



(43) International Publication Date
14 September 2017 (14.09.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/156222 A1

(51) International Patent Classification:

C07D 295/26 (2006.01) A61K 31/495 (2006.01)
C07D 295/037 (2006.01) A61P 35/00 (2006.01)
C07D 241/04 (2006.01) A61P 29/00 (2006.01)

(21) International Application Number:

PCT/US2017/021502

(22) International Filing Date:

9 March 2017 (09.03.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/305,741 9 March 2016 (09.03.2016) US

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

(72) Inventors: MCBRIDE, William; 7915 Naylor Avenue,
Los Angeles, CA 90045 (US). RUCHALA, Piotr, Pawel;
1641 Veteran Ave. Apt. #5, Los Angeles, CA 90024 (US).
MICEWICZ, Ewa; 1641 Veteran Ave. Apt. #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, DJ, 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, KH, KN,
KP, KR, KW, KZ, LA, LC, LK, LR, LS, 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, ST, 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).

Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

— with international search report (Art. 21(3))

(54) Title: RADIOMITIGATING COMPOUNDS, COMPOSITIONS AND METHODS RELATED THERETO

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



WO 2017/156222 A1

RADIOMITIGATING COMPOUNDS, COMPOSITIONS AND METHODS RELATED THERETO

5 RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Patent Application serial number 62/305,741, filed March 9, 2016. This application is hereby incorporated by reference in its entirety.

10 GOVERNMENT INTEREST

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

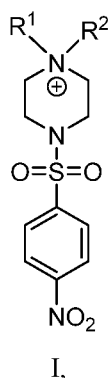
15 The global use and storage of radioactivity is increasing rapidly. Millions of radioactive sealed sources are used around the world for legitimate and beneficial commercial applications such as cancer treatment, food and blood sterilization, oil exploration, remote electricity generation, radiography, and scientific research. Isotopes in use in these applications include Cesium-137, Cobalt-60, Strontium-90, Americium-241,
20 Iridium-192, Plutonium-238, Plutonium-239, Curium-244, Radium-226, and Californium-252. Currently, there are tens of thousands of civilian locations worldwide with radioactive material, about 5,000 of which contain sources of 1,000 curies or greater. Many of these radiological sources are no longer needed and have been abandoned or orphaned; others are poorly guarded, making the risk of theft or sabotage significant.

25 Fundamental to radiation exposure and injury is DNA strand breaks, resulting in genetic instability and DNA deletions which are involved in cell death, cellular dysfunction, as well as long-term consequences such as birth defects and cancer. Most 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.
30 Because of this, these compounds are not practical countermeasures in a radiation incident. 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.

Thus, there is a continuing need for new compounds, compositions, and methods for treating and mitigating the effects of exposure to radiation.

5 SUMMARY

In one aspect, the invention relates to compounds having the structure for Formula (I):



10 and pharmaceutically acceptable salts thereof, wherein R¹ and R² are as defined herein.

In some embodiments, the invention relates to pharmaceutical compositions of a compound of Formula (I) and a pharmaceutically acceptable carrier.

In another aspect, the invention relates to methods of mitigating an effect of ionizing radiation on a cell, organ, tissue, or organism, comprising contacting the cell, organ, tissue,
15 or organism with at least one compound or composition of the invention.

In yet another aspect, the invention relates to methods of treating or preventing inflammation or cancer by administering a compound or composition of the invention to an organism.

20 BRIEF DESCRIPTION OF THE DRAWING

Figure 1 shows the mitigation against total body radiation lethality in C3H mice by compound QS1.

Figure 2 shows the pharmacokinetic curve for the triflate salt of QS1 when it is
25 injected subcutaneously in mice ($t_{1/2}$ is 23.5 min).

Figure 3 is a plot showing the dose response of QS1 given 24h after WBI (LD_{70/30}) at 5 daily s.c. doses of 20 mg/kg.

Figure 4 is a plot showing the dose response of QS1 given 24h after WBI (LD_{70/30}) at 5 daily s.c. doses of 10 mg/kg.

Figure 5 is a plot showing the dose response of QS1 given 24h after WBI (LD_{70/30}) at 5 daily s.c. doses of 5 mg/kg.

Figure 6 is a plot showing the dose response of QS1 given 24h after WBI (LD_{70/30}) at 5 daily s.c. doses of 1 mg/kg.

Figure 7 is a plot showing the single dose response of QS1 given 24h after WBI (LD_{70/30}) at a s.c. dose of 5 mg/kg.

Figure 8 is a plot showing the dose response when QS1 administered orally, given 24h after WBI (LD_{70/30}) at 5 daily doses of 5 mg/kg.

Figure 9 is a plot showing the dose response when QS1 administered orally, given 24h after WBI (LD_{70/30}) at a single dose of 5 mg/kg.

Figure 10 is a plot showing QS1 mitigation ability of late pneumonitis after local thorax radiation exposure in C3H mice after 14Gy LTI.

Figure 11 is a plot showing QS1 mitigation ability of late pneumonitis after local thorax radiation exposure in C3H mice after 16Gy LTI.

Figure 12 is a plot showing QS1 mitigation ability of late pneumonitis after local thorax radiation exposure in C3H mice after 18Gy LTI.

Figure 13 is a plot showing QS1 mitigation capacity of late fibrosis in C57Bl/6 mice after 14Gy LTI.

Figure 14 is a plot showing QS1 mitigation capacity of late fibrosis in C57Bl/6 mice after 16Gy LTI.

Figure 15 is a plot showing QS1 mitigation capacity of late fibrosis in C57Bl/6 mice after 18Gy LTI.

Figure 16 is a plot showing QS1 mitigation ability of intestinal ARS in C3H mice after 20 Gy abdominal X-irradiation.

Figure 17 is a plot showing QS1 mitigation ability of intestinal ARS in C57Bl/6 mice after 20 Gy abdominal X-irradiation.

Figure 18 is a plot showing a comparison between QS1 level in plasma in non-radiated vs radiated LD_{70/30} mice, with QS1 delivered at different time points after radiation (24h or 72h).

Figure 19 is a plot showing QS1 level in plasma measured in non-radiated mice over a 24h time period.

Figure 20 shows the flow cytometry data for Annexin+PI+ population assessed at 24h after 0 or 2Gy irradiation of Til-1 cells treated with different concentration of QS1 in vitro.

5 **Figure 21** is a bar graph summarizing the flow cytometry data for Annexin+PI+ population assessed at 24h after 0Gy irradiation of Til-1 cells treated with different concentration of QS1 in vitro.

10 **Figure 22** is a bar graph summarizing the flow cytometry data for Annexin+PI+ population assessed at 24h after 2Gy irradiation of Til-1 cells treated with different concentration of QS1 in vitro.

Figure 23 is a bar graph showing the viability of Til-1 cells treated with different concentration of QS1 (25, 10, 1 or 0 μ M), measured at 6, 24 or 48h after 0 or 2Gy cells irradiation without LPS cell stimulation.

15 **Figure 24** is a bar graph showing the viability of Til-1 cells treated with different concentration of QS1 (25, 10, 1 or 0 μ M), measured at 6, 24 or 48h after 0 or 2Gy cells irradiation with LPS cell stimulation.

Figure 25 is a bar graph showing the Caspase 3/7 activity in Til-1 cells treated with different concentration of QS1 (25, 10, 1 or 0uM), measured at 6, 24 or 72h after 0 Gy cells irradiation. The addition of LPS did not affect the results.

20 **Figure 26** is a bar graph showing the Caspase 3/7 activity in Til-1 cells treated with different concentration of QS1 (25, 10, 1 or 0uM), measured at 6, 24 or 72h after 2 Gy cells irradiation. The addition of LPS did not affect the results.

25 **Figure 27** is a bar graph showing the Caspase 9 activity in Til-1 cells treated with different concentration of QS1 (25, 10, 1 or 0uM), measured at 6, 24 or 72h after 0 Gy cells irradiation. The addition of LPS did not affect the results.

Figure 28 is a bar graph showing the Caspase 9 activity in Til-1 cells treated with different concentration of QS1 (25, 10, 1 or 0uM), measured at 6, 24 or 72h after 2 Gy cells irradiation. The addition of LPS did not affect the results.

30 **Figure 29** depicts the flow cytometry data showing the emergence of a CD11+Ly6C+Ly6G+ population of immature myeloid cells in the spleens of C3H mice, 30h after WBI that is increased by a single 5mg/kg QS1 s.c. injection.

Figure 30 is two bar graphs showing the summary of population CD11+ or CD11+Ly6C+Ly6G+ cells in spleen at 30h, 48h or 7d after WBI +/- QS1.

Figure 31 is two bar graphs showing the summary of population CD11+ or CD11+Ly6C+Ly6G+ cells in BM at 30h, 48h or 7d after WBI +/- QS1.

Figure 32 is two bar graphs showing the summary of population CD11+ or CD11+Ly6C+Ly6G+ cells in or blood at 30h, 48h or 7d after WBI +/- QS1.

DETAILED DESCRIPTION

General

Certain compounds disclosed herein mitigate the effects of ionizing radiation. Without wishing to be bound by theory, the compounds disclosed herein may protect against deleterious effects of ionizing radiation by promoting repair of DNA damage caused by exposure to radiation. As disclosed herein, certain compounds were applied in mice 24 hours after exposure to TBI and increased the survival of the mice compared to a control group. Pharmaceutical compositions using compounds of the invention have potential to improve the outcome of radiation exposure, and therefore they may be useful in the cancer radiotherapy, as well as in a radiological emergency. In addition, the compounds and compositions disclosed herein are can be used to mitigate an effect of ionizing radiation on a cell, organ, tissue, or organism.

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. All 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 "acyl" is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)-, preferably alkylC(O)-.

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

5 The term "acyloxy" is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)O-, 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.

10 The term "alkoxyalkyl" refers to an alkyl group substituted with an alkoxy group and may be represented by the general formula alkyl-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 alkenyls" and "substituted alkenyls", 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 alkyl groups, as discussed below, except where stability is prohibitive. For example, substitution of alkenyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated.

20 An "alkyl" group or "alkane" is a straight chained or branched non-aromatic hydrocarbon which is completely saturated. Typically, a straight chained or branched alkyl 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-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, pentyl, hexyl, pentyl and octyl. A C₁-C₆ straight chained or branched alkyl group is also referred to as a "lower alkyl" group. An alkyl group with two open valences is sometimes referred to as an alkylene group, such as methylene, ethylene, propylene and the like.

25 Moreover, the term "alkyl" (or "lower alkyl") as used throughout the specification, examples, and claims is intended to include both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl 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 hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an

amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), -CF₃, -CN and the like. Exemplary substituted alkyls are described below. Cycloalkyls can be further substituted with alkyls, alkenyls, alkoxys, alkylthios, aminoalkyls, carbonyl-substituted alkyls, -CF₃, -CN, and the like.

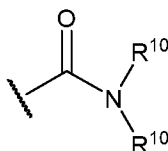
The term “C_{x-y}” when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups that contain from x to y carbons in the chain. For example, the term “C_{x-y}alkyl” refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from x to y carbons in the chain, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc. C₀ alkyl indicates a hydrogen where the group is in a terminal position, a bond if internal. The terms “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 heteroatoms in the chain. As applied to carbocyclic structures, such as aryl and cycloalkyl groups, “C_{x-y}” indicates that the ring comprises x to y carbon atoms. As applied to heterocyclic structures, such as heteroaryl and heterocyclyl groups, “C_{x-y}” indicates that the ring contains from x to y carbons and heteroatoms. As applied to groups, such as aralkyl and heterocyclylalkyl 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 heteroatoms.

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 general formula alkylS-.

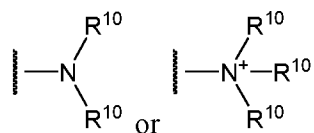
The term “alkynyl”, as used herein, refers to an aliphatic group containing at least one triple bond and is intended to include both “unsubstituted alkynyls” and “substituted alkynyls”, the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the 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 alkyl groups, as discussed above, except where stability is prohibitive. For example, substitution of alkynyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated.

The term “amide”, as used herein, refers to a group



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

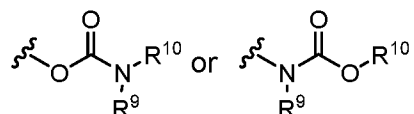
The term “aminoalkyl”, as used herein, refers to an alkyl group substituted with an amino group.

The term “aralkyl”, as used herein, refers to an alkyl group substituted with an aryl 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 7-membered ring, more preferably a 6-membered ring. The term “aryl” also includes polycyclic 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, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like.

5 The term “carbamate” is art-recognized and refers to a group



wherein R⁹ and R¹⁰ independently represent hydrogen or a hydrocarbonyl group, such as an alkyl group, or R⁹ and R¹⁰ taken together with the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

10 The terms “carbocycle”, and “carbocyclic”, as used herein, refers to a saturated or unsaturated ring in which each atom of the ring is carbon. The term carbocycle includes both aromatic carbocycles and non-aromatic carbocycles. Non-aromatic carbocycles include both cycloalkane rings, in which all carbon atoms are saturated, and cycloalkene rings, which contain at least one double bond. “Carbocycle” includes 5-7 membered
 15 monocyclic and 8-12 membered bicyclic rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated and aromatic rings. Carbocycle includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term “fused carbocycle” refers to a bicyclic carbocycle in which each of the rings shares two adjacent atoms with the other ring. Each ring of a fused carbocycle may be selected
 20 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., cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits, is included in the definition of carbocyclic. Exemplary “carbocycles” include cyclopentane, cyclohexane, bicyclo[2.2.1]heptane, 1,5-
 25 cyclooctadiene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]oct-3-ene, naphthalene and adamantane. Exemplary fused carbocycles include decalin, naphthalene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]octane, 4,5,6,7-tetrahydro-1H-indene and bicyclo[4.1.0]hept-3-ene. “Carbocycles” may be substituted at any one or more positions capable of bearing a hydrogen atom.

30 A “cycloalkyl” group is a cyclic hydrocarbon which is completely saturated. “Cycloalkyl” includes monocyclic and bicyclic rings. Typically, a monocyclic cycloalkyl group has from 3 to about 10 carbon atoms, more typically 3 to 8 carbon atoms unless

otherwise defined. The second ring of a bicyclic cycloalkyl may be selected from saturated, unsaturated and aromatic rings. Cycloalkyl includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term “fused cycloalkyl” refers to a bicyclic cycloalkyl in which each of the rings shares two adjacent atoms with the other ring. The second ring of a fused bicyclic cycloalkyl may be selected from saturated, unsaturated and aromatic rings. A “cycloalkenyl” group is a cyclic hydrocarbon containing one or more double bonds.

The term “carbocyclalkyl”, as used herein, refers to an alkyl group substituted with a carbocycle group.

