Provided herein are compositions, including intranasal compositions, which include geranylgeranyl acetone (GGA) and/or derivatives thereof and methods for treating a neural disease, disorder or condition with the same. Also provided herein are methods of treating inflammatory bowel disease with geranylgeranyl acetone (GGA) and/or derivatives thereof. Further provided are methods of treating chronic liver disease (CLD) with geranylgeranyl acetone (GGA) and/or derivatives thereof. Still further are provided methods for treating other hepatic and cardiac disorders.
THERAPEUTIC USES FOR GERANYLGERANYL ACETONE AND DERIVATIVES THEREOF
CROSS-REFERENCE TO RELATED APPLICATIONS


FIELD OF THE INVENTION

[0002] This invention provides therapeutic compositions suitable for intranasal administration, which include geranylgeranyl acetone (GGA) and/or derivatives thereof. This invention also provides therapeutic methods for treating a neural disease, disorder or condition by the intranasal administration of compositions that include geranylgeranyl acetone (GGA) and derivatives thereof. Preferably, GGA or the GGA derivative is enriched in the all trans isomer, compared to the relative amount of the trans isomer in the mixtures of cis and trans isomers of GGA or the GGA derivative.

[0003] This invention further provides therapeutic methods for treating inflammatory bowel disease (IBD) or a related disorder or condition by the administration of compositions that include geranylgeranyl acetone (GGA) and derivatives thereof. This invention also provides therapeutic methods for treating chronic liver disease (CLD) or a related disorder or condition or acute liver injury or failure by the administration of compositions that include GGA and derivatives thereof. Furthermore this invention provides therapeutic methods for treating cardiac ischemia and repurification injury or a related disorder or condition by the administration of compositions that include GGA and derivatives thereof.

STATE OF THE ART

[0004] Geranylgeranyl acetone (GGA) has the formula: 

and is reported to have neuroprotective and related effects. See, for example, PCT Pat. App. Pub. Nos. WO 2012/03 1028, WO 2013/052148, and WO 2013/130654, each of which is incorporated herein by reference in its entirety.
Inflammatory bowel disease (IBD) is generally characterized by diarrhea, cramping, abdominal pain, weight loss, rectal bleeding, tiredness, anemia, fistulas, perforations, obstruction of the bowel and frequent need for surgical intervention. It encompasses a number of disorders including Crohn’s disease, ulcerative colitis, indeterminate colitis, microscopic colitis and collagenous colitis. Such disorders may at times begin clinically with a more benign or milder presentation, resembling irritable bowel syndrome (IBS) which can subsequently progress to increasing inflammation accompanying the IBS and may ultimately develop full-blown IBD. The precise causes of IBD and IBS remain unknown.

Chronic liver disease (CLD) is marked by the gradual destruction of liver tissue over time. Several liver diseases can fall under this category, including without limitation, cirrhosis and fibrosis, the latter of which is often the precursor to cirrhosis, non-alcoholic fatty liver disease, and non-alcoholic steatohepatitis.

Cirrhosis is the result of acute and chronic liver disease and is characterized by the replacement of liver tissue by fibrotic scar tissue and regenerative nodules leading to a progressive loss of liver function. Fibrosis and nodular regeneration results in the loss of the normal microscopic lobular architecture of the liver. Fibrosis represents the growth of scar-tissue resulting from, for example, infection, inflammation, injury, and even healing. Over time, the fibrotic scar tissue slowly replaces the normal functioning liver tissue resulting in a decreasing amount of blood flow to the liver leaving the liver incapable of fully processing nutrients, hormones, drugs, and poisons that are found in the bloodstream. More common causes of cirrhosis include alcoholism, hepatitis C, viral infections, ingestion of toxins, and fatty liver, but many other possible causes also exist.

Liver injury is some form of trauma sustained to the liver. This can occur through either a blunt force such as a car accident, or a penetrating foreign object such as a knife. Liver injuries constitute 5% of all traumas, making it the most common abdominal injury.

