophenyl)sulfonyl)-4-(3-phenoxybenzyl)piperazine
9	5243457		4-benzyl-1-((4-nitrophenyl)sulfonyl)piperidine

10	6571802		1-(4-(methylthio)benzyl)-4-((4-nitrophenyl)sulfonyl)piperazine
11	AST5814142		3-cyano,7-methyl-2-(4-((4-nitrophenyl)sulfonyl)piperazin-1-yl)quinoline
12	AST6538836		3-cyano,7,8-dimethyl-2-(4-((4-nitrophenyl)sulfonyl)-1,4-diazepan-1-yl)quinoline

Example 2

The **ability of compounds from Example** 1 to mitigate **radiation-induced apoptosis** *in vitro* relative to control values (100%) is shown in **Figure 1**. Briefly, 100,000 small-molecules were screened **at** 10 μM **final concentration** in 1% dimethyisuifoxide **(DMSO)** using the viability of a **murine** lymphocyte line as a readout (Mitigation cell **viability** %). Ten thousand Til-1 **murine** lymphocyte cells were dispensed into each well of 3S4~well plates using a **Multidrop** 384 **(Thermo** Scientific, **Waltham, MA)** The Til-1 ceils were **irradiated** at the dose of 2Gy. After 1 hour, the **small-molecules** were added. Twenty-four hours after the radiation, cell viability was assayed by **lummesec-bascd measurement of** ATP production (ATPlite, Perkiti-Elmer, Waliham, **MA)** with a SpectraMax *MS* **microplate** reader (Molecular Devices, Sunnyvale, **CA).** The **Z' factor** for the assay was > 0.5. See Zhang, J. H., Chung, **T.** D., **Oldenburg, K. R.** "A Simple Statistical Parameter for Use in

Evaluation and Validation of .High **Throughput Screening Assays,"** *J Biomol Screen* 4:67, 1999. A positive readout was >130 % **of the control** irradiated value. Compounds 1-7 showed **activity, including** a 4-nitrophenyl sulfonamide **derivative** (Compound 5). This suggests a minimum moiety **for** efficacy. The piperazine group afforded additional efficacy beyond the common **sulfonamide** core suggesting that both moieties contribute although they were not **in** themselves sufficient for full **activity.** See **Figure 1.**

Example 3

The top 5 **performers** from **Example** I were tested *in vivo for* their ability to mitigate against lethality f om whole body irradiation. See Table 2.

Briefly, Animal Whole Body Irradiation (WBI) Assays were conducted with **C3H**f/Kam and C57B16/J mice. The **mice** were bred and maintained in a strict **gnotobiotic** environment **in** the American Association of Laboratory **Animal** Care-Accredited Animal Facilities of Department of Radiation Oncology, UCLA. The **Animal** Care and Use Committee approved all experiments, which were **performed** in accordance with ail local and **national** guidelines for **the** care and use of animals. Mice, **9**–12 weeks old, were given WBI using a **Gamma** ceil 40 irradiator (Csi 37 source; Atomic Energy of Canada, Ltd.) at a dose rate **of** 67 **Gy/** rain. Mice **were monitored** for at least 30 days and defined criteria for humane euthanasia was used as **an** endpoint.

Compounds were **typically** dissolved in 15μL DMSO and **suspended in** 1mL of I% Cremphor **EL** in water for administration in 0.2mL volumes. This amount of Creraophor did not significantly alter **the** response to WBL All mice, including controls, received the same diluent as the experimental groups. The chosen compounds **were administered** to the mice 5 times at **24h** intervals, starting 24 hours after WBI at LD70/30 (7.725 Gy for the O H strain) doses. Similar data were obtained with a single dose and at 48 hours after radiation exposure **in** both mouse strains. Both subcutaneous and oral routes were effective. **The** compounds provided greatly elevated animals survival level as compared to control group.

All 5 compounds were effective but Compound 2 (5355512) and Compound 3 (5346360) were effective at 5mg/kg injected subcutaneously whereas the others required a greater quantity of the tested compound (e.g., **75mg/kg).** indeed, Compound 2 and Compound **3** gave 100% survivors at day 30 at the lowest dosage of 5mg/kg which was superior to **the** higher doses of 40 tug/kg arid **75** mg/kg. See **Figure 2 A-E.**

Table 2

Compound	Compound ID	*In Vitro*	Solubility (mol/L x 10^{-6})
1	5348300	188%	26.6
2	5355512	182%	66.1
3	5346360	174%	6.5
4	5347486	163%	20.4
5	5116319	161%	512.9

Example 4

Dose response experiments were executed in a manner similar to the WBI Assay described in Example 3. These experiments indicated that 5 mg/kg was more, or as, effective, than 1, 2, 10, 40, or 75 mg/kg for both Compound 2 (5355512) and Compound 3 (5346360) in C3H male mice. See Figure 3. Both Compound 2 (5355512) and Compound 3 (5346360) were effective in C57BI/6 female mice in this case mitigating against LD70/30 doses of 8.509 Gy due to the relative radtoresistaace of this strain relative to C3Hs. A single dose of 5mg/kg given 24 hours after WBI was effective (See Figure **4A** and 4B) and increasing the dose to 25 mg/kg did not improve efficacy. Some activity was retained if a single dose was given 48, but not 72, hours after WBI (See Figure 4C). When given orally by gavage, Compound 2 (5355512) in 5 daily doses starting at 24 hours post-WBI was effective at 5 mg/kg in both C3H and C5781/6 strains, but not at 25 mg/kg. (See **Figure 5)** Interestingly, Compound 3 (5346360) given by the same gavage schedule was inactive in both strains at cither dose.

Example 5

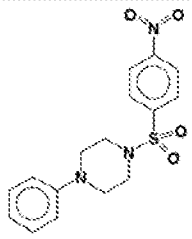
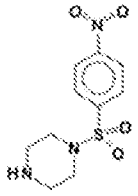
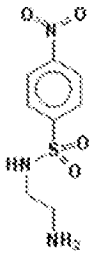
Probit analyses of the effect of varying the radiation dose with Compound 2 (5355512) (5mg/kg), and Compound 3 (5346360) (5 mg/kg), or 5 (5116319) (75 mg/kg) given subcutaneousiy for 5 days starting 24 hours after WBI, is shown in Figure 6, with 95% confidence limits shown for LD50 values. The dose-response curves are steep with the dose modifying factors varying with the level of effect and drug, but were in the range 1.04-1.09. Such factors have to be considered against the level of the control and the reason for

lethality. **In this** case, hematological **insufficiency** and **not** infection is the cause of death **and** as a resuit the radioresistance of the **C3H** strain is relatively high.

Example 6

Compounds P1, P2, and P3, analogs of Compound 2 (5355512), were **synthesized according to standard** protocols. See **Table 3.** The simplest MPSP (P1) was **effective** indicating that this was the optimum "core" structure. **Interestingly,** P1 **is** a **natural** breakdown **product** identified *in vivo* by mass spectrometry. WBI **irradiation** assays were conducted similar to those described in Example 3 except that compounds P1, P2, and P3 are soluble in water. The analogs were **injected subcutaneously** 5 times over 5 days at 5mg/kg. Compound **P2** elicited 100% survival after 30 **days.** See **Figure 7.**

Table **3;** Analogs **of 5355512**

Compound ID	Structure
5355512	
Compound P1	
Compound P2	

Compound P3	

Example?

The ability **of** active compounds to mitigate radiation-induced apoptosis was confirmed relative to inactive compounds in a f ow cytometric assay that **employed** annexin V for early stage apoptosis and **propidium** iodide **6** r late stage apoptosis (BD Biosciences) . (See Figures 8 and 9).