The term “carbonate” is art-recognized and refers to a group $-\text{OCO}_2\text{-R}^{10}$, wherein R^{10} represents a hydrocarbyl group.

The term “carboxy”, as used herein, refers to a group represented by the formula $-\text{CO}_2\text{H}$.

The term “ester”, as used herein, refers to a group $-\text{C}(\text{O})\text{OR}^{10}$ wherein R^{10} represents a hydrocarbyl group.

The term “ether”, as used herein, refers to a hydrocarbyl group linked through an oxygen to another hydrocarbyl group. Accordingly, an ether substituent of a hydrocarbyl group may be hydrocarbyl-O-. Ethers may be either symmetrical or unsymmetrical. Examples of ethers include, but are not limited to, heterocycle-O-heterocycle and aryl-O-heterocycle. Ethers include “alkoxyalkyl” groups, which may be represented by the general formula alkyl-O-alkyl.

The terms “halo” and “halogen” as used herein means halogen and includes chloro, fluoro, bromo, and iodo.

The terms “hetaralkyl” and “heteroaralkyl”, as used herein, refers to an alkyl group substituted with a hetaryl group.

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

The terms “heteroaryl” and “hetaryl” include substituted or unsubstituted aromatic single ring structures, preferably 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 “heteroaryl” and “hetaryl” also include polycyclic 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 cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine, and pyrimidine, 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”, “heterocycle”, 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 polycyclic 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 heterocyclic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocyclyls. Heterocyclyl groups include, for example, piperidine, piperazine, pyrrolidine, morpholine, lactones, lactams, and the like.

The term “heterocyclylalkyl”, as used herein, refers to an alkyl group substituted with a heterocycle 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 substituent, 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 trifluoromethyl are considered to be hydrocarbyl for the purposes of this application, but substituents such as acetyl (which has a =O substituent on the linking carbon) and ethoxy (which is linked through oxygen, not carbon) are not. Hydrocarbyl groups include, but are not limited to aryl, heteroaryl, carbocycle, heterocyclyl, alkyl, alkenyl, alkynyl, and combinations thereof.

The term “hydroxyalkyl”, as used herein, refers to an alkyl group substituted with a hydroxy group.

The term “lower” when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, 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 alkyl”, for example, refers to an alkyl group that contains ten or fewer carbon atoms, preferably six or fewer. In certain embodiments, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy
5 substituents defined herein are respectively lower acyl, lower acyloxy, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy, whether they appear alone or in combination with other substituents, such as in the recitations hydroxyalkyl and aralkyl (in which case, for example, the atoms within the aryl group are not counted when counting the carbon atoms in the alkyl substituent).

10 As used herein, “mitigating” means reducing the negative effects caused by 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.

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

15 The terms “polycyclyl”, “polycycle”, and “polycyclic” refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls) in which two or more atoms are common to two adjoining rings, e.g., the rings are “fused rings”. Each of the rings of the polycycle can be substituted or unsubstituted. In certain embodiments, each ring of the polycycle contains from 3 to 10 atoms in the ring, preferably
20 from 5 to 7. When a polycyclic substituent is attached through an aryl or heteroaryl ring, that substituent may be referred to herein as an aryl or heteroaryl group, while if the polycyclic substituent is attached through a cycloalkyl or heterocyclyl group, that substituent may be referred to herein as a cycloalkyl or heterocyclyl group. By way of example, a 1,2,3,4-tetrahydronaphthalen-1-yl group would be a cycloalkyl group, while a
25 1,2,3,4-tetrahydronaphthalen-5-yl group would be an aryl group.

The term “silyl” refers to a silicon moiety with three hydrocarbyl moieties attached thereto.

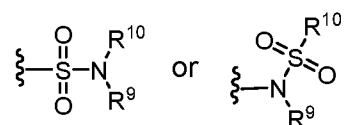
The term “substituted” refers to moieties having substituents replacing a hydrogen on one or more carbons or heteroatoms of the moiety. It will be understood that
30 “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the

term “substituted” is contemplated to include all permissible substituents of organic compounds.

In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, 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 alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate. Unless specifically stated as “unsubstituted,” references to chemical moieties herein are understood to include substituted variants. For example, reference to an “aryl” group or moiety implicitly includes both substituted and unsubstituted variants.

The term “sulfate” is art-recognized and refers to the group $-\text{OSO}_3\text{H}$, or a pharmaceutically acceptable salt thereof.

The term “sulfonamide” is art-recognized and refers to the group represented by the general formulae



wherein R^9 and R^{10} independently represents hydrogen or hydrocarbyl, such as alkyl, or R^9 and R^{10} taken together with the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

The term “sulfoxide” is art-recognized and refers to the group $-\text{S}(\text{O})-\text{R}^{10}$, wherein R^{10} represents a hydrocarbyl.

The term “sulfonate” is art-recognized and refers to the group SO_3H , or a pharmaceutically acceptable salt thereof.

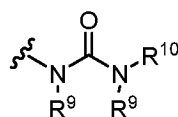
The term “sulfone” is art-recognized and refers to the group $-S(O)_2-R^{10}$, wherein R^{10} represents a hydrocarbyl.

5 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 $-C(O)SR^{10}$ or $-SC(O)R^{10}$ wherein R^{10} represents a hydrocarbyl.

The term “thioether”, as used herein, is equivalent to an ether, wherein the oxygen is replaced with a sulfur.

10 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 hydrocarbyl, such as alkyl, or either occurrence of R^9 taken together with R^{10} and the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

15 “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 to 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.

20 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). A common method for making a prodrug is to include one or more selected moieties which are hydrolyzed under physiologic conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity
25 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, some or all of the compounds of formula I in a formulation represented above can be replaced with the corresponding suitable prodrug, e.g., wherein a hydroxyl in the parent compound is presented as an ester or a carbonate or carboxylic acid present in the
30 parent compound is presented as an ester.

“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, trifluoroacetyl, benzyl, benzyloxycarbonyl ("CBZ"), tert-butoxycarbonyl ("Boc"), trimethylsilyl ("TMS"), 2-trimethylsilyl-ethanesulfonyl ("TES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl ("Fmoc"), nitro-veratryloxycarbonyl ("NVOC") and the like. Representative hydroxylprotecting groups include, but are not limited to, those where the hydroxyl group is either acylated (esterified) or alkylated such as benzyl and trityl ethers, as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers (e.g., TMS or TIPS groups), glycol ethers, such as ethylene glycol and propylene glycol derivatives and allyl ethers.

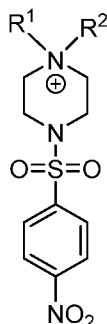
As used herein, a therapeutic that "prevents" a disorder or condition refers to a compound that, in a statistical sample, reduces the occurrence of the disorder or condition in the treated sample relative to an untreated control sample, or delays the onset or reduces the severity of one or more symptoms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

Compounds

In certain embodiments, the invention relates to compounds having the structure of
5 Formula I:

Formula I

wherein each of R¹ and R², independently, is substituted or unsubstituted alkyl, aryl,
10 heteroaryl, aralkyl, or heteroaralkyl or a pharmaceutically acceptable salt thereof.
Preferably, R¹ is substituted or unsubstituted alkyl, aralkyl, or heteroaralkyl, most
preferably substituted or unsubstituted lower alkyl, such as methyl. In certain embodiments,
R² is aryl, such as phenyl. In certain embodiments, R¹ is substituted or unsubstituted lower
alkyl and R² is aryl. In certain embodiments, R¹ is methyl and R² is phenyl.

15 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
20 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
25 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. In these embodiments, the compound may be associated with a suitable counter-ion (e.g., I⁻, Br⁻, Cl⁻, CF₃SO₃⁻). In some embodiments, 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. 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 or may be exchanged for a pharmaceutically acceptable counter-ion, for administration to a subject. Pharmaceutically acceptable salts are discussed later.

In certain embodiments, compounds of the invention may be prodrugs of the compounds of Formula I, 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 *in 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 stereocenter. In certain such embodiments, compounds of the invention may be enriched in one or more diastereomer. 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 I, 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 I). 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 I). 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 I, 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 I). 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 I). 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 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 I), 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
5 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.

Pharmaceutical Compositions

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

Embodiments of the invention include pharmaceutical compositions of compounds
15 of Formula I 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
20 compound of the invention, 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
25 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
30 modulator and/or other pharmaceutically active agent in a physiologically-acceptable carrier. 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 intraperitoneally) 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, Lippincott Williams & Wilkins, 2000 and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 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 composition(s) are dissolved or suspended in a parenterally acceptable liquid vehicle. Among acceptable 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, 1,3-butanediol, Ringer's solution, and isotonic sodium chloride solution and dextrose solution. The aqueous formulation 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 microparticulate 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, intra-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 ingredient(s) 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 phosphate, calcium sulfate, or sodium phosphate); granulating and disintegrating agents (e.g., cellulose derivatives including microcrystalline cellulose, starches including potato starch, croscarmellose sodium, alginates, or alginic acid); binding agents (e.g., sucrose, glucose, sorbitol, acacia, alginic acid, sodium alginate, gelatin, starch, pregelatinized starch, microcrystalline cellulose, magnesium aluminum silicate, carboxymethylcellulose sodium, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, 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, humectants, 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 ingredient(s) 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 carboxylic 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 thixotropic 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 ingredient(s) 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 release 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 (i) 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 which 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, nanoparticles, 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 biomolecule, such as those selected from proteins, lipoproteins, glycoproteins, and polysaccharides.

In some embodiments, the composition can be incorporated into microspheres, microcapsules, nanoparticles, liposomes, or the like for controlled release. Furthermore, the composition may include suspending, solubilizing, 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 are, e.g., biodegradable/bioerodible polymers such as polygalactin, poly-(isobutyl cyanoacrylate), poly(2-hydroxyethyl-L-glutamine) and, poly(lactic 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., polydimethyl siloxane) or biodegradable (e.g., poly(caprolactone), poly(lactic acid), poly(glycolic acid) or poly(ortho esters) or combinations thereof).

In all embodiments, the compound or other 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, diastereomers, 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 regiospecific 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 limited to, acid addition salts, such as those made with hydrochloric, hydrobromic, hydroiodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic pyruvic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, carbonic, cinnamic, mandelic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, benzenesulfonic, p-toluene sulfonic, cyclohexanesulfamic, salicylic, p-aminosalicylic, 2-phenoxybenzoic, and 2-acetoxybenzoic 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 not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide 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: (1) water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal-chelating agents, such as citric acid, ethylenediamine tetraacetic 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 blood 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 full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same.

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.

5 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 required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. By
10 “therapeutically effective amount” is meant the concentration of a compound that is sufficient to elicit the desired therapeutic effect. It is generally understood 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
15 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).

20 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
25 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 carried 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
30 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 this 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.

Methods

Radiomitigation

In certain aspects, the invention provides a method 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 of the invention (e.g., a compound of Formula I) or composition disclosed herein. The cell, organ, tissue, or organism may be contacted with a compound or composition of the invention before, during, or after exposure to ionizing radiation. In certain embodiments, the compounds of Formula I mitigate tissue damage induced by exposure to ionizing radiation.

The cell, organ, tissue, or organism may be contacted with a compound of the invention before, during, or after exposure to ionizing radiation. In some embodiments, the compound may be administered prophylactically, 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 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 mitigators. In certain embodiments, compounds of Formula I are administered in conjunction with other therapies, such as radiation therapy.

The organism may be any subject 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 cell 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.

Inflammation

In certain aspects, the invention provides methods for treating or preventing 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, scleritis, 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 dermatitides, 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, burns, bullous disorders, or ischemia of the skin or mucous membranes, several forms of ichthyoses, epidermolysis bullosae, hypertrophic scars, keloids, cutaneous changes of intrinsic aging, photoaging, frictional 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, atherosclerosis, 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

In certain aspects, the invention provides methods for treating or preventing cancer. The actual symptoms associated with cancer are well known and can be determined by a person of ordinary skill in the art by taking into account one or more factors, including, without limitation, the 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 will know how to determine if an individual is a candidate for treatment as disclosed herein.

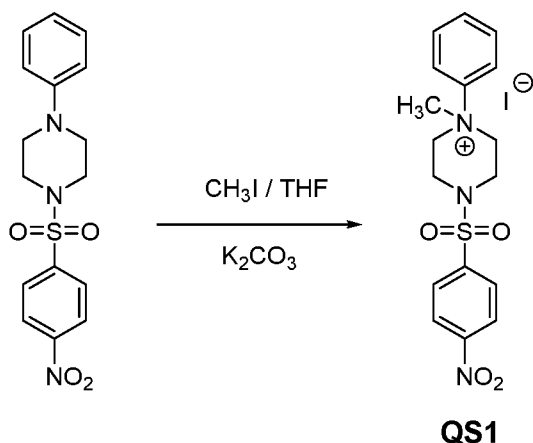
Exemplary forms of cancer which may be treated by the subject methods include, but are not limited to, leukemia, non-Hodgkin's lymphoma, prostate cancer, bladder cancer, lung cancer (including either small cell or non-small cell cancer), colon cancer, kidney cancer, liver cancer, breast cancer, cervical cancer, endometrial or other uterine cancer, ovarian cancer, skin cancer (e.g., melanoma), testicular cancer, cancer of the 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.

EXEMPLIFICATION

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.

Example 1 - Synthesis of QS1

Scheme 1



5

Briefly, 3.47 g (0.01 mole) of 1-[(4-nitrophenyl)sulfonyl]-4-phenylpiperazine (MW=347.39 g/mole) (see International Publication No. WO 2014/182789) was placed in 250 mL round bottom flask equipped with magnetic stirrer. Then, 100 mL of anhydrous tetrahydrofuran (THF), 6.3 mL of iodomethane (MW=141.94 g/mole, d=2.28 g/mL) and 6.9 g of anhydrous anhydrous potassium carbonate (K₂CO₃, MW=138.21 g/mole) were added and the reaction mixture was agitated for 48 h. Subsequently, non-soluble K₂CO₃ was filtered off and remaining filtrate evaporated using rotary evaporator (bath temp 35 °C). Remaining residue was extracted with water (5 x 30 mL) and combined extracts freeze-dried. Obtained solid residue was purified using semi-preparative RP-HPLC giving 1.6 g of QS1 (MW=489.33 g/mole) (yield=32.8%).