Acute liver failure is the appearance of severe complications rapidly after the first signs of liver disease (such as jaundice), and indicates that the liver has sustained severe damage (loss of function of 80-90% of liver cells). The complications are hepatic encephalopathy and impaired protein synthesis (as measured by the levels of serum albumin and the prothrombin time in the blood). The 1993 classification defines hyperacute as ‘within 1 week, acute as 8-28 days and subacute as 4-12 weeks. It
reflects the fact that the pace of disease evolution strongly influences prognosis. Acetaminophen hepatotoxicity is, by far, the most common cause of acute liver failure in both the United States and the United Kingdom. Toxicity of acetaminophen arises often due to its quinone metabolite. Acetaminophen overdose results in more calls to poison control centers in the US than overdose of any other pharmacological substance. Signs and symptoms of paracetamol toxicity may initially be absent or vague. Untreated overdose can lead to liver failure and death within days. Renal failure is also a possible side effect.

[0010] Coronary heart disease (CHD) is the narrowing or blockage of the coronary arteries, usually caused by atherosclerosis. Atherosclerosis (sometimes called "hardening" or "clogging" of the arteries) is the buildup of cholesterol and fatty deposits (called plaques) on the inner walls of the arteries. These plaques can restrict blood flow to the heart muscle by physically clogging the artery or by causing abnormal artery tone and function.

Without an adequate blood supply, the heart becomes starved of oxygen and the vital nutrients it needs to work properly. This can cause chest pain called angina. If blood supply to a portion of the heart muscle is cut off entirely, or if the energy demands of the heart become much greater than its blood supply, a heart attack (injury to the heart muscle) may occur.

[0011] Cardiac ischemia may be asymptomatic or may cause chest pain, known as angina pectoris. It occurs when the heart muscle, or myocardium, receives insufficient blood flow. This most frequently results from atherosclerosis, which is the long-term accumulation of cholesterol-rich plaques in the coronary arteries. Ischemic heart disease is the most common cause of death in most Western countries and a major cause of hospital admissions.

SUMMARY OF THE INVENTION

[0012] In one aspect of the invention, an intranasal composition is provided, the composition comprising an effective amount of geranygeranyl acetone (GGA) or a GGA derivative including GGA conjugates, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0013] In another aspect of the invention, an enteric composition is provided, the composition comprising an effective amount of geranygeranyl acetone (GGA) or a GGA derivative including GGA conjugates, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
[0014] Preferably, the GGA or the GGA derivative includes the all-iron (hereinafter "trans") form or substantially the trans form of the GGA or the GGA derivative. As used herein, "substantially" in the context of cis/trans configurations refers to at least 80%, more preferably at least 90%, yet more preferably at least 95%, and most preferably at least 99% of the desired configuration, which can include at least 80%, more preferably at least 90%, yet more preferably at least 95%, and most preferably at least 99% of the trans isomer. In certain preferred embodiments of the invention, the GGA or a GGA derivative exists at least 80%, or at least 90%, or at least 95%, or at least 99% in the trans isomer.

[0015] In certain aspects, this invention relates to pharmaceutical uses, as disclosed herein, of geranylgeranyl acetone (GGA) and GGA derivatives, pharmaceutical compositions of isomers of geranylgeranyl acetone, preferably synthetic geranylgeranyl acetone, and GGA derivatives, and methods of using such compounds and pharmaceutical compositions. In certain aspects, this invention relates to a 5-trans isomer compound of formula VI:

\[ \text{VI} \]

wherein VI is at least 80% in the 5E, 9E, 13E configuration. In one embodiment, this invention utilizes a compound, which is synthetic 5E, 9E, 13E geranylgeranyl acetone. In another embodiment, the synthetic 5E, 9E, 13E geranylgeranyl acetone is free of 5Z, 9E, 13E geranylgeranyl acetone. In another aspect, this invention utilizes a pharmaceutical composition comprising synthetic GGA or synthetic 5E, 9E, 13E GGA, and at least one pharmaceutical excipient.

[0016] Another aspect of this invention relates to a synthetic 5-cis isomer compound of formula VIl:

\[ \text{VII} \]

wherein VIl is at least 80% in the 5Z, 9E, 13E configuration, or a ketal thereof of formula XII:
wherein each $R_{70}$ independently is $C_1-C_6$ alkyl, or two $R_{70}$ groups together with the oxygen atoms they are attached to form a 5 or 6 membered ring, which ring is optionally substituted with 1-3, preferably 1-2, $C_2-C_6$ alkyl groups. Preferably, the two $R_{70}$ groups are the same. In one embodiment, $R_{70}$ is, methyl, ethyl, or propyl in another embodiment, the cyclic ring is:

![Diagram of cyclic ring structure]

[0017] GGA and GGA derivatives utilized herein can be employed as a passive carrier where they are not covalently bound to a drug and as covalent conjugates of drugs for administering these drugs intranasally. When employed as a passive carrier, GGA or the GGA derivative is mixed, but not covalently bonded, with the drug and optionally with other excipients for facilitating the intranasal delivery of that drug. GGA and GGA derivatives useful for these purposes are provided herein and will be apparent to the skilled artisan upon reading this disclosure.