Example S

NPSPs were tested for their **anti-inflammatory** ability using murine macrophages. **Compound** 2 (5355512) showed anti-inflammatory **activity** being able to inhibit iipopolysaecharide (LPS)-induced production of tumor necrosis factor **and** other **inflammatory** cytokines. Briefly, **peritoneal** macrophages (PMs) were induced by intraper toneal. injection of 150 μg M1S4 16 **(innate Immunotherapeut cs, NZ)** and harvested on day 4 by peritoneal wash out with PBS. Culture supernatants were Iiarvcsted at 24hrs and cytokines tested by ELISA (BD Biosciences, SD). **Compound** 2 (5355512) and Compound 3 **(5346360)** inhibit TNF-α production when added to **stimulated** peritonea! **macrophages** 1 hr after **LPS** measured by ELISA. See **Figure 10A. Additionally,** all NPSPs and **compound** 5 (5116319) were able to **inhibit TNF-a** production. See **Figure 108.**

Additionally, bone marrow-derived macrophages (BMDMs) were **derived by** 7 **days culture** of marrow **cells** in **medium containing** 10% FBS and **CSF-1** conditioned medium. The serum concentration was reduced to 2% FBS 16**h** before **stimulation** with LPS for 30 **mint, treatment** with drug and **incubation** for another 3.5h (4h total with LPS). Total **cellular RNA** was isolated by trizol **and cDNA synthesized** using **iScript from** BioRad. **Gene** expression was measured by qPCR and analyzed using the standard curve method, normalized to L32, Compound 2 (5355512) and Compound 3 (5346360) inhibit expression

of TNF-α mRNA, and other cytokines, when added to bone marrow-derived macrophages 1 hr after LPS measured by RT-PCR. See Figure 11.

In vivo, compound 2 (5355512) showed anti-inflammatory activity reflected by its ability to generate myeloid suppressor cells (data not shown).

To determine if compound 2 (5355512), injected subcutaneously would affect the activation status of induced peritoneal macrophages, compound 2 (5355512) was given subcutaneous!}' to control or WBI (5 Gy) and peritoneal macrophages harvested at day 4 as before. Ceils from these groups of mice were incubated for 24 h with LPS or LPS then 512 (See Figure 12). Surprisingly, treatment with Compound 2 (5355512) *in vivo* "primed" induced peritoneal ceils to produce- TNF-a in response to LPS to almost the same extent as WBI alone. However, this "'priming" effect was less when WBI and Compound 2 (5355512) were combined in vivo. Also, in keeping with the data in Figures 10 and 11, the addition of Compound 2. (5355512) in vitro blunted TNF-a production.

Example 9

Compound 2 (5355512) also increased the number of endogenous colony forming units in the spieeos of mice that had received L070/30 radiation doses which is a measure of ability to generate hematopoietic stem cells and myeloid suppressors. The compounds increased survival when given 5 times at 24 hour intervals, starting 24 hours after abdominal or lung irradiation. For example. Compound 2 (5355512) increased the total endogenous CFU in spleens and average endogenous CFU per spleen at 10 days after whole body irradiation (WBI) at varying doses (e.g. 6.5Gy, 7.0 Gy, and 7.5Gy). (See Figure 13).

Example 10

Further *in vivo* experiments similar to Example 3 were conducted except a localized radiation was used to demonstrate mitigation of abdominal radiation with compound 2 (5355512) at increased radiation doses. See Figure 14 Additionally, *in vivo* experiments demonstrated mitigation of radiation pneumonitis and fibrosis after local thoracic irradiation. Addition of compound 2 (5355512) supported survival of C3H mice and C57 mice to 100 days post thoracic radiation (14 and 18 Gy). (See Figure 15)

Example 11

The Lewis lung (LLC) **model of artificial metastasis** was used to **test** the effects **of the** drug o« **the** growth of tumor **lung** colonics *in vivo* and on **radiation** response. This was chosen because it **is** easy to see any **drug** effects on growth promotion and **radioproteciion** is multiple tumors simultaneously. **Specifically,** C57B1/6 mice and C3H1 *mice* were **injected intravenously** with $5x10^4$ tumor cells. Subcutaneous injections of compound 2 (5355512) were started on day 4 when the tumors were already established in the lung. **A** daily dose of 20mg/kg for **5** days was used to bias the experiment **in favor** of any tumor growth promotion. **Local** thoracic irradiation **(LTI)** was started on day 5 with 4 **Gy** daily doses **for** 3 days. This is higher than conventional 2 Gy to **compensate** for the rapid growth **of murine tumors,** but **is** still well within the higher ranges used **clinically** in hypofractionated exposures. The colonies were counted **on** day 14. **Figure 16** shows that **compound** 2 (5355512) **significantly** ($P<0.05$) decreased the **number** of lung **tumor** colonics assessed **on** day 14 by 20%. The colonies were also **smaller** in size. LTI alone decreased the number of colonies by 40%. This was not further decreased by the **suboptimal** drug **treatment.** Thus, compounds given to **mice** bearing Lewis Lung tumors decreased the number of tumor **colonies** that grew with and without **lung** irradiation **demonstrating** that the compounds did not protect tumors and indicating that they may be useful in patients receiving radiation therapy for cancer, protecting normal tissue from damage while exerting anti-tumor action.

As described herein, all embodiments or subcombinations may be used **in** combination with ail other embodiments **or** subcombinations, unless mutually exclusive.

The embodiments illustrated and discussed in this specification are intended only to teach those skilled **in** the art the best way known to the inventors to make and use the invention. Nothing in this specification should be considered as limiting the scope of the present invention. All examples presented are representative and non-limiting. The above-described **embodiments of the** invention maybe modified or varied, without departing from the invention, as **appreciated by** those skilled **in** the art in light of the above teachings. It is therefore to be understood that, within the scope of the claims and their equivalents, the **invention** may be **practiced** otherwise than as **specifically** described.

Incorporation by Reference

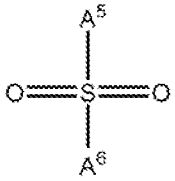
All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individoal publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application,, including any definitions herein, will control.

Equivalents

While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the clairas below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

We Claim

1. **A compound having** the **structure of Formula I;**



Formula I

wherein;

A5 is a secondary or **tertiary** amino **substituent, and**

A* is **a** substituted or **unsubstituted** aryl or **heteroaryl** group.

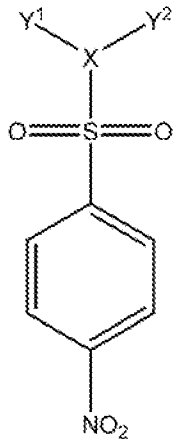
2. A **compound of claim** 1, **wherein** the **aryl or heteroaryl** group bears at least one substituent including a nitro substitutes

3. The compound **of claim** 2, wherein the nitro **substituent** is disposed **at** a **position on** A^6 distal **to** the sulfonyl, e.g., **A"** is a **4-nitrophcnyl** group **optionally** siibstitiited with **1-4 adds**tional substituents.

4. **The compound** of any precedi ng **claim,** wherein **A5 is** a heterocyclic amine, **such as** a piperidine, piperazine, **or** morpholine **ring**

5. The **compound of any** one **of claims** 1-3, whcreio **A*** is **acyclic,** such **as** $NR^{15}R^{16}$, **wherein** each **of** R^{15} and R^{16}, independently, is **H,** alkyl, **alkenyl,** alkynyf **aryl, heferoary!,** aralkyl, or heteroaralkyl, provided that R^{15} and R^{16} arc **not** both *H.*

6. *A* compound of claim 1, having the structure of Formula II:



Formula II

wherein:

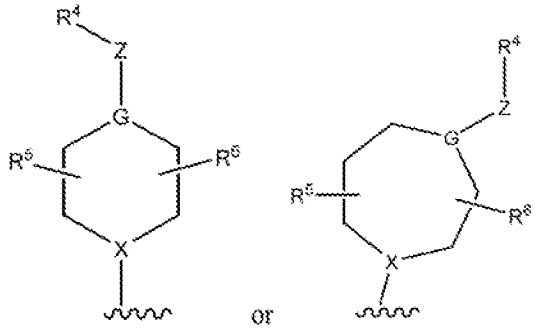
X is N or -C(H)-, **preferably** N; and

Y^1 and Y^2 **are** each independently lower alkyl **or** Y^1 and Y^2 taken **together** with X form a heteroeyeiyl ring.

7. The **compound of claim 6,** wherein Y^1 **and** Y^2 are each ethyl.

8. The **compound** of claim 6, wherein Y^1 and Y^2 taken together **form** a **piperaxine** ring

9. The compound **of claim 6**, wherein Y^1 and Y^2 taken together with X form:



wherein

X is N;

G *is* selected **from** N or -C(H)-, **preferably** N;

Z is absent or selected from **substituted** or unsubstituted aikyl, heteroalkyi, aikenyl, **or alkynyl;**

R^4 is absent or selected from substituted or unsubstituted aryl (e.g., phenyl) and heteroaryi; and

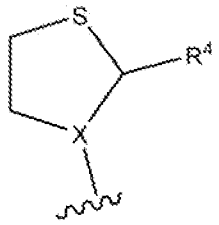
R^5 **and** R^* are each **independently** absent or lower alkyi.