10

15

Analytical RP-HPLC was performed on a Varian ProStar 210 HPLC system equipped with ProStar 325 Dual Wavelength UVVis detector with the wavelengths set at 220 nm and 280 nm (Varian Inc., Palo Alto, CA). Mobile phases consisted of solvent A, 0.1% TFA in water, and solvent B, 0.1% TFA in acetonitrile. Analysis was performed with an analytical reversed-phase C4 XBridge™ BEH300 column, 4.6×150 mm, 3.5 μm (Waters, Milford, MA), applying linear gradient of solvent B from 0 to 100% over 100 min (flow rate: 1 ml/min). MS: *m/z* 361.54. ¹H NMR (400MHz, (CD₃)₂SO): 8.38 (d, 2H), 8.0 (d, 2H), 7.82 (d, 2H), 7.59 (m, 2H) 7.50 (m, 1H), 4.41 (m, 2H), 4.09 (m, 2H), 3.68 (m, 2H), 3.4 (m, 3H), 3.17 (m, 2H) ppm.

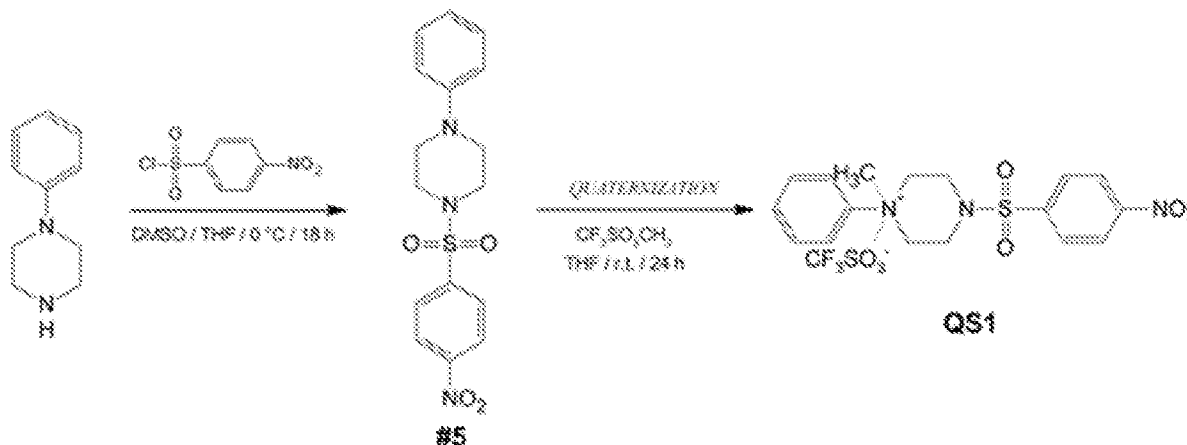
20

25

In a similar fashion, the triflate of QS1 was synthesized in a 10g quantity as outlined in Scheme 2.

5

Scheme 2



Example 2 - *In vivo* Mitigation of Effects of Total Body Irradiation

10

Compound QS1 was tested *in vivo* for its ability to mitigate against lethality from total body irradiation (TBI). Briefly, animal TBI assays were conducted with C3Hf/Kam mice. Mice, 9–12 weeks old, were given TBI using a Gamma cell 40 irradiator (Cs137 source; Atomic Energy of Canada, Ltd.) at a dose rate of 61 Gy/min. Mice were monitored for at least 30 days and defined criteria for humane euthanasia was used as an endpoint.

15

Compound QS1 was dissolved in water for administration in 0.2mL volumes. All mice, including controls, received the same diluent as the experimental groups. Compound QS1 was administered, via subcutaneous injection, to the mice 5 times at 24h intervals, starting 24 hours after TBI at LD70/30 (7.725 Gy for the C3H strain) doses. Compound QS1 provided greatly elevated animals survival level as compared to control group (see Figure 1).

20

Example 3 - Radiomitigation Effects of QS1 on survival

25

The optimal dose of QS1 for mitigation of hematopoietic lethality (hARS) in gnotobiotic C3H/Sed male mice from the UCLA-Product Testing Core (9 weeks old, 8 animals per group) was determined following LD70/30 doses of whole body irradiation (WBI). QS1 was s.c. injected daily for 5 days, starting at 24 hours after WBI, within a dose

range of 1–20 mg/kg; in water. Mice were weighed every 2-3 days throughout the course to assess toxicity. The endpoint was lethality at day 30.

To establish the optimal treatment regimen, both multiple doses daily injection schedule (5x) as well as single dose (1x) of QS1 were performed. Based on initial drug dose response trials, the dose of 5 mg/kg was the most effective in mice and thus this was the dose chosen for the single treatment. As depicted in Figure 7, even the single dose of QS1 administered 24h after radiation seems to work at least partially effective.

To determine if QS1 could be given orally, both multiple doses as well as single dose of QS1 were administered. Again, the dose of 5 mg/kg was chosen. For this delivery route, the multiple dose arrangement was more successful. (See Figures 8 and 9)

The ability of QS1 to mitigate pneumonitis in C3H mice and late fibrosis in C57Bl/6 mice after local thoracic irradiation (LTI) was tested (Figures 10-15), as was its ability to mitigate intestinal acute radiation syndrome (I-ARS) in both C3H and C57Bl/6 mice, which appears as lethality between 7 and 12 days after local abdominal irradiation (Figures 16 and 17). Some activity was seen against pneumonitis and I-ARS, but not fibrosis.

Example 4 - Pharmacological kinetics of QS1

The fundamental pharmacokinetic (PK) parameters were assessed using LC/MS/MS methodology, specifically a Multiple Reaction Monitoring (MRM) approach. C3H/Sed male mice were treated s.c. with a dose of QS1 of 10 mg/kg for this purpose. Non-irradiated and WBI (LD_{70/30}) mice received QS1 (sc injections). QS1 given either 24h or 72 h after WBI. Blood was collected frequently over a 24h period, and QS1 level in plasma measured. As shown in Figure 18 and 19, QS1 could not be detected in plasma for longer than 3-4 h after injection, in keeping with its solubility and small size.

Example 5 - Effect of QS1 on cell viability

Detection of apoptosis using flow cytometry. To measure apoptosis, or programmed cell death, the Annexin/PI assay was implemented. This assay does only distinguishes when cells are tracked from Annexin V and PI negative (viable, or no measurable apoptosis), to Annexin V positive and PI negative (early apoptosis with intact membranes), and finally to Annexin V and PI positive (end stage apoptosis and death). As seen in Figure 20, Til-1, murine lymphoma cells, were co-cultured with different concentration of QS1 for 24 (data shown) or 48h after 2Gy irradiation; the percent of Annexin V and PI positive population was determined by flow cytometry. Figures 21 and

22 summarize the percentage for every row of Figure 20. Compared to control (non-treated cells), QS1 is anti-apoptotic, with a dose response curve at 24h. By 48h, the effect is swamped by overcrowded dying cells.

5 **Quantitative evaluation of proliferation and cytotoxicity of cultured mammalian cells.** Adenosine TriPhosphate (ATP) is a marker for cell viability that can be monitored by a luminescence assay. Its concentration declines very rapidly when the cells undergo necrosis or apoptosis. As summarized in Figures 23 and 24, Til-1 were co-cultured with different concentrations (1, 10 or 25uM) of QS1 for 6, 24 or 48h after 2Gy irradiation, +/- LPS cells stimulation. While little or no changes were observed at 6h timepoint, at 24h low, but typical for this assay in our hands, increase of viability in cells treated with QS1 in comparison to control, non-treated cells was observe. At 48h the effect is declined, probably because of excess necrosis.

15 **To deeper evaluate the apoptosis in mammalian cells, the Caspase-Glo® 3/7 and Caspase-Glo® 9 assays were performed.** The luminescent assay measures caspase-3 and -7 or -9 activities. These members of the cysteine aspartic acid-specific protease (caspase) family play key effector roles in apoptosis. Luminescent signal, generated by caspase cleavage is proportional to the amount of caspase activity present. As shown in Figures 25-28, Til-1 cells, were co-cultured with different concentrations (1, 10 or 25uM) of QS1 for 6, 24 or 72h after 2Gy irradiation. Caspase 3/7 activity was not observed during chosen time points, but there is a dose response observed in caspase 9 at 72h post radiation, showing less apoptotic cells with QS1 treated conditions.

25 **Mechanism of action.** Previous flow cytometry studies showed that treatment of mice or macrophages with the parent compound (#5) suppressed ionizing radiation driven pro-inflammatory response, and increased the representation of the CD11b⁺Ly6G⁺Ly6C⁺ cell population in the spleen, blood, and bone marrow, and this immature myeloid cell population is crucial for mitigation with #5. QS1 influenced myeloid cell reprogramming in a similar way, flow cytometry was adapted to evaluate the percent in myeloid subsets in blood, bone marrow, and spleen, with emphasis on the CD11b⁺Ly6G⁺Ly6C⁺ cells that are required for activity of the parent molecule.

30 As described herein, all embodiments or subcombinations may be used in combination with all 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 may be modified or varied, without departing from
5 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
10 in their entirety as if each individual 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.

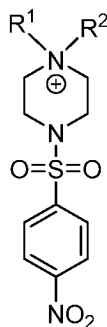
Equivalents

While specific embodiments of the subject invention have been discussed, the above
15 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 claims 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.

20

We Claim

1. A compound having the structure of Formula I:



Formula I

wherein each of R¹ and R², independently, is substituted or unsubstituted alkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein R¹ is substituted or unsubstituted lower alkyl.

3. The compound of claim 1, wherein R¹ is methyl, ethyl, propyl, butyl, or pentanyl.

4. The compound of claim 1, wherein R¹ is methyl.

5. The compound of any one of claims 1 to 4, wherein R² is aryl.

6. The compound of claim 5, wherein R² is phenyl.

7. The compound of claim 1, wherein R¹ is methyl and R² is phenyl.

8. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof of any preceding claim and a pharmaceutically acceptable excipient or solvent.

9. A method of mitigating an effect of ionizing radiation on a cell, organ, tissue, or organism, comprising contacting the cell, organ, tissue, or organism with at least one

compound or a pharmaceutically acceptable salt thereof or composition of any preceding claim.

5 10. The method of claim 9, wherein the compound or composition is administered before, during, or after exposure to ionizing radiation.

11. A method of treating inflammation in an organism, comprising administering to the organism a compound of any one of claims 1-7 or a pharmaceutically acceptable salt thereof or a composition of claim 8.

12. The method of claim 11, wherein the inflammation is inflammation of the lungs.

10 13. A method of treating cancer in an organism, comprising administering to the organism a compound of any one of claims 1-7 or a pharmaceutically acceptable salt thereof or a composition of claim 8.

14. The method of any one of claims 9-13, wherein the organism is a mammal.

15 15. The method of claim 14, wherein the mammal is a human.