[0018] Provided herein are compounds, compositions, and methods for intranasal administration and delivery. In some embodiments, the compounds are conjugates of GGA or GGA derivatives with other drugs where rapid onset of a therapeutic serum concentration is desired and can be tolerated. The conjugate are provided such that once delivered into the blood it will degrade into safe GGA (or other carrier compound) and the active drug through hydrolysis by water in the blood, through reduction by, for example, thiol-containing components of the blood such as glutathione, or through the action of endogenous enzymes such as lipases, etc.

[0019] In another aspect, utilized herein are drug conjugates of GGA or drug conjugates of GGA derivatives, that are therapeutically useful for intranasal formulation and delivery to a subject. In some embodiments, provided herein are compounds of formula [G-L-j-D, wherein $j$ is 1-10, preferably, 1-5, more preferably, 1-3, or still more preferably, 1; $i$, G is GGA or a GGA derivative, $L$ is a bond or a linker, which is preferably cleaved in vivo to provide an effective concentration of the drug G. GGA or the GGA derivatives utilized herein are described herein and/or are known to the skilled artisan. In one embodiment, $L$ is a single or a double bond. In another embodiment, $L$ is a linker of formula $\equiv N\cdash L_1\cdash CO\cdash \equiv$, $\equiv N\cdash L_2\cdash O\cdash \equiv$, $\equiv N\cdash
The drug can be any drug, preferably one that contains one or more -CO₂H, -OH, -N₂H₂, and/or -SH, and such other groups that can be covalently conjugated as provided herein. L₁ is preferably a straight or branched chain linker group of 1 to 15 atoms consisting of carbon, nitrogen, oxygen, phosphorus, sulfur, wherein the number of heteroatoms is preferably no more than 5.

As will be apparent to the skilled artisan, compounds of formula G-L-D exclude those that have a -O-O- bond resulting from the L-G or the L-D bonding. In some embodiments, L₁ comprises a C₃-C₁₀ alkylene or C₁-C₆ heteroalkylene, C₃-C₁₀ cycloalkyl, C₁-C₁₀ heterocyclyl moiety, which is optionally substituted. Certain preferred substituents include C₁-C₆ afkyl, -OH, amino, C₁-C₆ alkylamino, or di C₁-C₆ alkylamino, C₃-C₆ cycloalkyl, C₁-C₁₀ heteroaryl, or C₂-C₁₅ heterocyclyl. In some embodiments, L₁ comprises an amino acid moiety. In some embodiments, L₁ is a di, tri, tetra, or pentapeptide, preferably comprising 1, more preferably 2, and still more preferably 3 or more naturally occurring amino acids.

In some embodiments, the compositions utilized herein contain a drug, and GGA or a GGA derivative as a non-covalently bound carrier. In these embodiments, the drug is not covalently bound to GGA or a GGA derivative directly or via a linker.

In some embodiments, conjugated and admixed drugs include the following exemplary and non-limiting drugs for treating the respective indications indicated after each drug: Forteo - osteoporosis; Ceredist (TRH) - ataxia; Byetta (GLP-1) - diabetes; Sandostatin (GHI) - acromegaly; Victoza (GLP-1) - diabetes; Gonal-f (FHS) - infertility; Neupogen (G-CSF) - neutropenia; Kepivance - mucositis in cancer; Natrecor (B type naturietic protein) - congestive heart failure; Calcitonin for hypercaemia; ACTH for infantile spasms; Oxytocin for premature delivery in pregnancy; Copaxone for multiple sclerosis; Beta-interferon for multiple sclerosis; and Alpha-interferon for viral hepatitis.