10. The **compound** of claim 9, **wherein** G is N and R^1 is selected **from** phenyl, 4~fluoropheryl and 3-chlorophenyl.

11. The **compound** of any one of claims 6-10, **wherein Z** is absent.

12. The **compound of any** one of claims **6-10, wherein Z** is **prop-2-en-l-yl** and R^4 is phenyl

13. The compound of ciaini 6, wherein Y^1 and Y^2 taken together with X **form:**



wherein X is -C(H)-, and

R^4 is absent or seieeted from **substituted** or unsubsfitiited aryl (e.g., phenyi) and **heteroaryi, such as** a **halogen-substituted** phenyl group, e.g., **4-fhjoropheny! or** 3-chlorophenyl.

14. A **pharmaceutical** compositioii comprising a compound of any preceding claim and a pharmaceutically acceptable excipient **or** solvent.

15. A method of mitigating an effect of ionizing radiation on a ceil, organ, tissue, or **organism, comprising** contacting the **ceil,** organ, tissue, or **organism with** at ieast one compound **or composition** of arty **preceding** claim.

16. The method of claim 15, wherein the compound or composuion is administered before, during, or after exposure to ionizing radiation.

17. A meihod of treating inflammation in an organism, comprising administering to the organism a compound or composition of any one of claims 1-14.

18. A method of treating cancer in an organism, comprising administering to the organism a compound or composition of any one of claims i-14.

19. The meihod of any one of claims J5-18, wherein the organism is a mammal.

Figure 1.

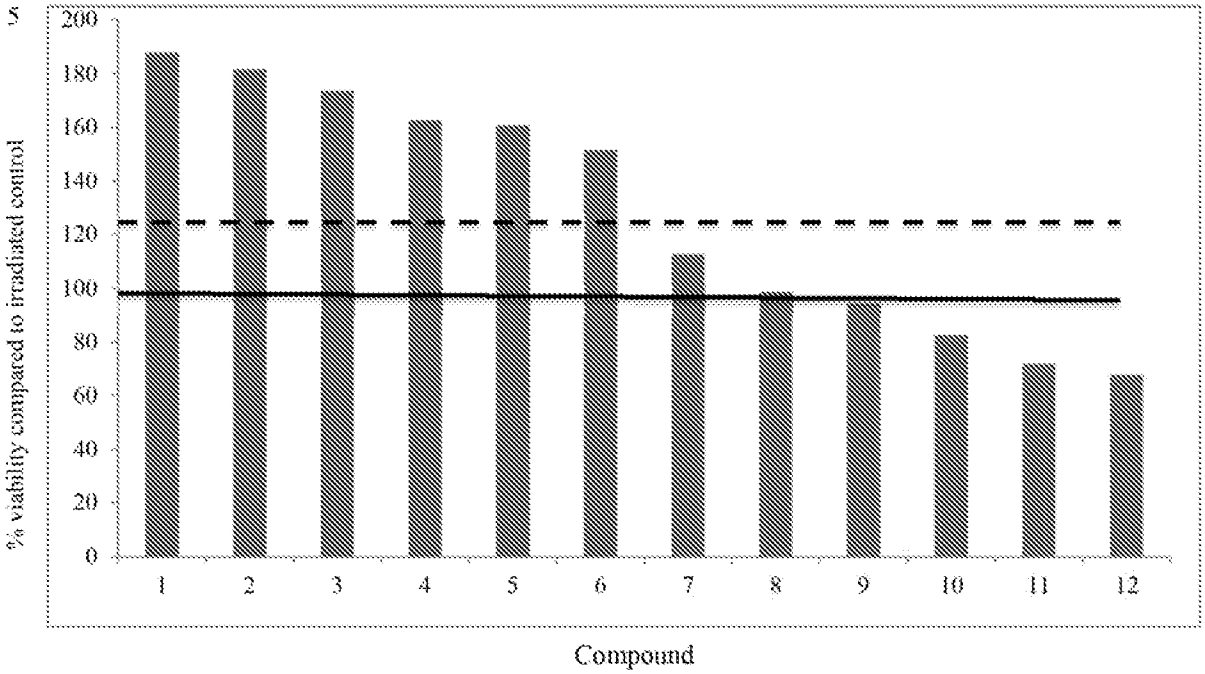
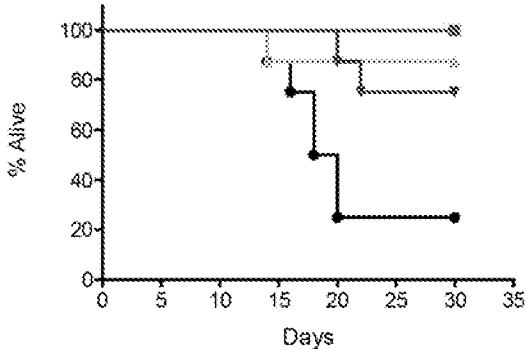
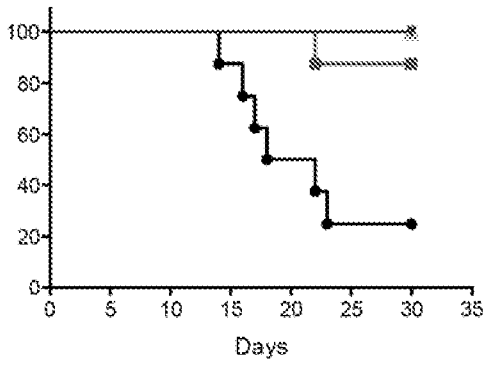

% viability compared to irradiated control
200
180
160
140
120
100
80
60
40
20
0
1
2
3
4
5
6
7
8
9
10
11
12
Compound

Figure 2.

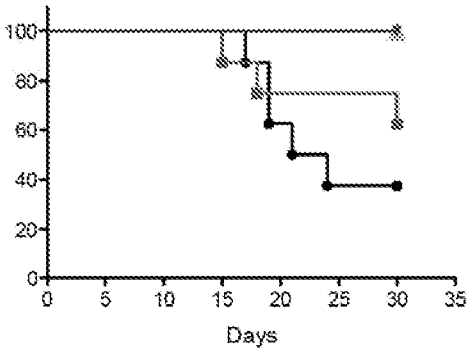
A.



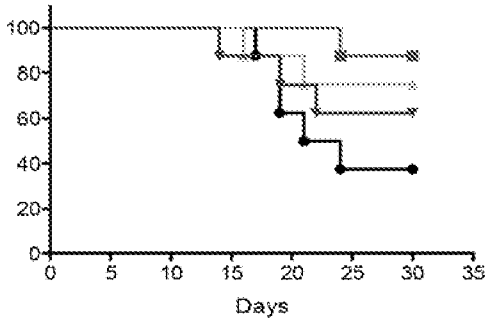
B.



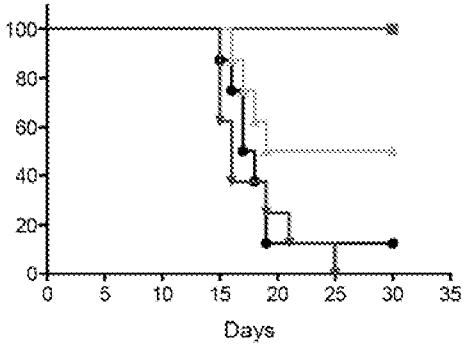
C.



D.



E.



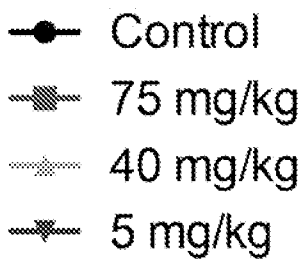


Figure 3.