Figure 1

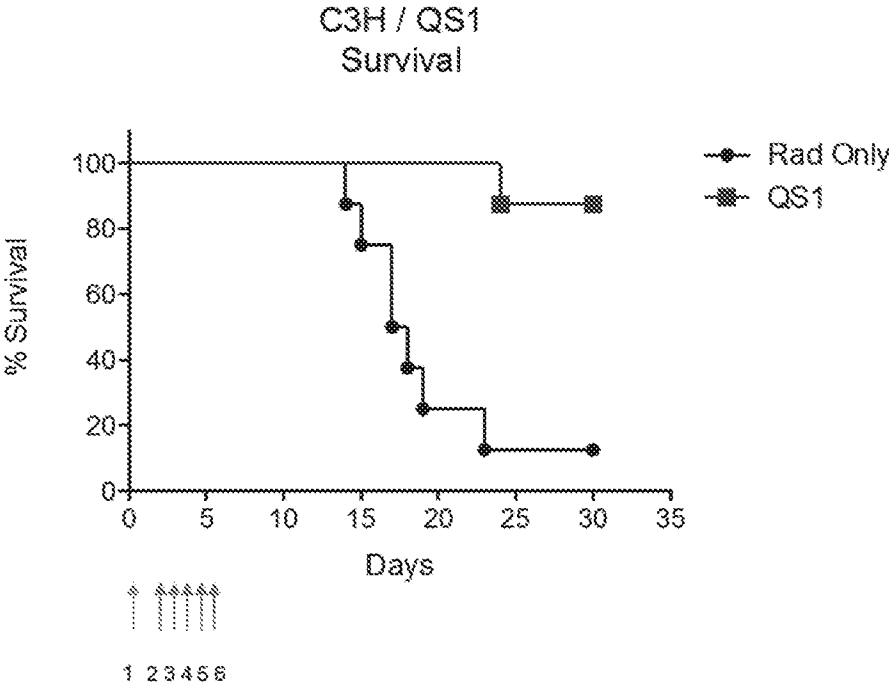


Figure 2

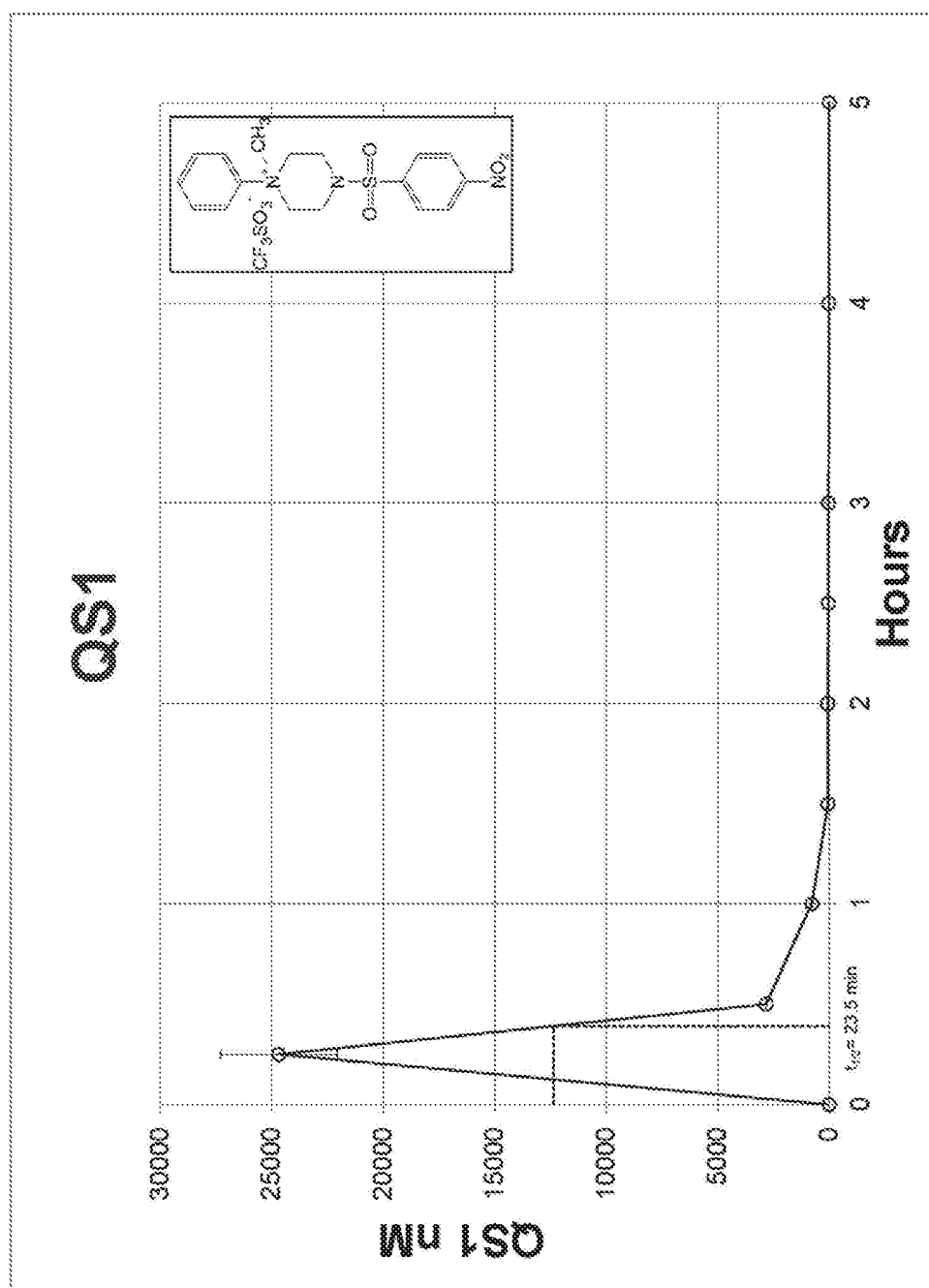


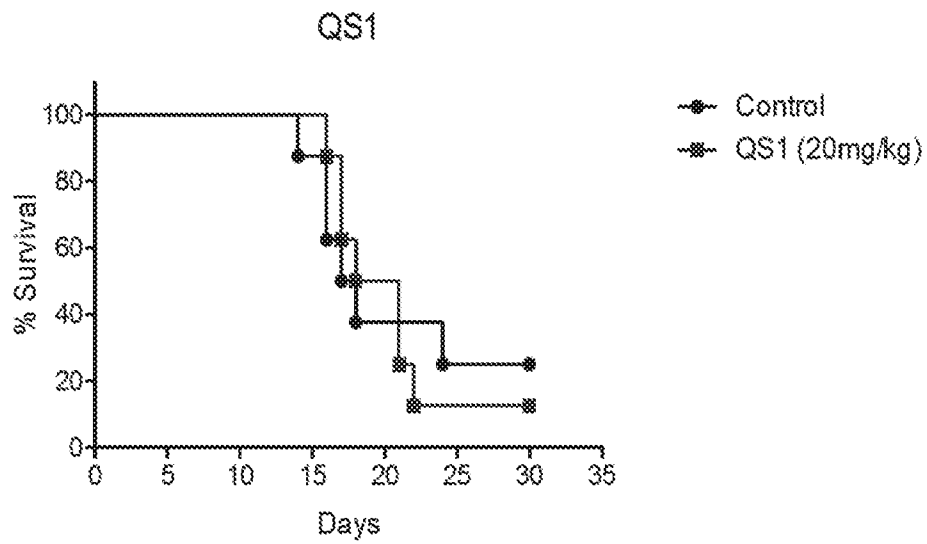
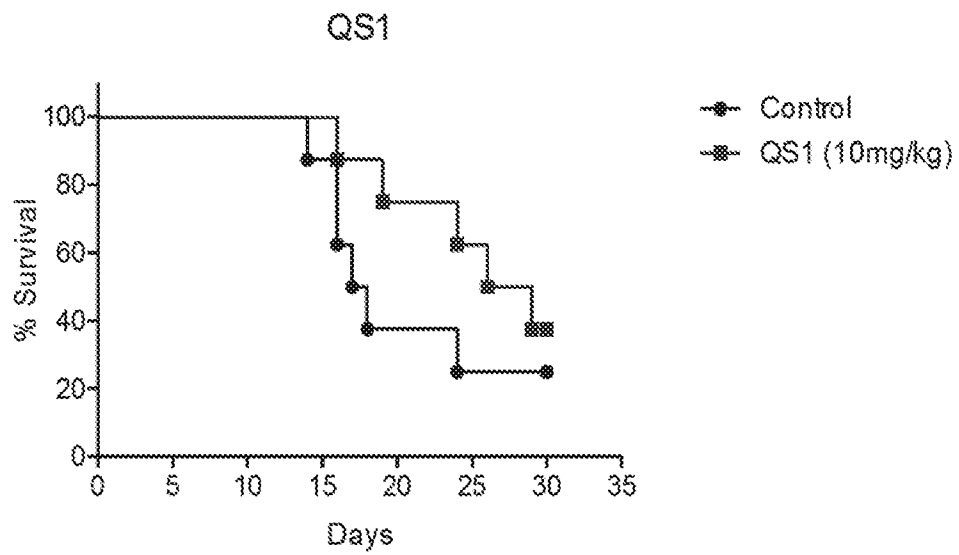
Figure 3**Figure 4**

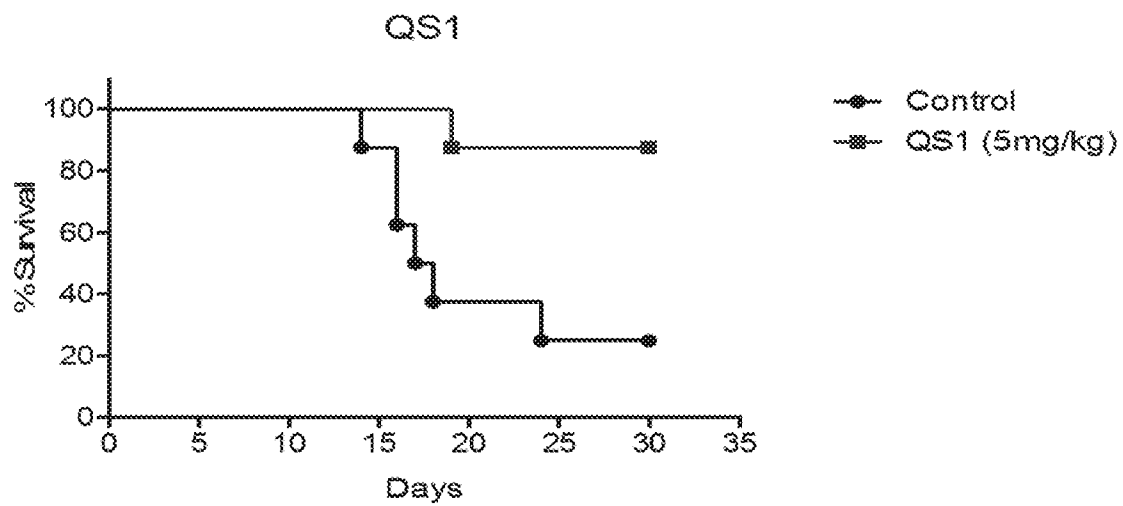
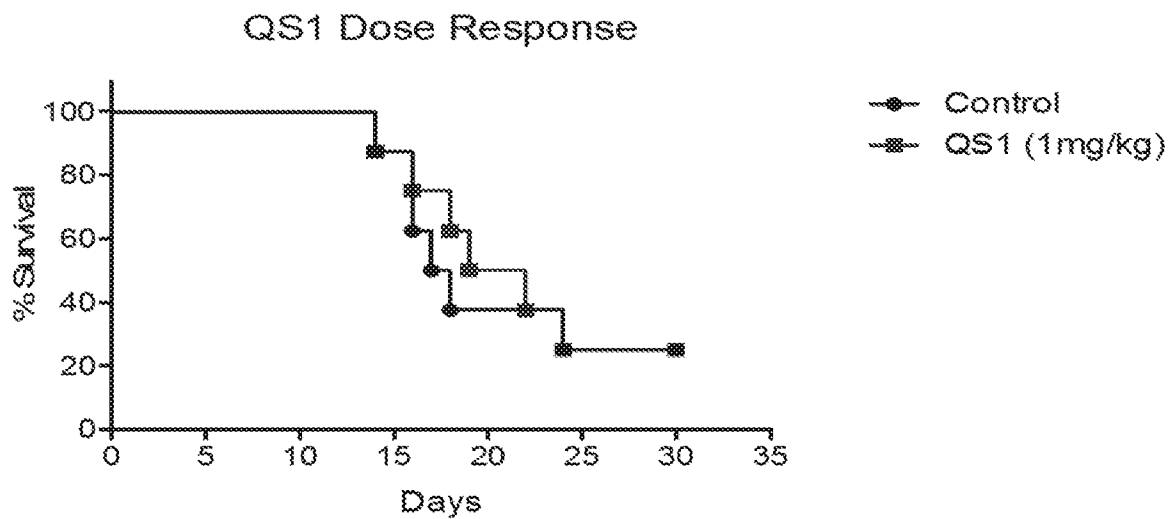
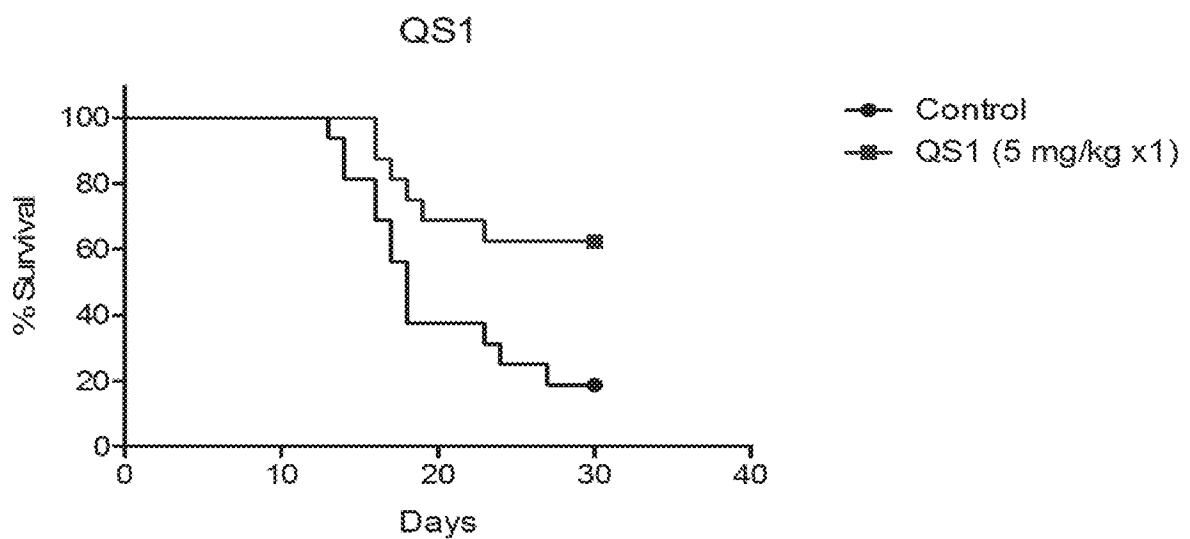
Figure 5**Figure 6****Figure 7**

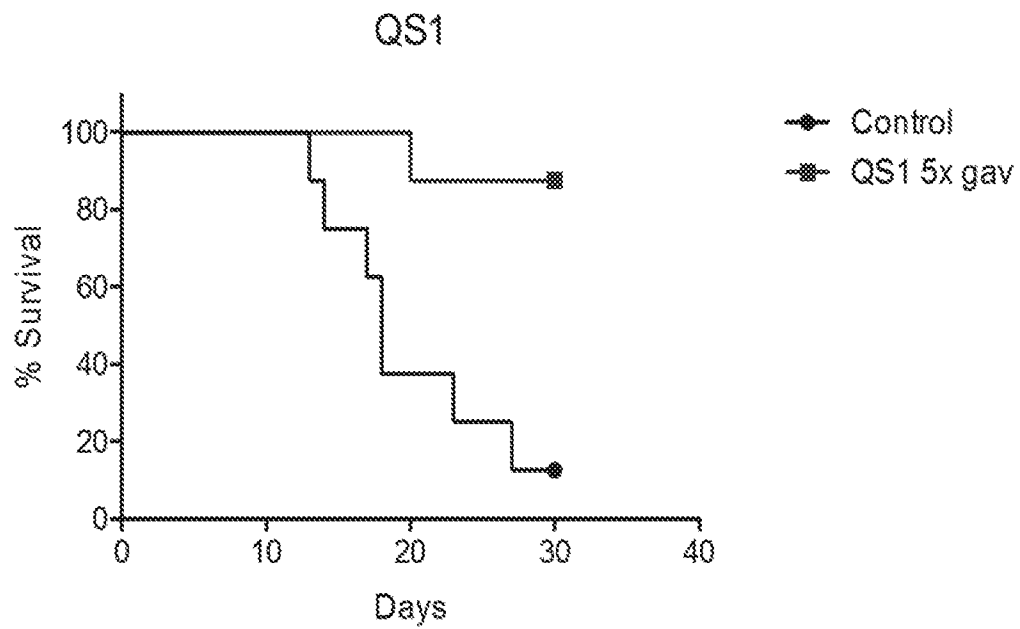
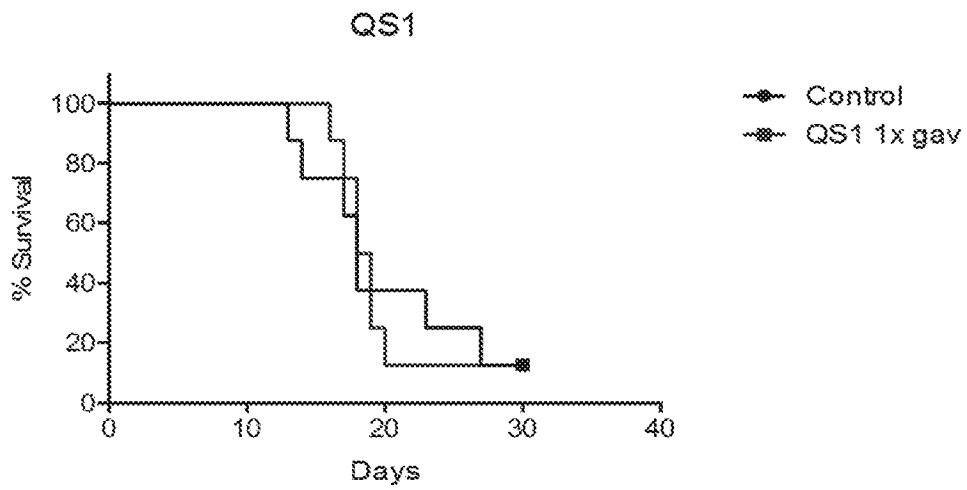
Figure 8**Figure 9**