Additional drugs include but are not limited to: antibiotics, such as Vancomycin, Daptomycin, Pristamycin 1A and IB, or Linezolid, etc.; analgesics, such as the aminopyridine, Flupirtine, or opiates such as Morphine or Codeine, etc; and steroidal or non-steroidal anti-inflammatory drugs, such as but not limited to dexamethasone and ibuprofen, indometacin, or naproxen, respectively.
In another aspect utilized herein are compounds wherein G6A or a derivative thereof is conjugated to an anti-cancer agent or another drug as disclosed herein. In one embodiment, the GGA conjugate is of formula:

wherein \( R^1 - R^2 \), \( m \), and \( n \) are defined as in Formula (I) herein, \( 1^m \) is a bond or a linker joining the isoprenyl portion to the Drug, and the Drug is preferably an antibiotic, or a glaucoma drug, or is an antitumor agent, or is an antiviral agent. In certain preferred embodiments, the linker is a bond, methylene, or carbonyl. In certain other preferred embodiments, the linker joins the isoprenyl portion to a carbonyl moiety, or an oxygen, nitrogen, or sulfur atom of the drug. In yet another preferred embodiment, \( R^2 - R^4 \) are methyl, and \( m \) and \( n \) are 1. Such conjugates are formulated and administered in accordance with this invention.

In some embodiments, the compounds include esters of geranylgeranyl alcohol (GGOH) and such other alcohols as utilized herein. Such esters can include the GGOH esters of NSAID carboxylic acids such as ibuprofen and naproxen. Furthermore, carbonates can attach drugs with alcohol groups to such alcohols utilized herein, and carbamates can attach drugs with amines having at least one \( \text{N-H} \) hydrogen.

Certain non-limiting GGA derivatives utilized in this invention include, farnesyl acetone, farnesyl alcohol, farnesyl carbamate, geranyl geranyl (GG) alcohol, GG carbamate. In some embodiments, the GGA derivative is

wherein \( r \) is 0, 1, 2, 3, or 4, and wherein the structures include cis and trans forms and mixtures thereof.

In some embodiments, the drug that is conjugated to GGA or a GGA derivative is a small molecule, such as but not limited to Argatroban® or Zofran® (GlaxoSmithKline, London, U.K.) or vancomycin. In some embodiments, the drug that is conjugated to GGA or a GGA derivative is a peptide, such as but not limited to thyrotropin-releasing hormone, (pyro)Glu-His-Pro-NH\(_2\), having a MW=362. In some embodiments, the drug that is conjugated to GGA or a GGA derivative is a peptide, such as but not limited to teriparatide.
comprising the first 34 amino acids of human parathyroid hormone (PTH), having a
MW=4,118, or a growth hormone, a 191 amino acid peptide, having a MW=22,124. In some
embodiments, the drug that is conjugated to GGA or a GGA derivative is an antibody, such
as but not limited to herceptin.

[0027] In some embodiments, the drug conjugate is joined to GGA or the GGA derivative
via a Schiff’s base linkage. In some embodiments, the drug conjugate is joined to GGA or
the GGA derivative via a sulfenylated amide linkage. In some embodiments, the drug
conjugate is joined to GGA or the GGA derivative via an ester linkage. In some
embodiments, the drug conjugate is joined to GGA or the GGA derivative via an amide
linkage. In some embodiments, the drug conjugate is joined to GGA or the GGA derivative
via an urea linkage. In some embodiments, the drug conjugate is joined to GGA or the GGA
derivative via a carbonate linkage.

[0028] It is contemplated that the administration of an effective amount of these
intranasal formulations improves pharmaceutical activities such as a more rapid onset of
biological activity, and/or a means by which GGA or a GGA derivative can bypass first pass
metabolism relative to the administration of a conventional, i.e., non-intranasal formu-
lation comprising the comparable amount of GGA or a GGA derivative. It is further contem-
plated that such intranasal formulations are better tolerated by patients having difficulty
with swallowing (e.g., and without limitation, for patients that suffer from amyotrophic lateral
sclerosis (ALS), also known as Lou Gehrig’s disease). By avoiding the gastrointestinal tract,
the intranasal formulations of GGA or a GGA derivative avoid stomach acid induced
conversion of the all cis form to a mixed cis- and cis-form. In some embodiments, at least
one of the double bonds in GGA or the GGA derivative of the intranasal formulation is in the
cis configuration. In some embodiments, at least two or more of the double bonds in GGA
or the GGA derivative of the Intranasal formulation is in the cis configuration.