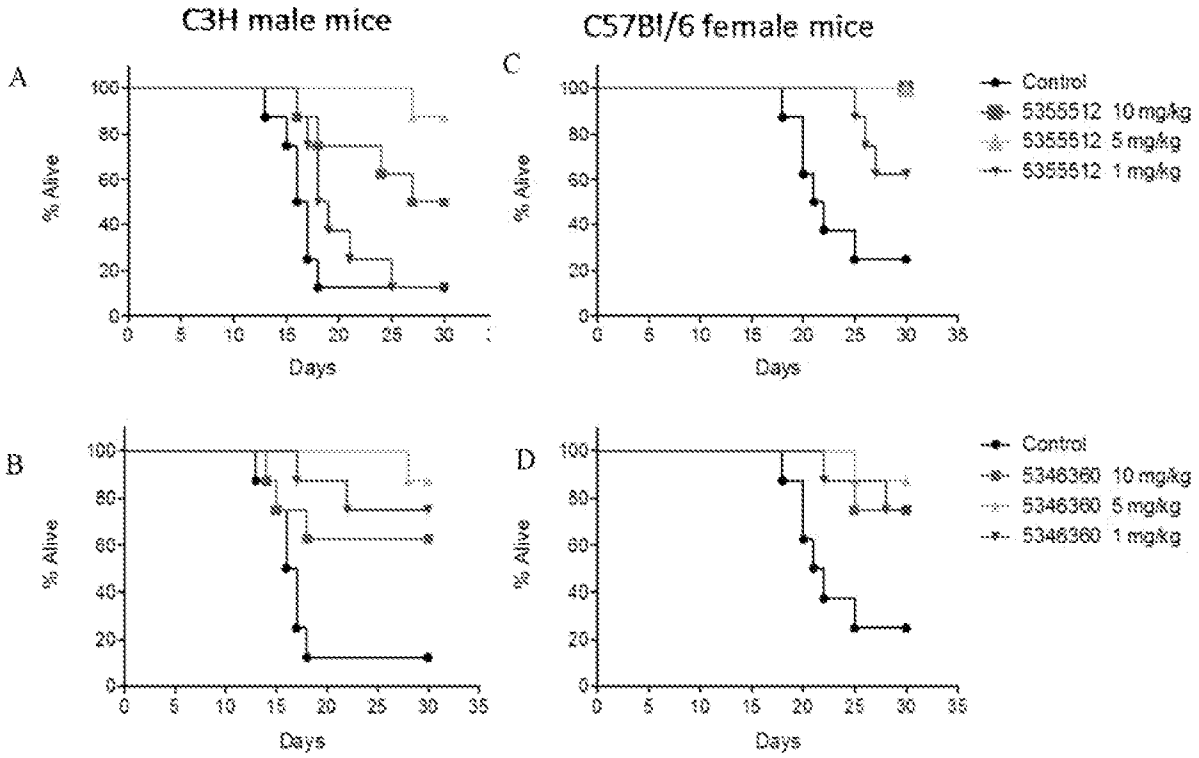

C3H male mice
C57Bl/6 female mice
A
B
C
D
% Alive
Days
Control
5355512 10 mg/kg
5355512 5 mg/kg
5355512 1 mg/kg
5346360 10 mg/kg
5346360 5 mg/kg
5346360 1 mg/kg

Figure 4.

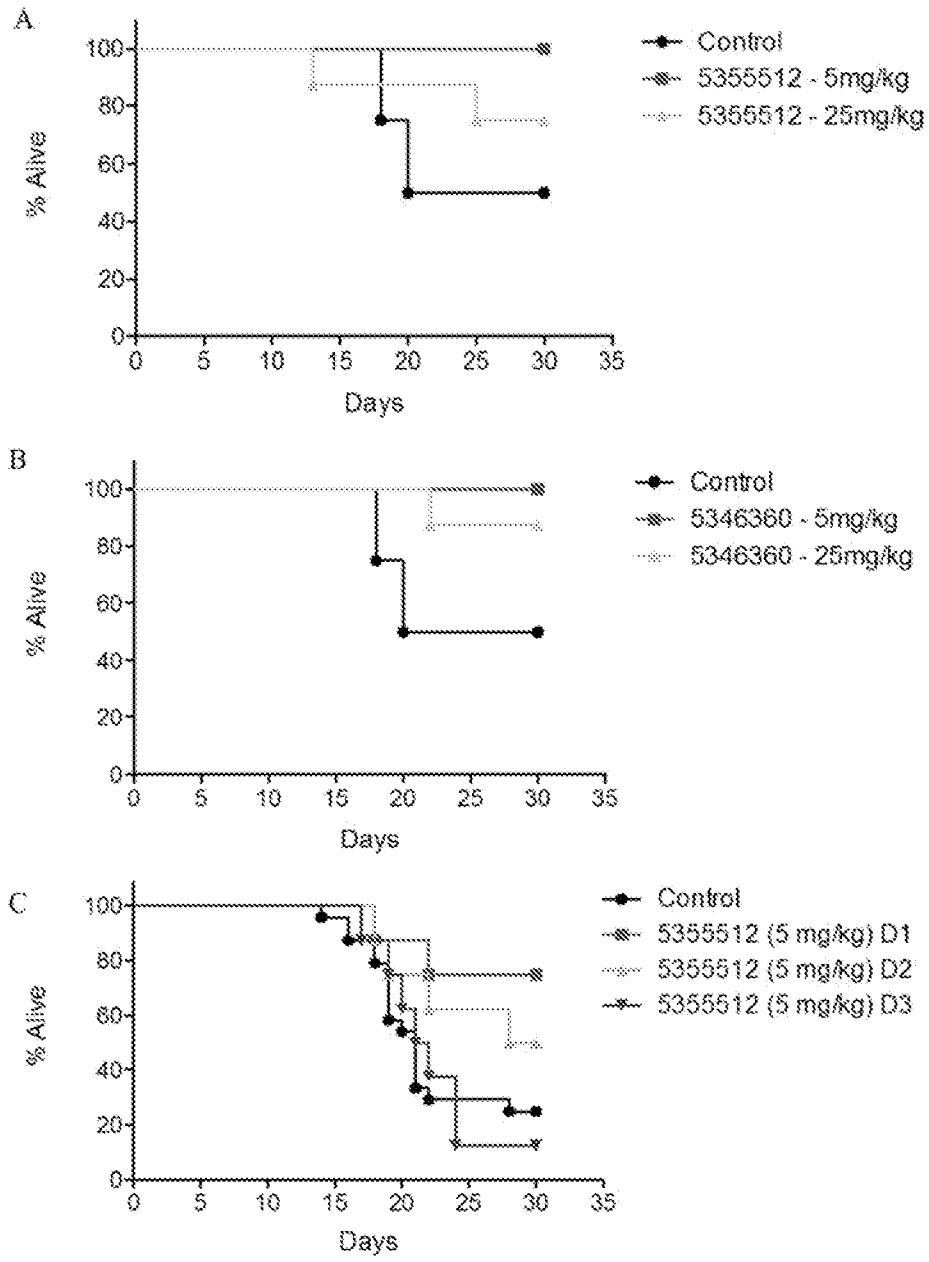

A
% Alive
Days
Control
5355512 - 5mg/kg
5355512 - 25mg/kg
B
% Alive
Days
Control
5346360 - 5mg/kg
5346360 - 25mg/kg
C
% Alive
Days
Control
5355512 (5 mg/kg) D1
5355512 (5 mg/kg) D2
5355512 (5 mg/kg) D3

Figure 5.