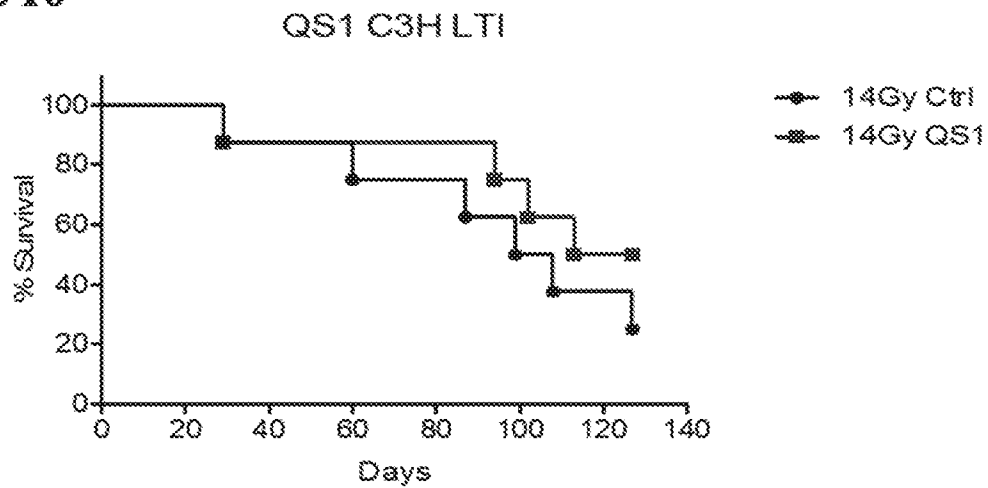
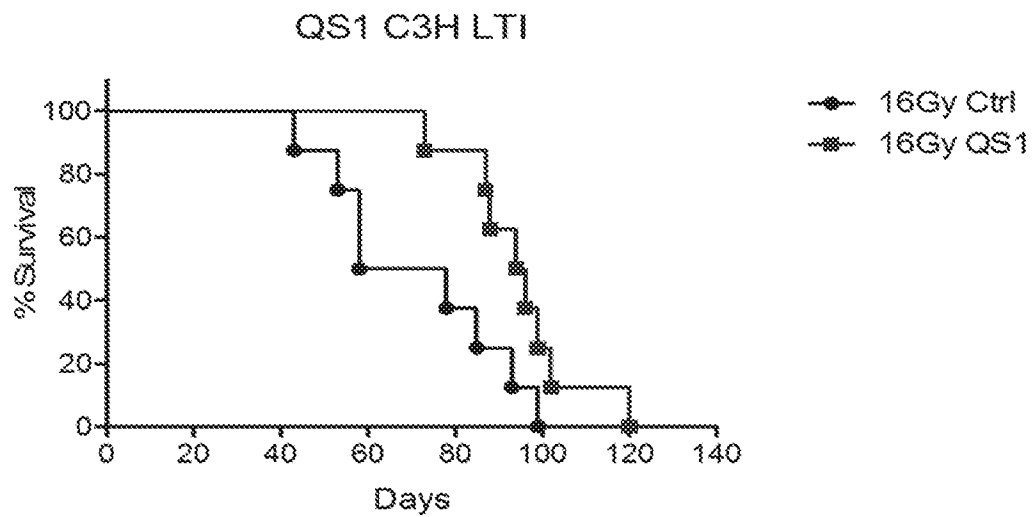
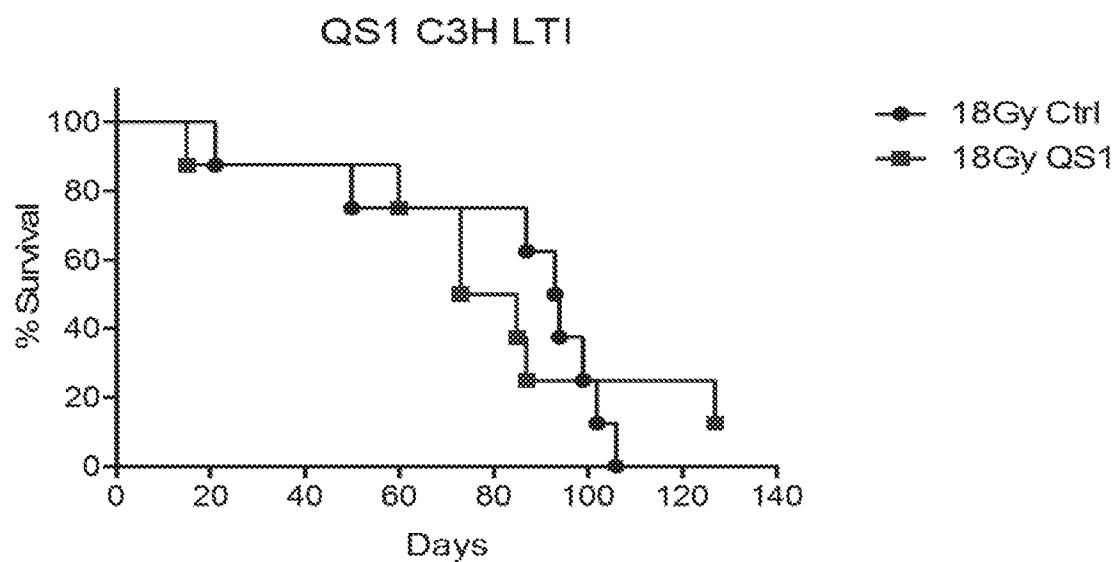
Figure 10**Figure 11****Figure 12**

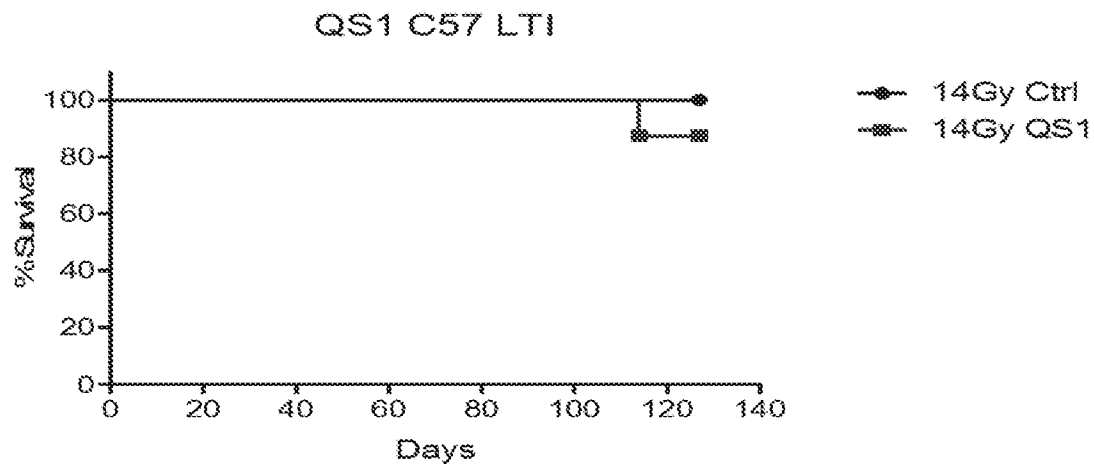
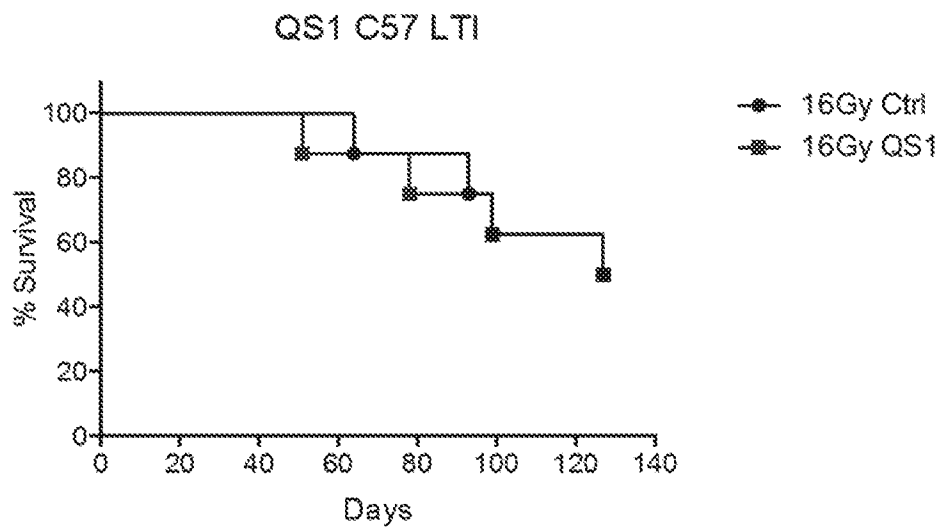
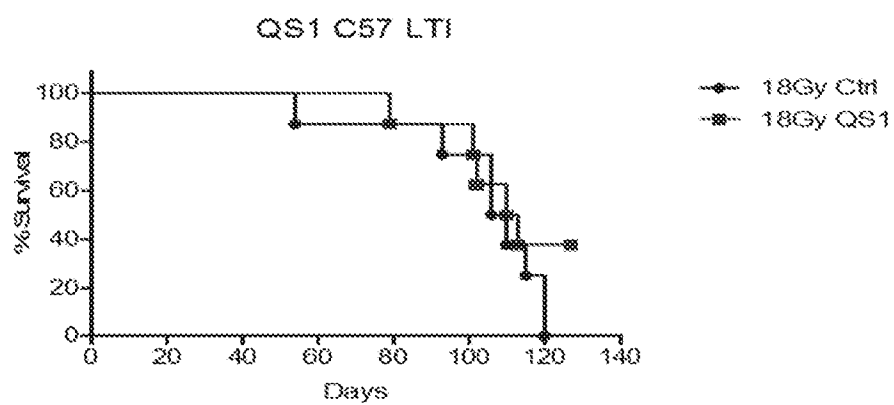
Figure 13**Figure 14****Figure 15**

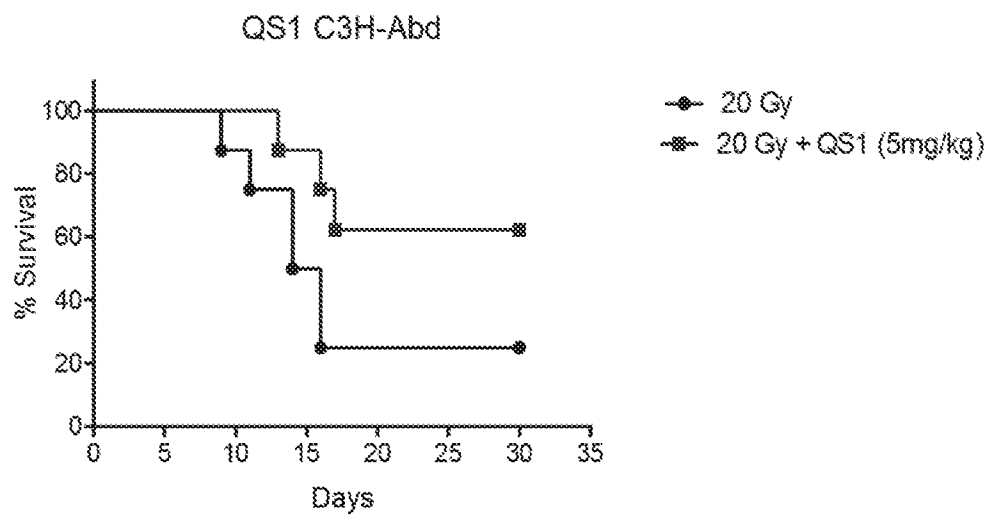
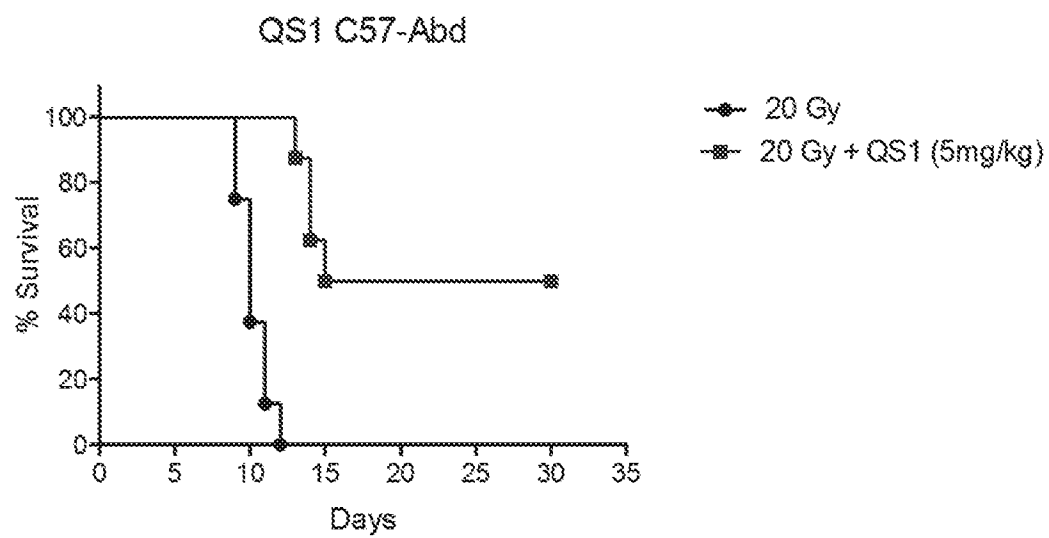
Figure 16**Figure 17**