[0029] As to intranasal delivery, the surface area of the nostril is small and thus can absorb
only a limited volume of any intranasal composition. As such, the concentration of the GGA
or the GGA derivative in the intranasal composition is contemplated to be sufficiently high
e.g., 0.1-20% (weight/volume) to compensate for the small volumes, e.g., 0.01-2 mL, of the
intranasal composition that are administered to each nostril, in certain embodiments, the
composition includes 0.1-5%, or preferably 5-10%, or more preferably 10-15% or 15-20%
(weigh t/volume) of GGA or a GGA derivative, or a pharmaceutically acceptable salt thereof.
The intranasal compositions described herein are contemplated to be administered to each or either nostril one or more times, e.g., 1, 2, 3, 4, 5, 6, 7 or 8 times per day. It is further contemplated that a sufficient time delay, e.g., of 1-30 minutes or more, such as time delays of 30 minutes, 1, 2, 3, 4, 8, 12, 24 or 48 hours may be used between each administration. Without being bound by theory, it is believed that each nostril can absorb only a limited volume of any intranasal composition and thus it quickly becomes saturated by the intranasal compositions described herein.

It is contemplated that an effective amount of GGA or a derivative thereof is efficiently administered by employing the intranasal compositions described herein. In some embodiments, the intranasal formulation of GGA or a derivative contains between 1-5, 5-50, 10-40, or 20-30 mg/kg day.

In certain embodiments, the composition is in the form of a solution or suspension. In other embodiments, said excipient comprises a bioadhesive and/or an intranasal absorption promoter. Said intranasal absorption promoter, in some embodiments, is one or more of a chelating agent, POE (9) lauryl alcohol, sodium glycocholate and lysophosphatidylcholine.

In some embodiments, it is contemplated that the GGA or the GGA derivative, or the drug conjugate of GGA or a GGA derivative, forms a micellar or a similarly aggregated structure. In some embodiments, which relate to physical mixtures of a drug and GGA or a GGA derivative, the drug is included in the micellar structure. Without being bound by theory, it is contemplated that GGA, a GGA derivative, or a GGA-drug conjugate utilized herein can form a micelle or a reverse micelle. A micelle has a hydrophilic portion exposed to a surrounding aqueous or hydrophilic phase. A reverse micelle has a hydrophobic portion exposed to a surrounding hydrophobic phase. As disclosed herein, both forms can be in equilibrium with each other, it is further contemplated that a conversion of a micelle to a reverse micelle and vice versa can allow; a facile asporation of GGA or the GGA derivative, or the drug conjugate of GGA or a GGA derivative from an aqueous phase into the intranasal mucosal layer and further into blood in a short period of time. In the process, the drug within or associated with the micelle migrates from the moist environment of the nostril into blood.
In another aspect of the invention, a method is provided for administering intranasally an effective amount of the compositions to a subject in need thereof. As used herein, subject or patient refers to a mammal, particularly preferably humans.

In another aspect of the invention, a method is provided for treating a neural disease, disorder or condition and/or reducing one or more negative effects of a neural disease, disorder or condition comprising administering intranasally an effective amount of any of the compositions described herein to a subject in need thereof.

According to another aspect of this invention, a method is provided for delivering a GGA derivative to the brain and/or the spinal cord of a patient, which method comprises administering an intranasal composition intranasally to said patient in an amount sufficient to introduce an effective amount of GGA derivative into the brain and/or the spinal cord. As used herein, an effective amount refers to a therapeutically effective amount or to an amount effectively measured in the brain and/or the spinal cord.

Some embodiments provided herein describe a method for inducing expression of a heat shock protein in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of GGA or a GGA derivative thereof, wherein the GGA or GGA derivative thereof is administered intranasally to said subject.

Other embodiments provided herein describe a method for inhibiting neural death in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of GGA or a GGA derivative thereof, wherein the GGA or GGA derivative thereof is administered intranasally to said subject.

In the enteric composition aspect, it is contemplated that the administration of an effective amount of these enteric formulations improves pharmaceutical activities such as an enhanced activity, improved serum half-life, and/or lower toxicity with reduced adverse side effects relative to the administration of a conventional, i.e., non-enteric formulation comprising the comparable amount of GGA or a GGA derivative. In one embodiment, the enteric formulation is a solid-dosage form. In another embodiment, the enteric formulation comprises one or more an enteric polymer and enteric coating as suitable pharmaceutically acceptable excipients. In another embodiment, the enteric formulation contains an effective amount of GGA or the GGA derivative.
In yet other embodiments, various bacterial and viral disorders, and cancers of the eye, the brain, and the spinal cord, and nerves, including without limitation, nerves in the brain, eye, and the spinal cord are treated in accordance with this invention. In some embodiments, the disorder is glaucoma. In another embodiment, the disorder is herpes.