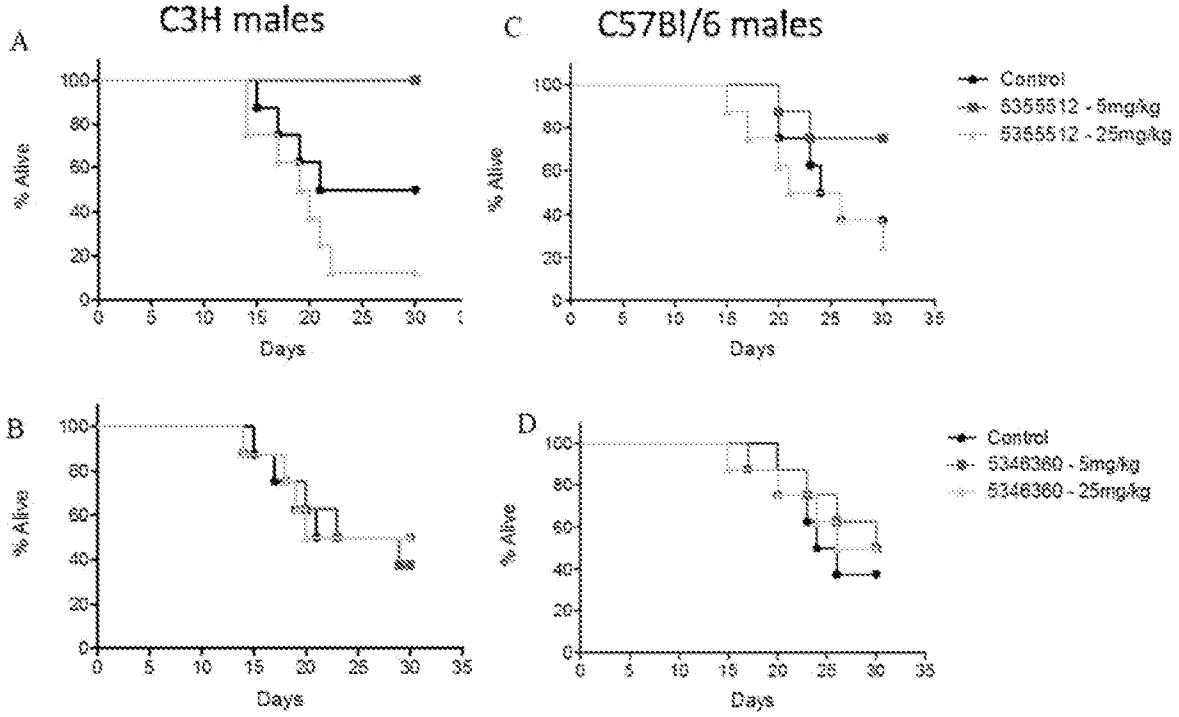

A
C3H males
% Alive
Days
C
C57Bl/6 males
% Alive
Days
Control
5355512 - 5mg/kg
5355512 - 25mg/kg
B
% Alive
Days
D
% Alive
Days
Control
5346360 - 5mg/kg
5346360 - 25mg/kg

Figure 6.

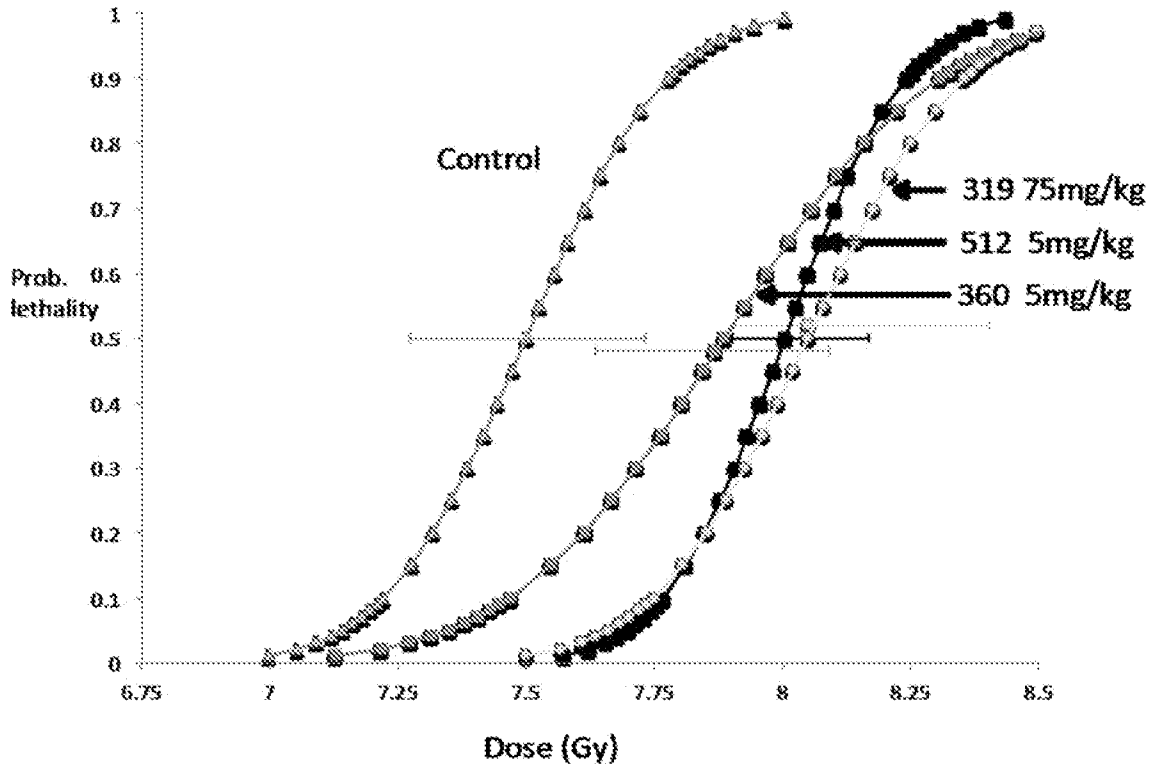

Prob. lethality
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
6.75
7
7.25
7.5
7.75
8
8.25
8.5
Dose (Gy)
Control
319 75mg/kg
512 5mg/kg
360 5mg/kg

Figure 7.

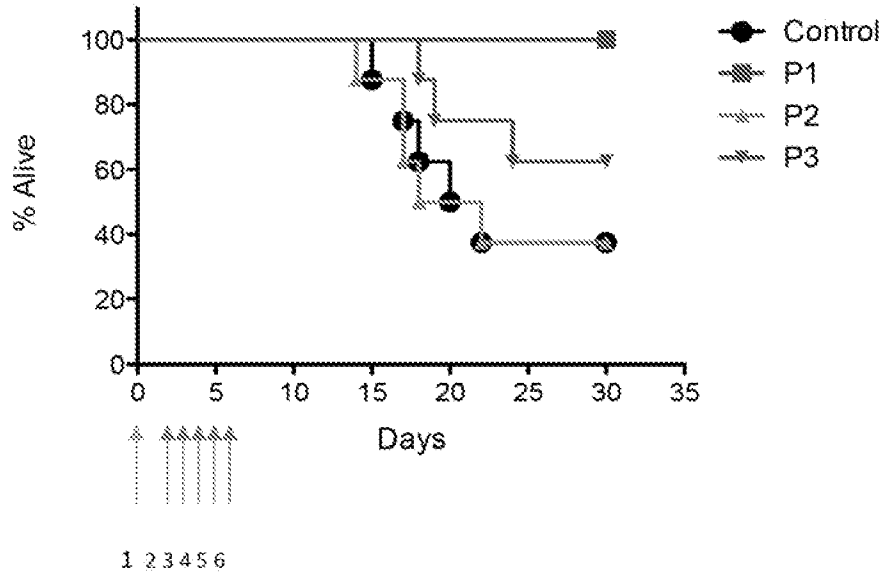

100
80
60
40
20
0
% Alive
0
5
10
15
20
25
30
35
Days
Control
P1
P2
P3
1 2 3 4 5 6

Figure 8.

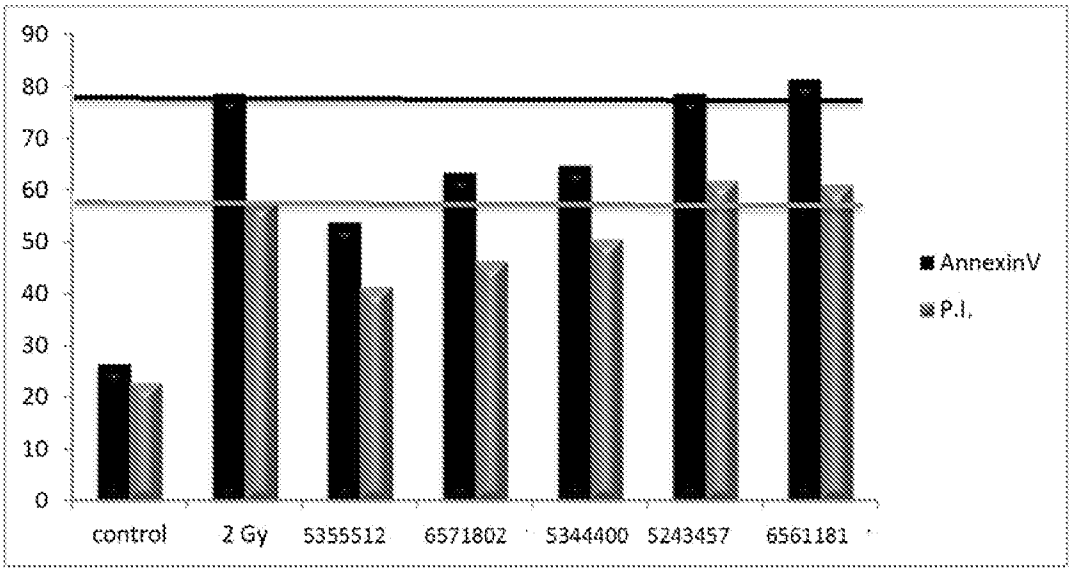

90
80
70
60
50
40
30
20
10
0
control
2 Gy
5355512
6571802
5344400
5243457
6561181
AnnexinV
P.I.