Figure 18

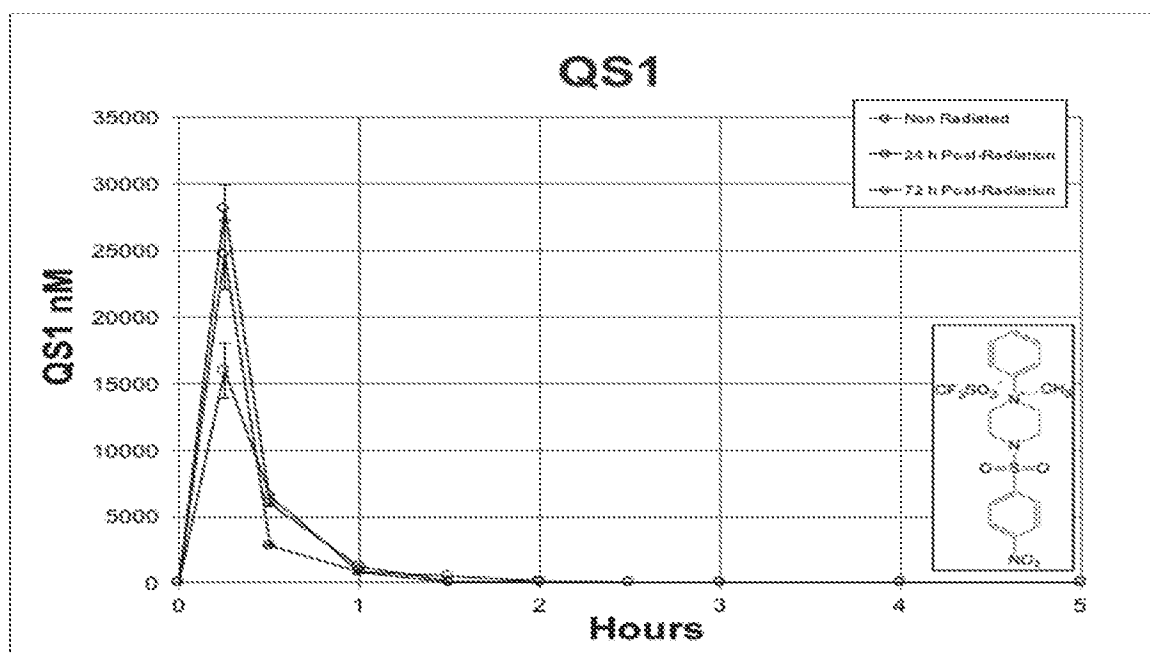


Figure 19

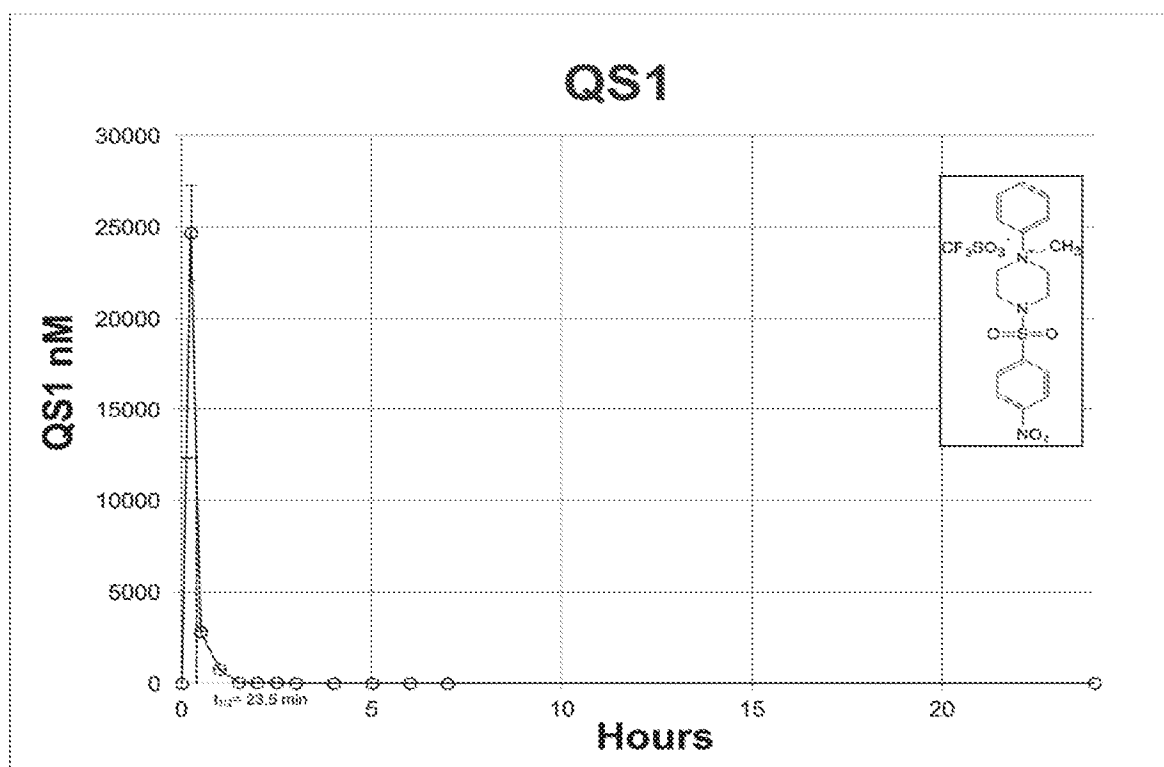


Figure 20

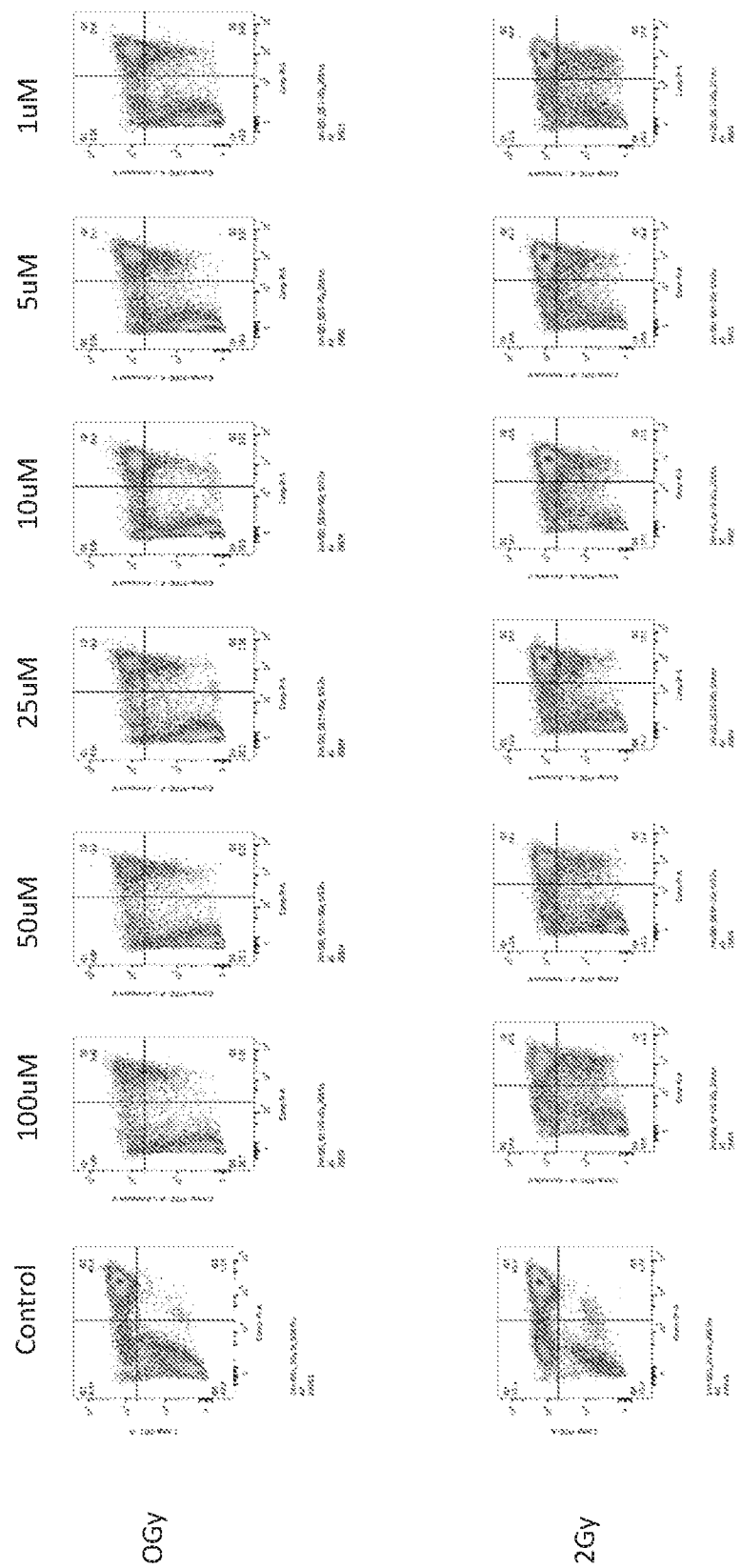


Figure 21

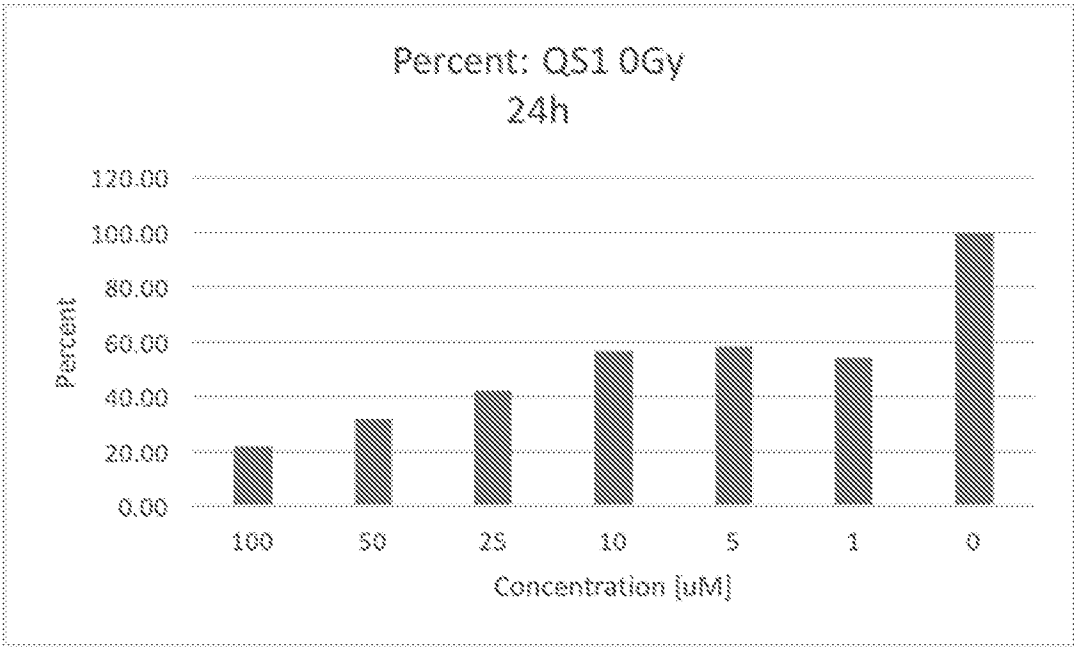


Figure 22

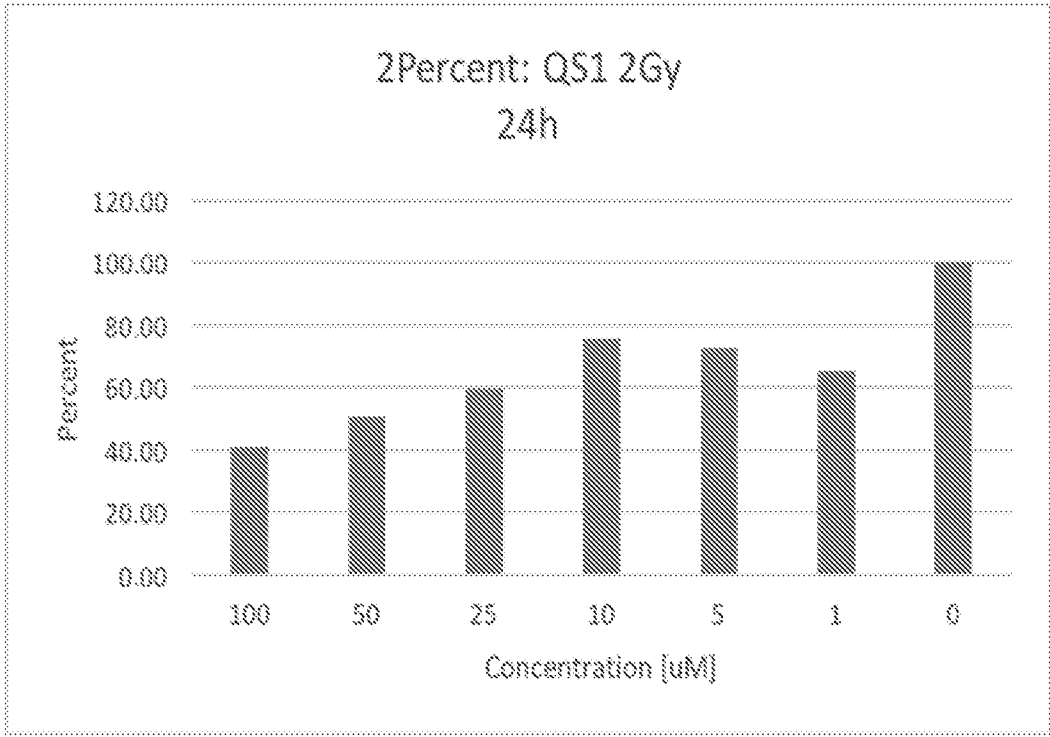


Figure 23