Another aspect provided herein describes GGA or GGA derivatives, drug conjugates, compositions thereof and related methods that are useful for the treatment of a subject via an intramusosal administrations, e.g., vaginal, rectal, other than the intranasal route. For example, GGA or the GGA derivatives, drug conjugates, compositions thereof can be formulated as suppositories for vaginal or rectal administration. Excipients for the treatment of intramusosal administrations, other than those described herein, are well known to the skilled artisan.

In one aspect of the invention, a method is provided of treating inflammatory bowel disease (IBD) or a related disorder or condition comprising administering a composition comprising an effective amount of geranygeranyl acetone (GGA) or a GGA derivative, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient to a subject in need thereof. As used herein, subject or patient refers to a mammal, particularly preferably human. In another aspect, a method is provided of upregulating HSP70 in stomach cells affected by IBD comprising contacting the stomach cells with an effective amount of GGA.

In another aspect of the invention, a method is provided of treating chronic liver disease or a related disorder or condition comprising administering a composition comprising an effective amount of geranygeranyl acetone (GGA) or a GGA derivative, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In another aspect, a method is provided of upregulating HSP70 in hepatic cells affected by a chronic liver disease comprising contacting the hepatic cells with an effective amount of GGA. In some embodiments, the hepatic cells are affected with cirrhosis, fibrosis, non-alcoholic fatty liver disease, or non-alcoholic steatohepatitis.

In another aspect of the invention, a method is provided of treating a disorder selected from liver injury, preferably acute liver injury (from trauma, surgery or as a side effect of cancer treatment), acute liver failure, preferably caused by drug toxicity such as acetaminophen toxicity, cardiac ischemia, myocardial infarction, repuffusion injury and heart transplants, or a related disorder or condition, comprising administering a
composition comprising an effective amount of geranyigeranyi acetone (GGA) or a GGA derivative, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, to a subject in need thereof. In some embodiments the (GGA) or a GGA derivative is administered to the subject in an emergency room setting.

[0045] In another aspect of the invention, a method is provided of treating a subject diagnosed with mild to moderate IBD following gastrectomy comprising administering a composition comprising an effective amount of geranyigeranyi acetone (GGA) or a GGA derivative, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In a preferred embodiment, the subjects are treated for 12 weeks.

[0046] Compounds, compositions and methods of the Invention described herein include the disclosures found in PCT application publication nos. WO 2012/03 1028, WO 2013/052148, and WO2013/130654 each of which is incorporated herein in its entirety by reference. All citations herein are incorporated herein by reference in their entirety.

DETAILED DESCRIPTION OF THE INVENTION

Definitions
[0047] It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a solvent" includes a plurality of such solvents.

[0048] As used herein, the term "comprising" or "comprises" is intended to mean that the compositions and methods include the recited elements, but not excluding others. "Consisting essentially of" when used to define compositions and methods, shall mean excluding other elements of any essential significance to the combination for the stated purpose. Thus, a composition or process consisting essentially of the elements as defined herein would not exclude other materials or steps that do not materially affect the basic and novel characteristic(s) of the claimed invention. "Consisting of" shall mean excluding more than trace elements of other ingredients and substantial method steps. Embodiments defined by each of these transition terms are within the scope of this invention.

[0049] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached
claims are approximations. Each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[0050] As used herein, \( C_m\text{--}C_n \), such as \( C_1\text{--}C_{10}, C_1\text{--}C_6 \) or \( C_1\text{--}C_4 \) when used before a group refers to that group containing \( m \) to \( n \) carbon atoms.

The term "about" when used before a numerical designation, e.g., temperature, time, amount, and concentration, including range, indicates approximations which may vary by ( +

\[ \text{or ( - )} \] \( 10 \% \), \( 5 \% \) or \( 1 \% \). \)

[0051] The term "alkoxy" refers to \(-\text{O-alkyl}\).

[0052] The term "nitro" refers to \(-\text{NO}_2\).