Figure 9.

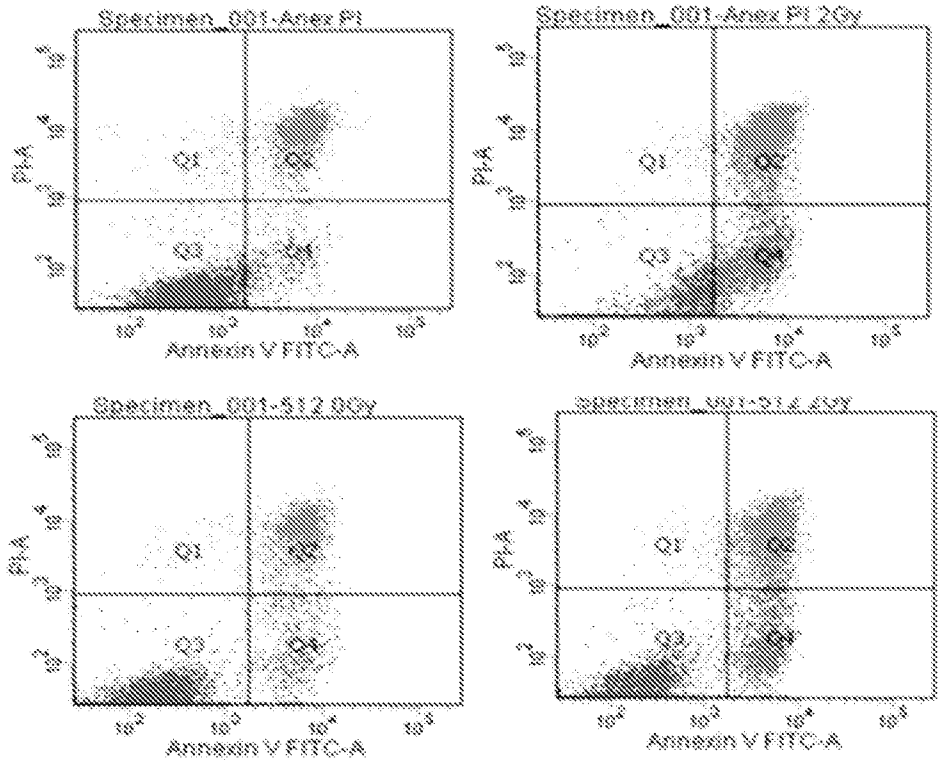
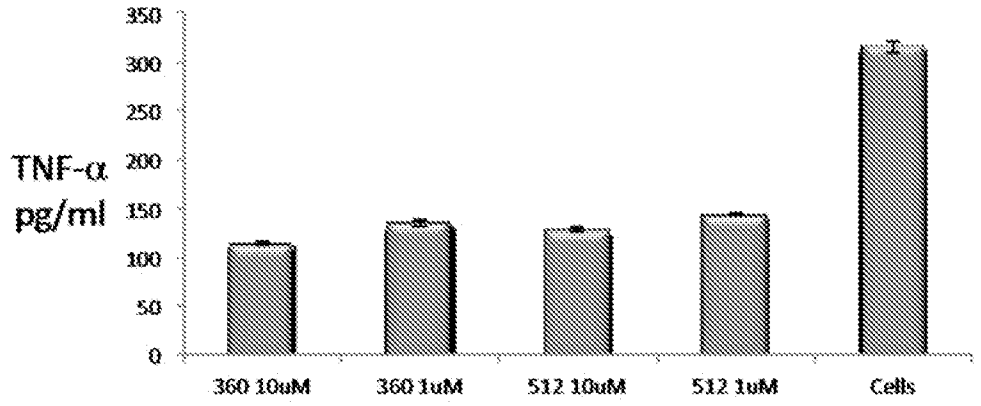

Specimen_001-Anex PI
Specimen_001-Anex PI 2Gy
Specimen_001-Anex PI 5 12 0Gy
PI-A
Annexin V FITC-A
Q1
Q2
Q3
Q4

Figure 10

A.


TNF-α pg/ml
350
300
250
200
150
100
50
0
360 10uM
360 1uM
512 10uM
512 1uM
Cells

B.

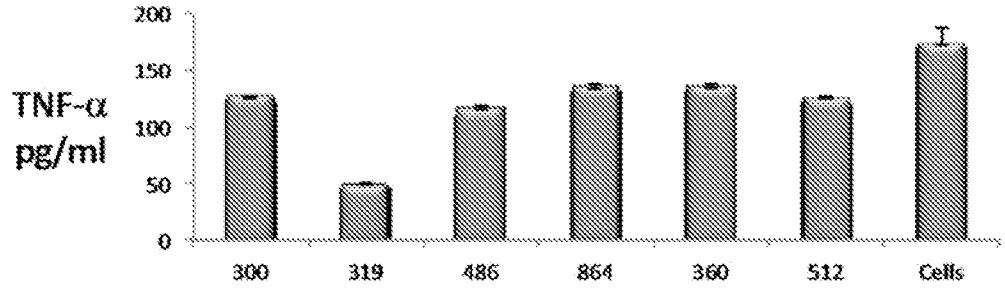

TNF-α pg/ml
200
150
100
50
0
300
319
486
864
360
512
Cells

Figure 11

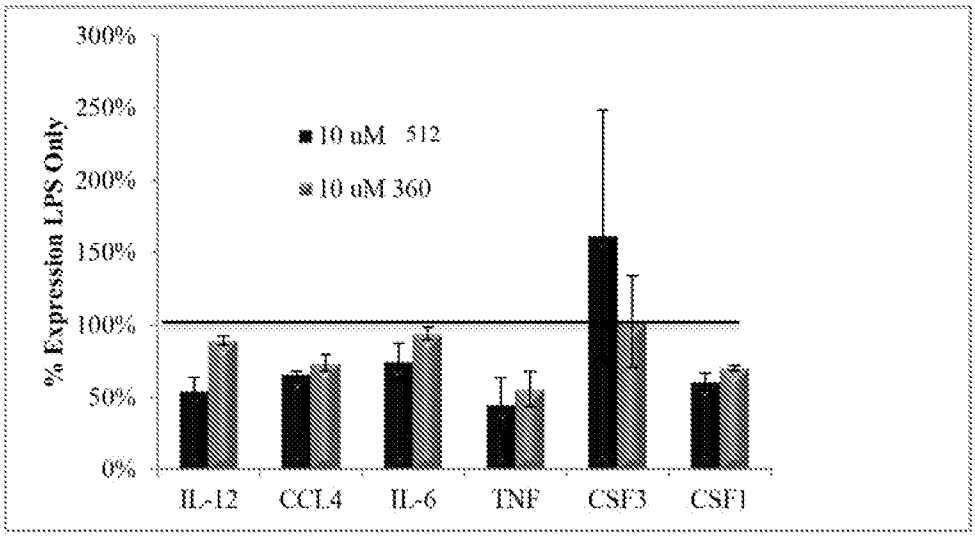

300%
250%
200%
150%
100%
50%
0%
% Expression LPS Only
10 uM 512
10 uM 360
IL-12
CCL4
IL-6
TNF
CSF3
CSF1