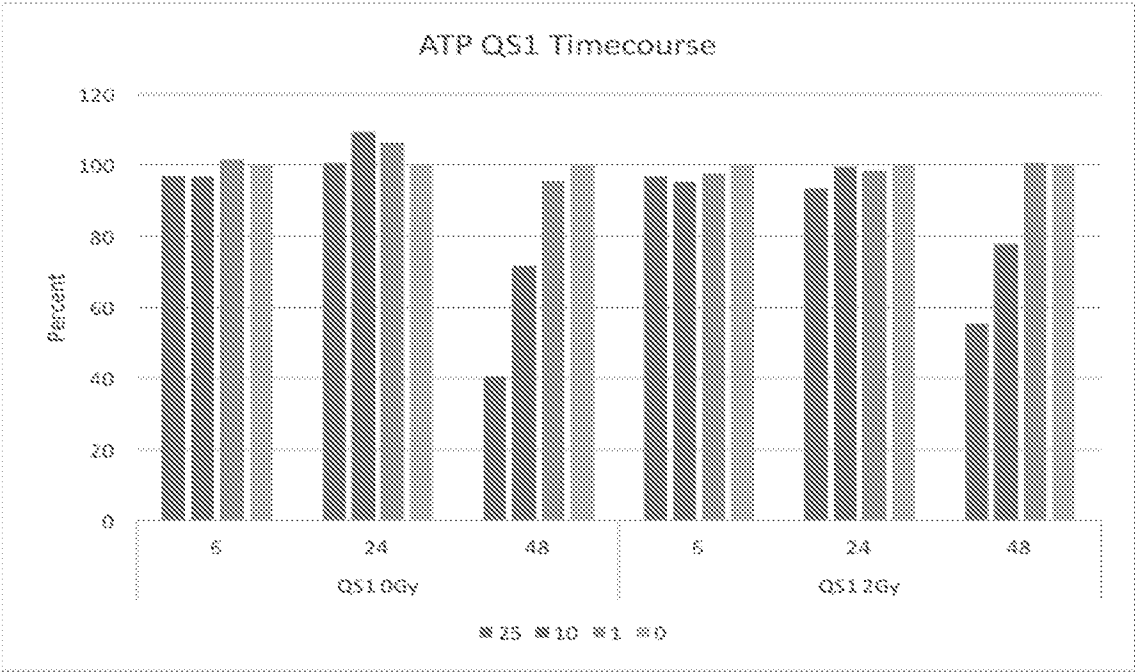


Figure 24

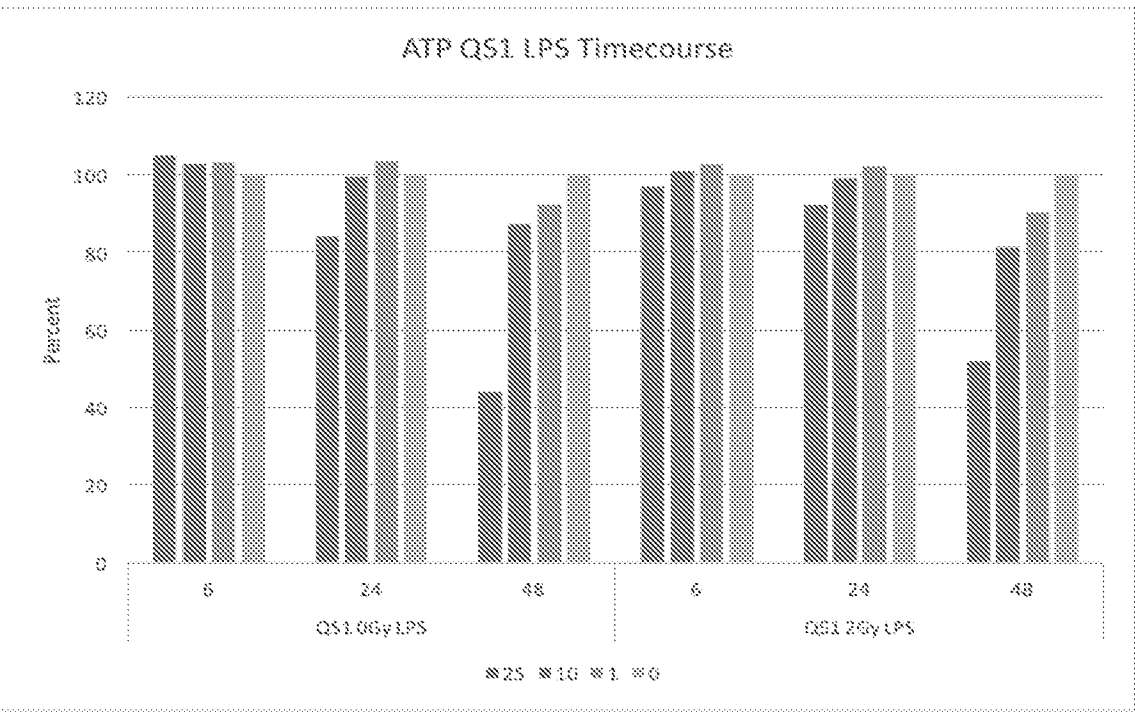


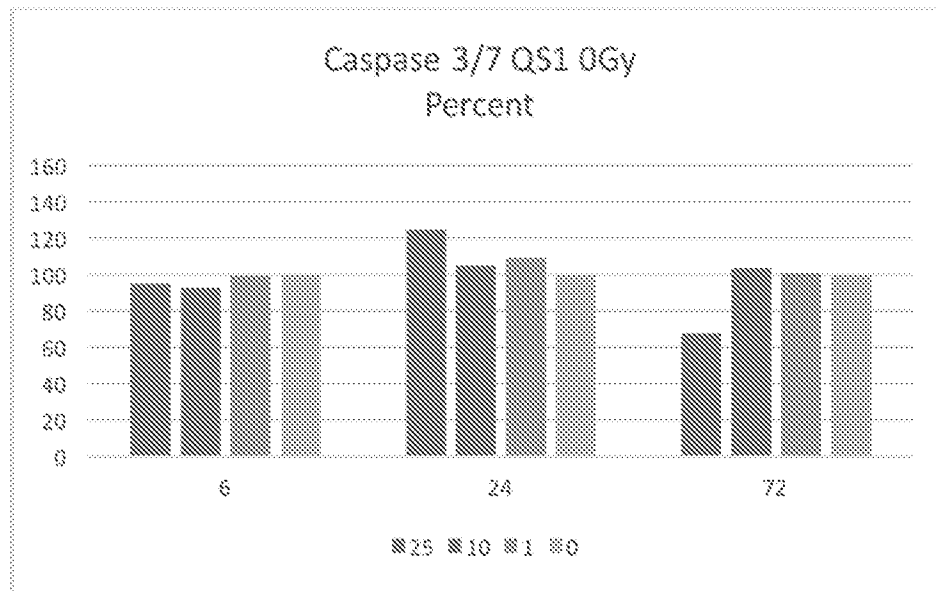
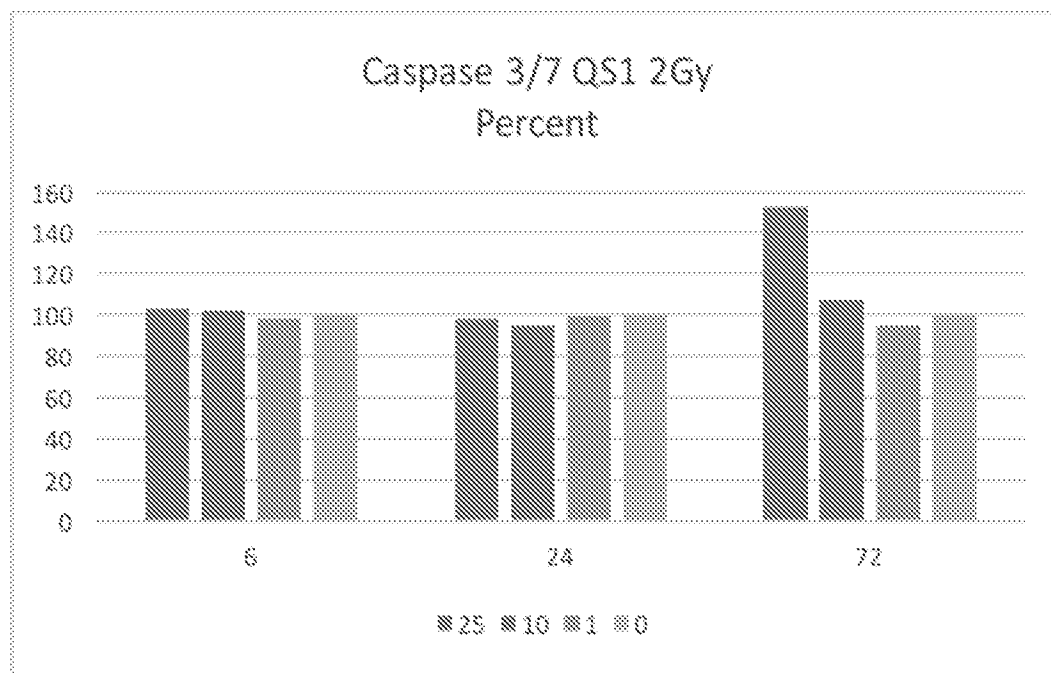
Figure 25**Figure 26**

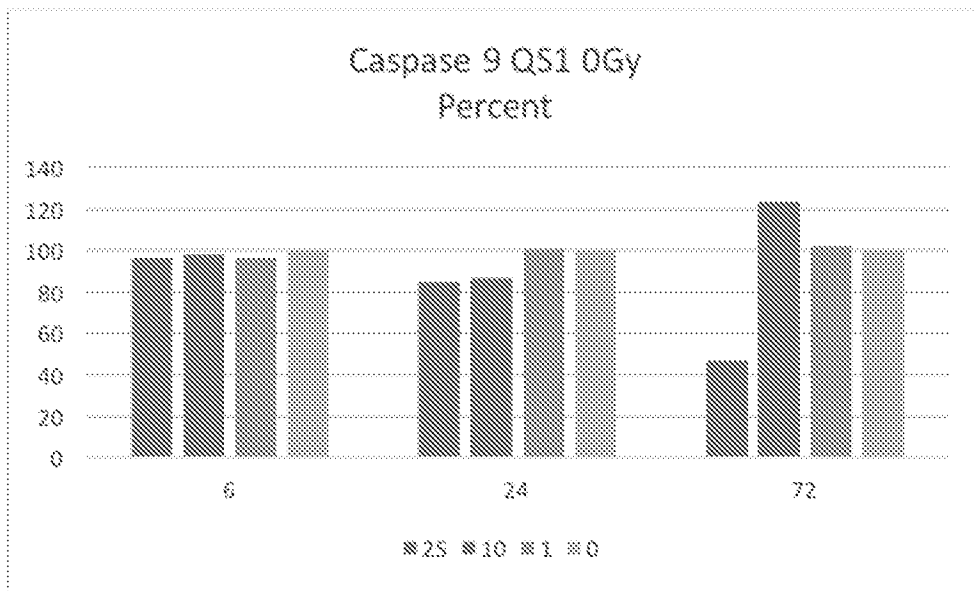
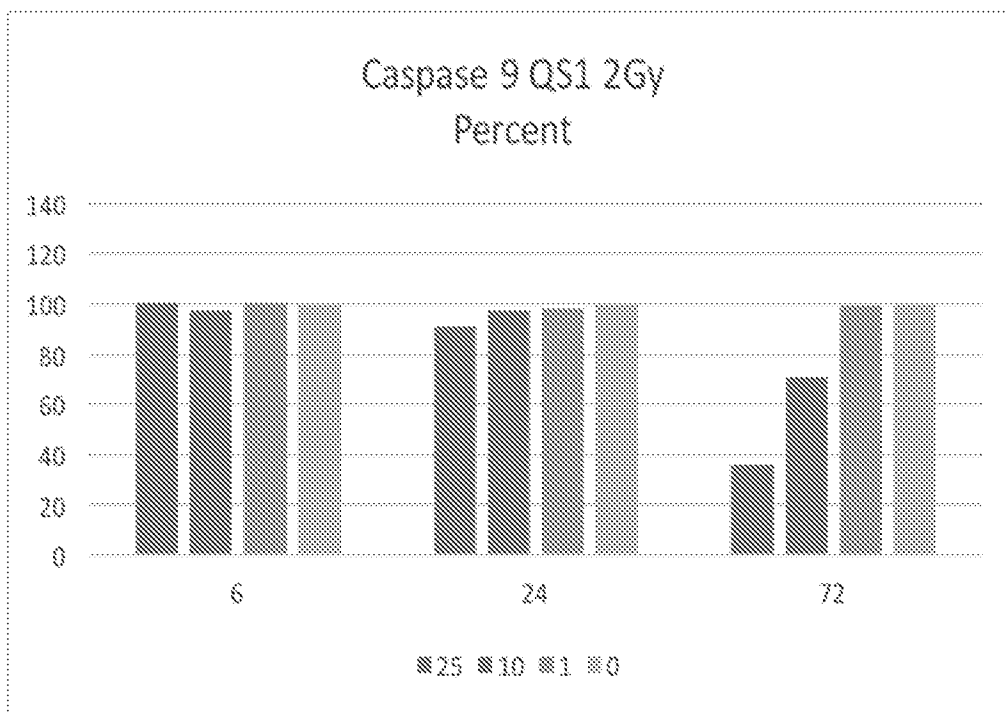
Figure 27**Figure 28**