[0053] The term "alkyl" refers to monovalent saturated aliphatic hydrocarbyl groups having from 1 to 10 carbon atoms (i.e., \( C_1\text{--}C_{10} \) alkyl) or 1 to 6 carbon atoms (i.e., \( C_1\text{--}C_6 \) alkyl), or 1 to 4 carbon atoms. This term includes, by way of example, linear and branched hydrocarbyl groups such as methyl (\( \text{CH}_3 \)), ethyl (\( \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3 \)), isopropyl (\( (\text{CH}_3)_2\text{CH}_2\text{CH}_3 \)), \( \text{n-propyl} \) (\( \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \)), \( \text{i-propyl} \) (\( (\text{CH}_3)_2\text{CH}_2\text{CH}_2\text{CH}_3 \)), \( \text{sec-butyl} \) (\( (\text{CH}_3)_2\text{CH}_2\text{CH}_2\text{CH}_3 \)), \( \text{isobutyl} \) (\( (\text{CH}_3)_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \)), \( \text{i-butyl} \) (\( (\text{CH}_3)_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \)), \( \text{n-pentyl} \) (\( (\text{CH}_3)_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \)), and \( \text{neopentyl} \) (\( (\text{CH}_3)_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \)).

[0054] The term "alkenyl" refers to monovalent aliphatic hydrocarbyl groups having from 2 to 25 carbon atoms or 2 to 6 carbon atoms and 1 or more, preferably 1, carbon carbon double bond. Examples of alkenyl include vinyl, allyl, dimethyl allyl, and the like.

[0055] The term "alkynyl" refers to monovalent aliphatic hydrocarbyl groups having from 2 to 10 carbon atoms or 2 to 6 carbon atoms and 1 or more, preferably 1, carbon carbon triple bond \(-\text{(C=C)}\). Examples of alkynyl include ethynyl, \( \text{propargyl}, \text{dimethyl} \text{propargyl} \), and the like.

[0056] The term "acyl" refers to \(-\text{C(0)-alkyl}\), where alkyl is as defined above.

[0057] The term "aryl" refers to a monovalent, aromatic mono- or bicyclic ring having 6-10 ring carbon atoms. Examples of aryl include phenyl and naphthyl. The condensed ring may or may not be aromatic provided that the point of attachment is at an aromatic carbon atom. For example, and without limitation, the following is an aryl group:
[0058] The term "-CO₂H ester" refers to an ester formed between the -CO₂H group and an alcohol, preferably an aliphatic alcohol. A preferred example includes -CO₂R⁺, wherein R is alkyl or aryl group optionally substituted with an amino group.

[0053] The term "chiral moiety" refers to a moiety that is chiral. Such a moiety can possess one or more asymmetric centers. Preferably, the chiral moiety is enantiomerically enriched, and more preferably a single enantiomer. Nonlimiting examples of chiral moieties include chiral carboxylic acids, chiral amines, chiral amino acids, such as the naturally occurring amino acids, chiral alcohols including chiral steroids, and the likes.

[0060] The term "cycloalkyl" refers to a monovalent, preferably saturated, hydrocarbyl mono-, bi-, or tricyclic ring having 3-12 ring carbon atoms. While cycloalkyl, refers preferably to saturated hydrocarbyl rings, as used herein, it also includes rings containing 1-2 carbon-carbon double bonds. Nonlimiting examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, and the like. The condensed rings may or may not be non-aromatic hydrocarbyl rings provided that the point of attachment is at a cycloalkyl carbon atom. For example, and without limitation, the following is a cycloalkyl group:

[0061] The term "halo" refers to F, Cl, Br, and/or I.

[0062] The term "heteroaryl" refers to a monovalent, aromatic mono-, bi-, or tricyclic ring having 2-14 ring carbon atoms and 1-6 ring heteroatoms selected preferably from N, O, S, and P and oxidized forms of N, S, and P, provided that the ring contains at least 5 ring atoms. Nonlimiting examples of heteroaryl include furan, imidazole, oxadiazole, oxazole, pyridine, quinoline, and the like. The condensed rings may or may not be a heteroatom containing aromatic ring provided that the point of attachment is a heteroaryl atom. For example, and without limitation, the following is a heteroaryl group:

[0063] The term "heterocyclyl" or heterocycle refers to a non-aromatic, mono-, bi-, or tricyclic ring containing 2-10 ring carbon atoms and 1-6 ring heteroatoms selected
preferably from N, O, S, and P and oxidized forms of N, S, and P, provided that the ring contains at least 3 ring atoms. While heterocyclyl preferably refers to saturated ring systems, it also includes ring systems containing 1-3 double bonds, provided that they ring is non-aromatic. Non-limiting examples of heterocyclyl include, azalactones, oxazoline, piperidinyi, piperazinyi, pyrroidinyl, tetrahyd rofu ranyl, and tetrahydropyranyl. The condensed rings may or may not contain a non-aromatic heteroatom containing ring provided that the point of attachment is a heterocyclyl group. For example, and without limitation, the following is a heterocyclyl group:

[0064] The term "hydrolyzing" refers to breaking an R\textsuperscript{H}-0-CO-, R\textsuperscript{H}-0-CS-, or an R\textsuperscript{H}-0-SO\textsubscript{2}- moiety to an R\textsuperscript{I}-OH, preferably by adding water across the broken bond. A hydrolyzing is performed using various methods well known to the skilled artisan, non-limiting examples of which include acidic and basic hydrolysis.