Figure 12

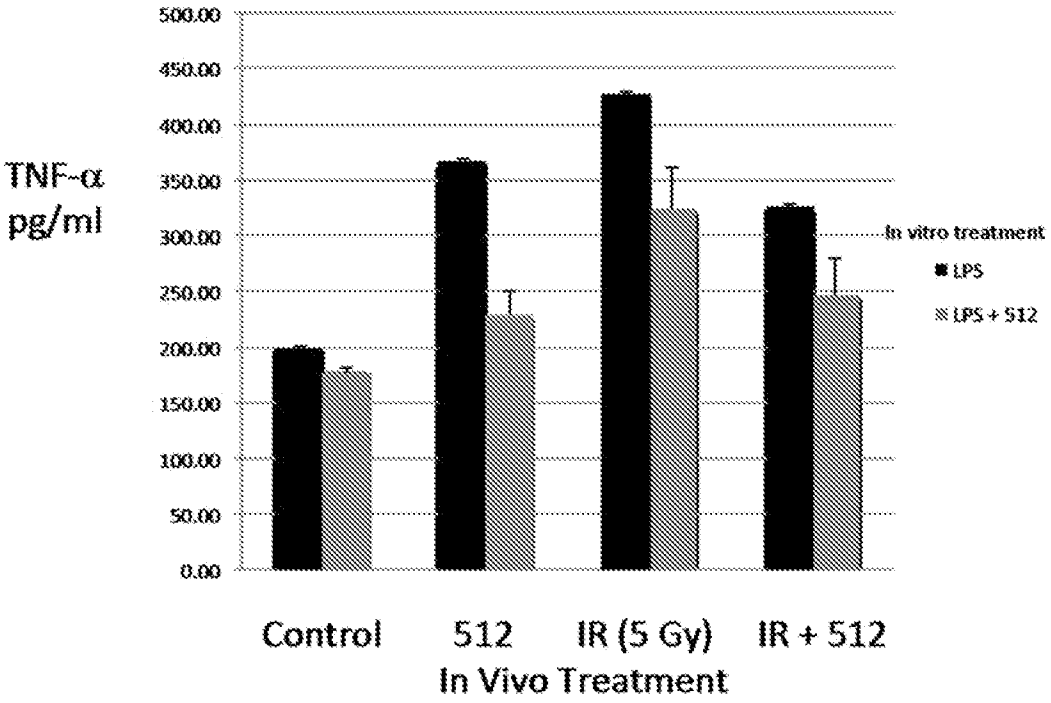
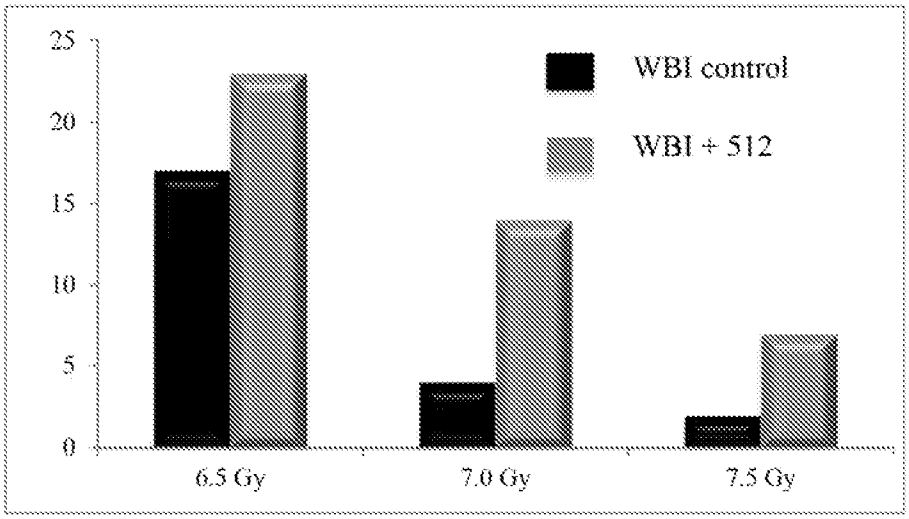

TNF-α
pg/ml
500.00
450.00
400.00
350.00
300.00
250.00
200.00
150.00
100.00
50.00
0.00
In vitro treatment
LPS
LPS + 512
Control
512
IR (5 Gy)
IR + 512
In Vivo Treatment

Figure 13

A.


25
20
15
10
5
0
WBI control
WBI + 512
6.5 Gy
7.0 Gy
7.5 Gy

B.

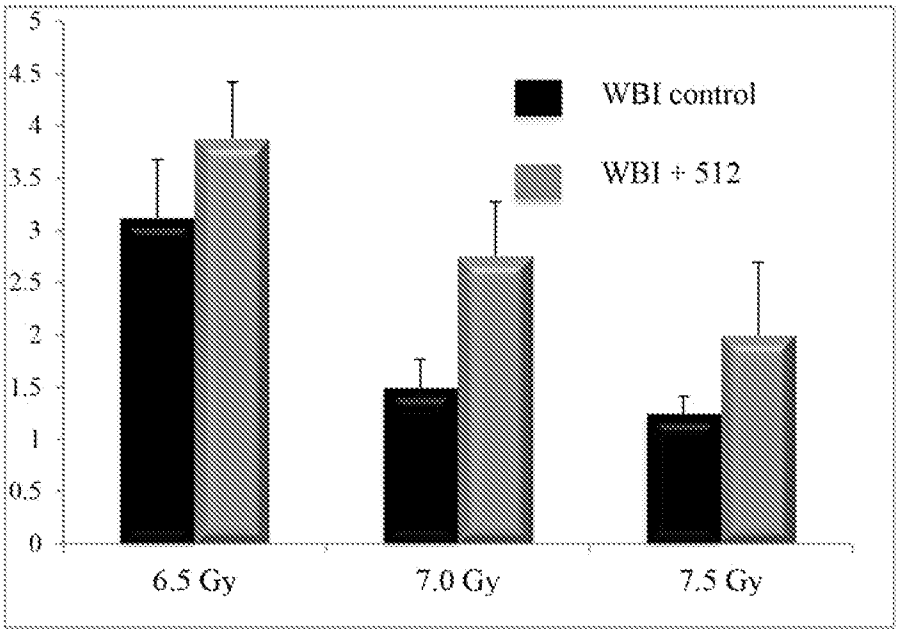

5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
WBI control
WBI + 512
6.5 Gy
7.0 Gy
7.5 Gy