Figure 29

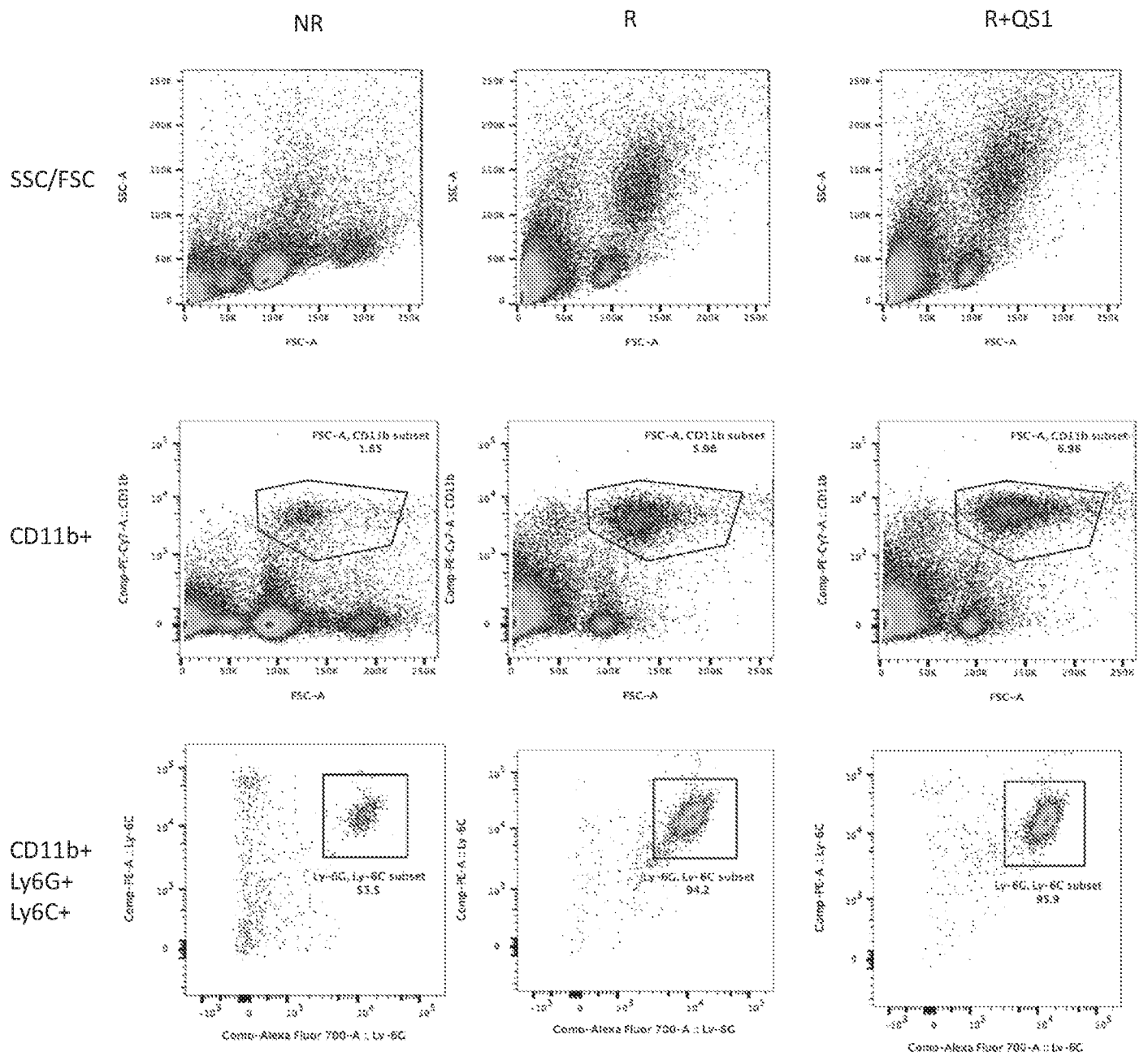


Figure 30

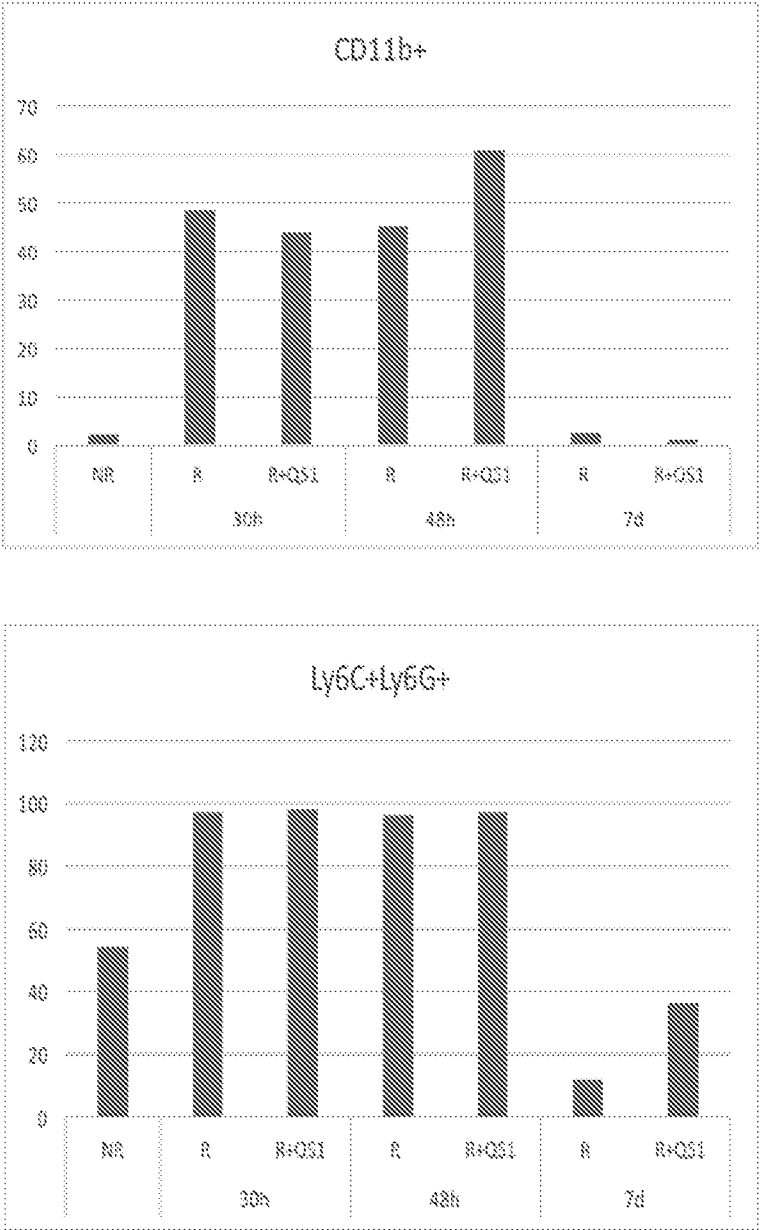


Figure 31

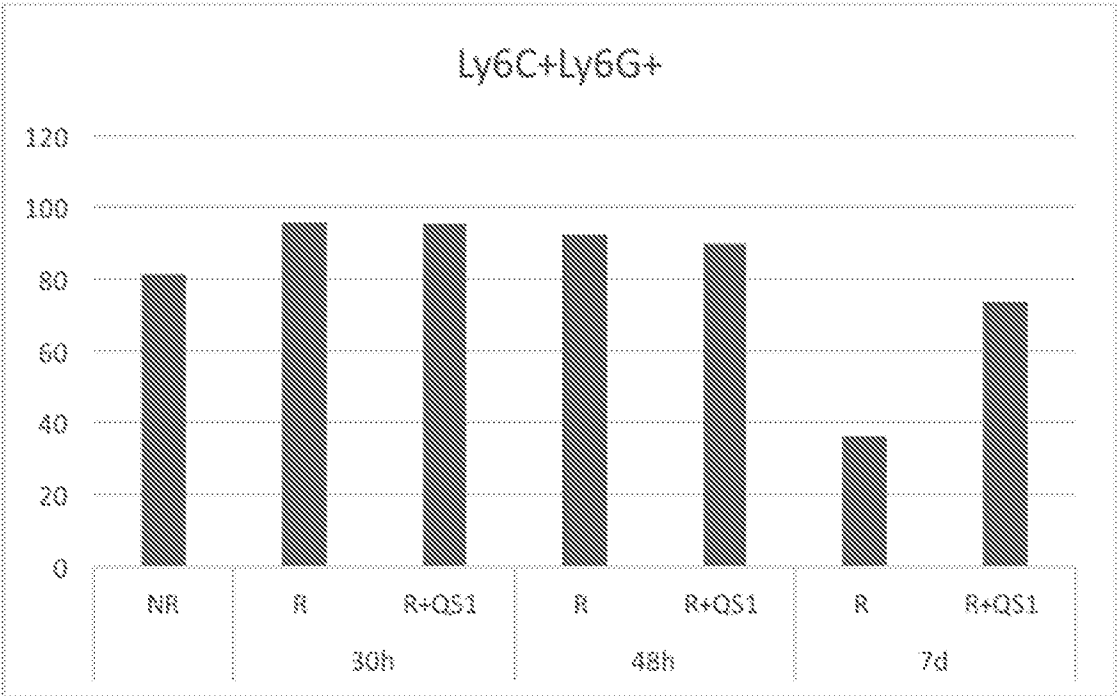
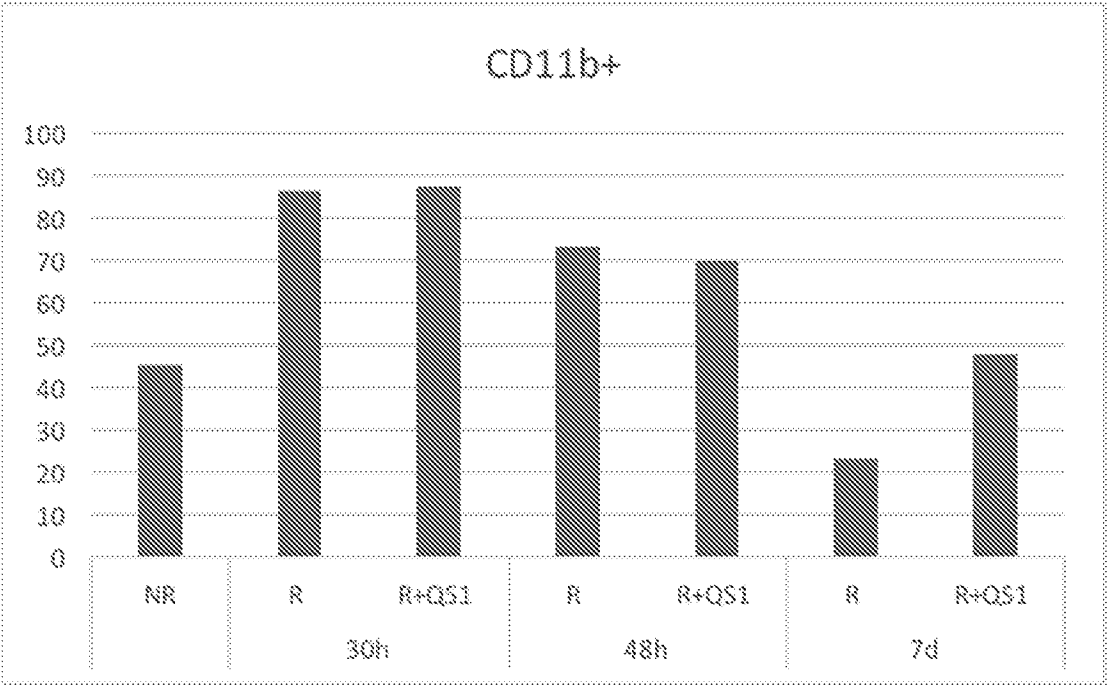
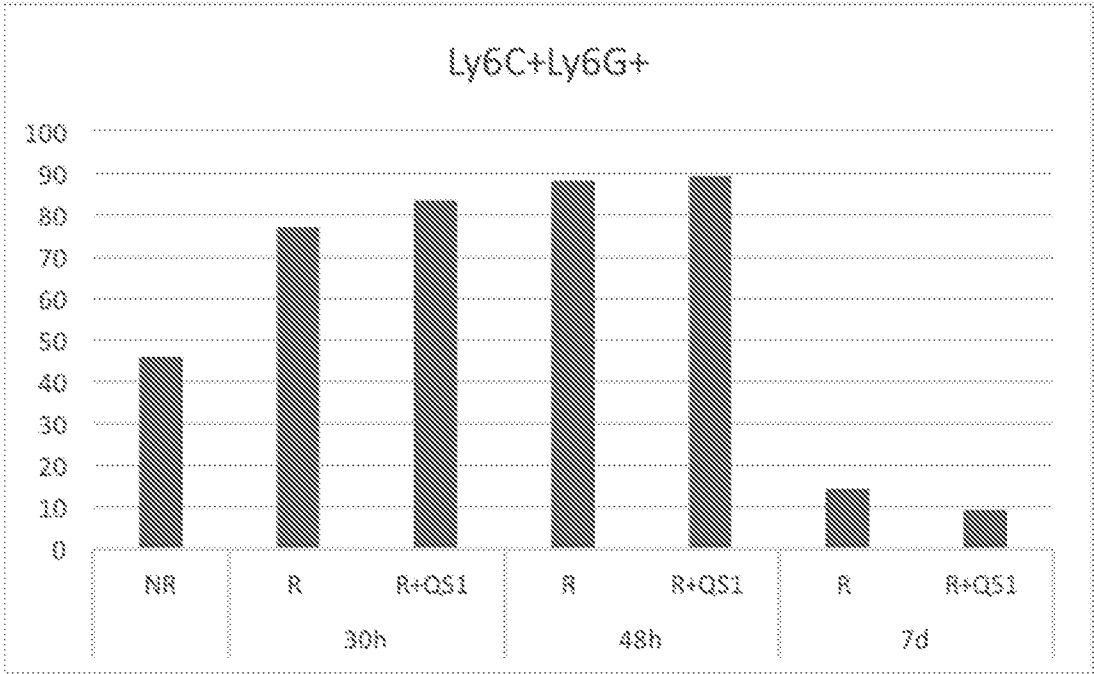
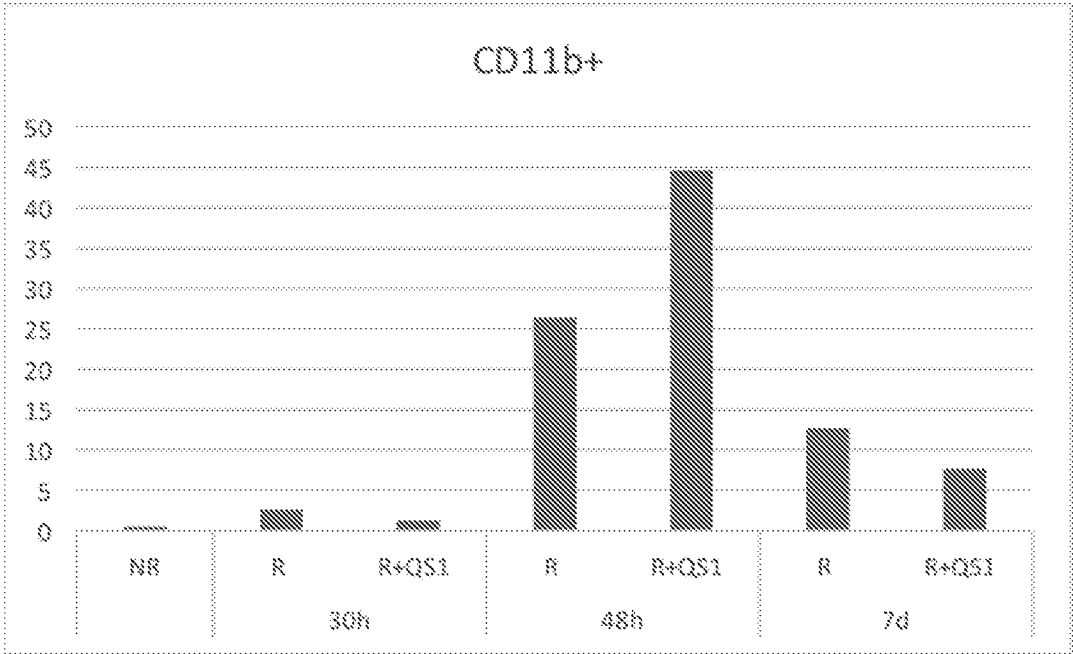


Figure 32



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2017/021502

A. CLASSIFICATION OF SUBJECT MATTER

IPC (2017.01) C07D 295/26, C07D 295/037, C07D 241/04, A61K 31/495, A61P 35/00, A61P 29/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC (2017.01) C07D 295/26, C07D 295/037, C07D 241/04, A61K 31/495, A61P 35/00, A61P 29/00, C07D 401/02

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

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

Databases consulted: THOMSON INNOVATION, Google Patents, CAPLUS, MARPAT, REGISTRY, Google Scholar

Search terms used: inflamm*, ionizing radiation, cancer, lung, *radio*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/182789 A2 THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [US] 13 Oct 2014 (2014/10/13) Whole document, specifically compound ID: 5355512 (see tables 1 and 3) and compound ID: 5344400 (see table 1).	1-15

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

☒ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

“&” document member of the same patent family

Date of the actual completion of the international search

29 May 2017

Date of mailing of the international search report

29 May 2017

Name and mailing address of the ISA:

Israel Patent Office

Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel

Facsimile No. 972-2-5651616

Authorized officer

SAAR Reshef

Telephone No. 972-2-5657822

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2017/021502

Patent document cited search report			Publication date	Patent family member(s)			Publication Date
WO	2014/182789	A2	13 Oct 2014	WO	2014182789	A2	13 Nov 2014
				WO	2014182789	A3	11 Dec 2014
				AU	2014262764	A1	17 Dec 2015
				CA	2911902	A1	13 Nov 2014
				CN	105579439	A	11 May 2016
				EP	2994457	A2	16 Mar 2016
				EP	2994457	A4	28 Sep 2016
				JP	2016523830	A	12 Aug 2016
				KR	20160005356	A	14 Jan 2016
				SG	11201509194S	A	30 Dec 2015
				US	2016090369	A1	31 Mar 2016
				US	2016221976	A1	04 Aug 2016