Figure 14

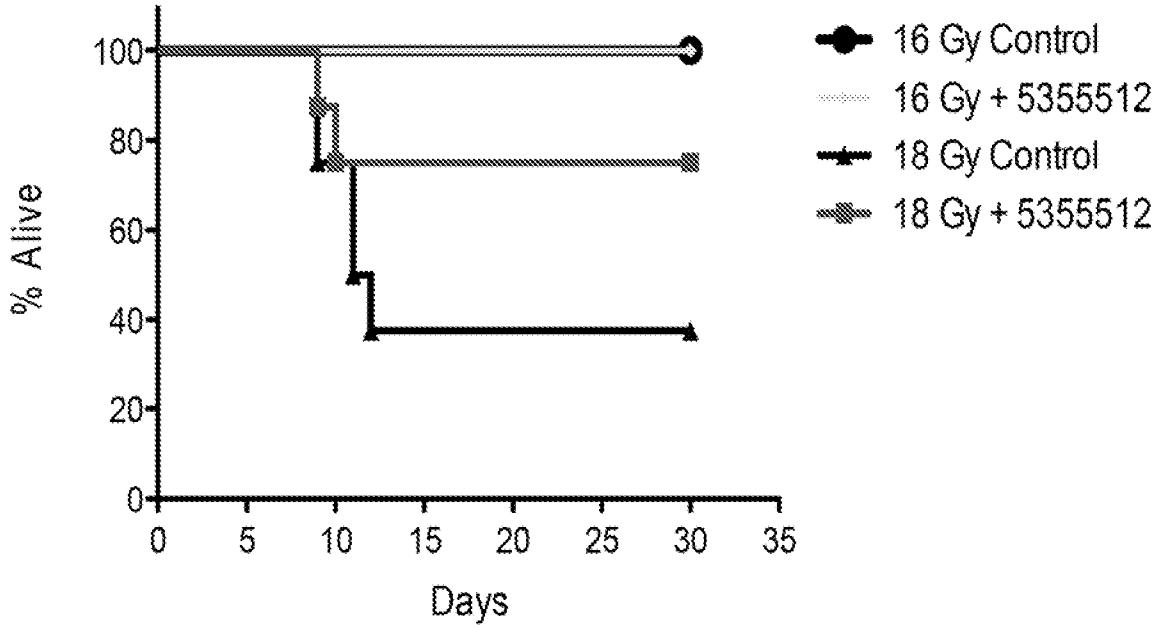
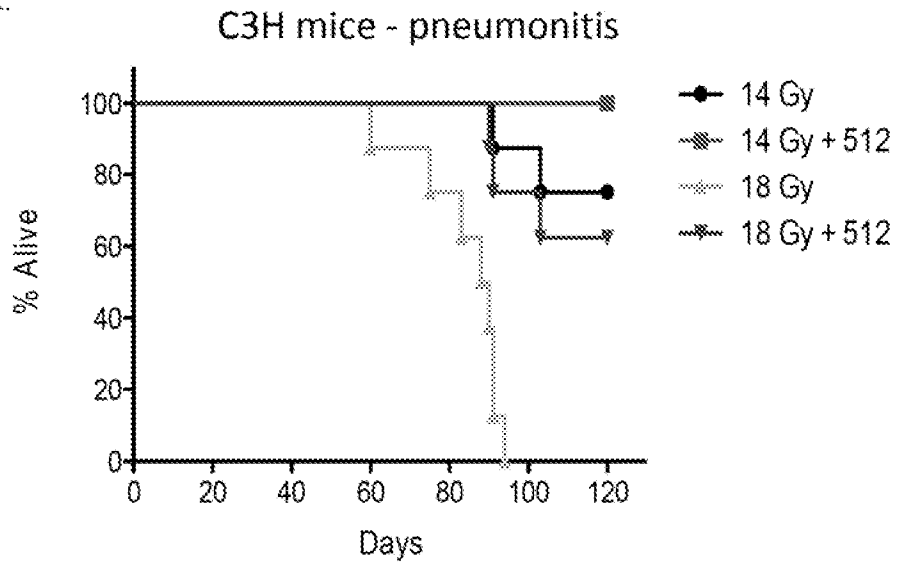

100
80
60
40
20
0
% Alive
0
5
10
15
20
25
30
35
Days
16 Gy Control
16 Gy + 5355512
18 Gy Control
18 Gy + 5355512

Figure 15

A.


C3H mice - pneumonitis
% Alive
100
80
60
40
20
0
0
20
40
60
80
100
120
Days
14 Gy
14 Gy + 512
18 Gy
18 Gy + 512

B.

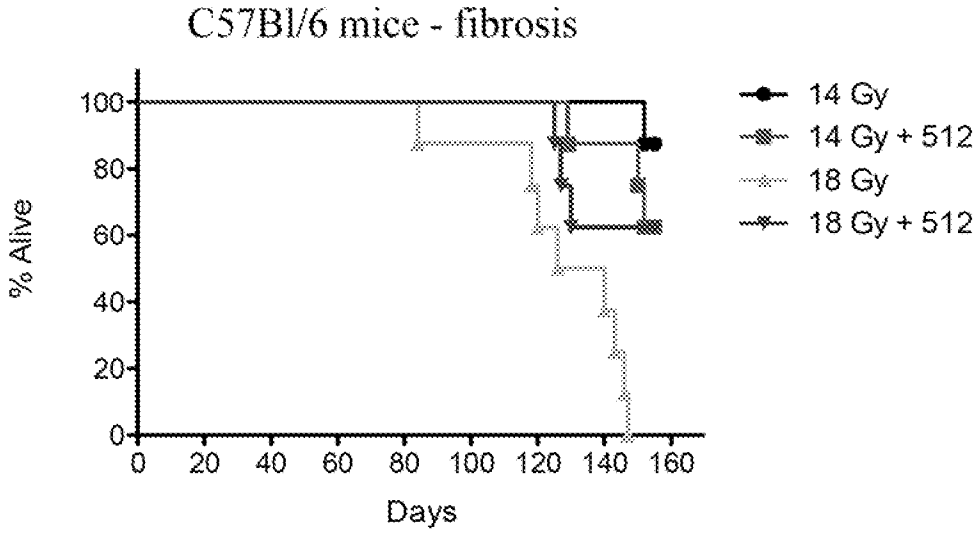
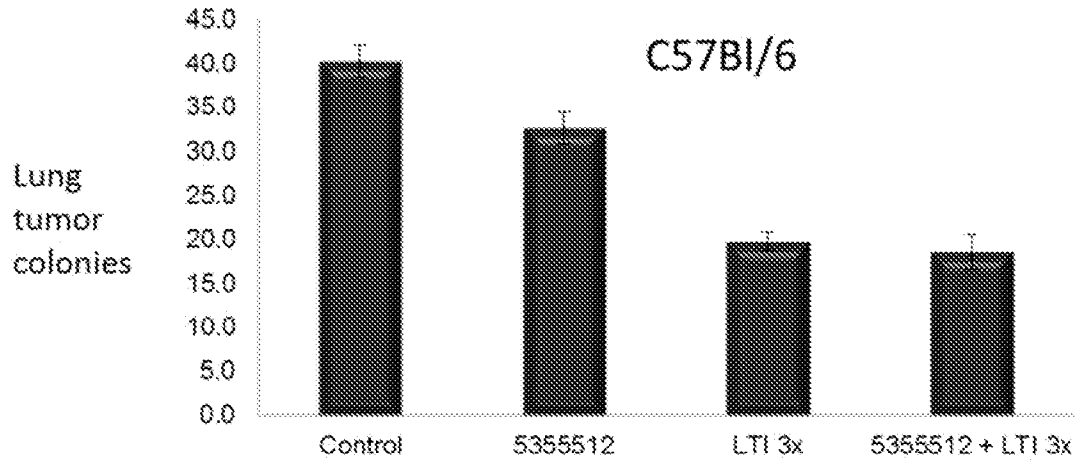
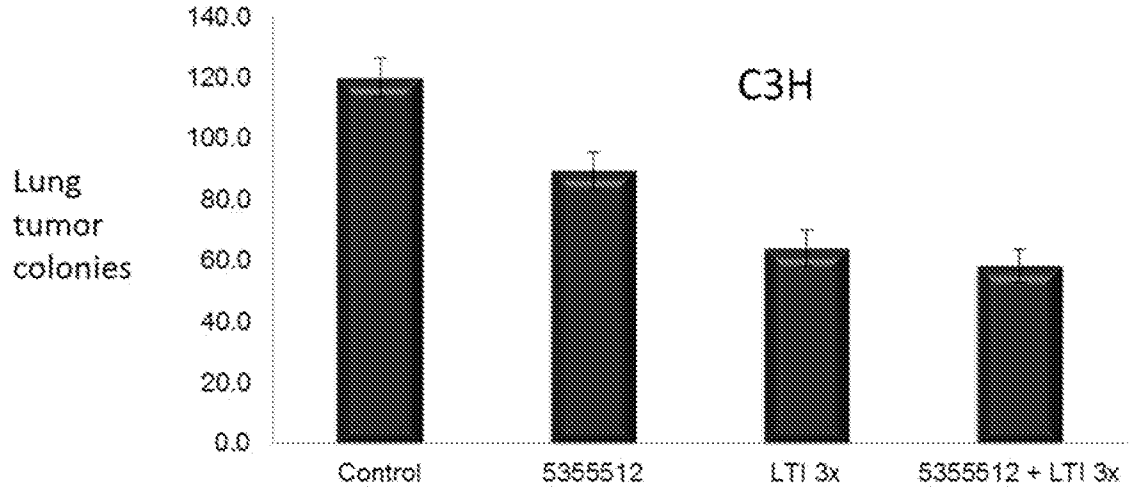

C57Bl/6 mice - fibrosis
% Alive
100
80
60
40
20
0
0
20
40
60
80
100
120
140
160
Days
14 Gy
14 Gy + 512
18 Gy
18 Gy + 512

Figure 16.

A.


C57Bl/6
Lung tumor colonies
45.0
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
Control
5355512
LTI 3x
5355512 + LTI 3x

B.


C3H
Lung tumor colonies
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
Control
5355512
LTI 3x
5355512 + LTI 3x