[0065] The term "oxo" refers to a C=0 group, and to a substitution of 2 geminal hydrogen atoms with a C=0 group.

[0066] The term "pharmaceutically acceptable" refers to safe and non-toxic for in vivo, preferably, human administration.

[0067] The term "pharmaceutically acceptable salt" refers to a salt that is pharmaceutically acceptable.

[0083] The term "salt" refers to an ionic compound formed between an acid and a base. When the compound provided herein contains an acidic functionality, such salts include, without limitation, alkali metal, alkaline earth metal, and ammonium salts. As used herein, ammonium salts include, salts containing protonated nitrogen bases and alkylated nitrogen bases. Exemplary, and non-limiting cations useful in pharmaceutically acceptable salts include Na, K, Rb, Cs, Ni\textsuperscript{2+}, Ca, Ba, imidazolium, and ammonium cations based on naturally occurring amino acids. When the compounds utilized herein contain basic functionaly, such salts include, without limitation, salts of organic acids, such as carboxylic acids and sulfuric acids, and mineral acids, such as hydrogen halides, sulfuric acid, phosphoric acid, and the likes. Exemplary and non-limiting anions useful in pharmaceutically acceptable salts include
oxalate, maleate, acetate, propionate, succinate, tartrate, chloride, sulfate, bisulfate, mono-, di-, and tri basic phosphate, mesylate, tosylate, and the likes.

[0069] The term “substantially pure trans isomer” refers to a trans isomer that is by molar amount 95%, preferably 96%, more preferably 99%, and still more preferably 99.5% or more a trans isomer with the rest being the corresponding cis isomer.

[0070] “Trans” in the context of GGA and GGA derivatives refer to the GGA scaffold as illustrated below:

\[
\begin{align*}
R^1 & \quad (R^2) \\
R^3 & \quad (R^4) \\
R^5 & \quad (R^6)
\end{align*}
\]

wherein \( R^i \) and \( R^j \) is defined herein and \( q \) is 0-2. As shown, each double bond is in a trans or Z configuration. In contrast, a cis form of GGA or a GGA derivative will contain one or more of these bonds in a cis or Z configuration.

[0071] The term “neuroprotective” refers to reduced toxicity of neurons as measured in vitro in assays where neurons susceptible to degradation are protected against degradation as compared to control. Neuroprotective effects may also be evaluated in vivo by counting neurons in histology sections.

[0072] The term “neuron” or “neurons” refers to all electrically excitable cells that make up the central and peripheral nervous system. The neurons may be cells with in the body of an animal or cells cultured outside the body of an animal. The term “neuron” or “neurons” also refers to established or primary tissue culture cell lines that are derived from neural cells from a mammal or tissue culture cell lines that are made to differentiate into neurons. “Neuron” or “neurons” also refers to any of the above types of cells that have also been modified to express a particular protein either extrachromosomally or intrachromosomally. “Neuron” or “neurons” also refers to transformed neurons such as neuroblastoma cells and support cells with in the brain such as glia.

[0073] The term “protein aggregates” refers to a collection of proteins that may be partially or entirely mis-folded. The protein aggregates may be soluble or insoluble and may be inside the cell or outside the cell in the space between cells. Protein aggregates inside the cell can be intranuclear in which they are inside the nucleus or cytoplasm in which they
are in the space outside of the nucleus but still within the cell membrane. The protein aggregates described in this invention are granular protein aggregates.

[0074] As used herein, the term “protein aggregate inhibiting amount” refers to an amount of compound that inhibits the formation of protein aggregates at least partially or entirely. Unless specified, the inhibition could be directed to protein aggregates inside the cell or outside the cell.

[0075] As used herein, the term “intracellular” or “intranuclearly” refers to the space inside the nuclear compartment of an animal cell.

[0076] The term “cytoplasm” refers to the space outside of the nucleus but within the outer cell wall of an animal cell.

[0077] As used herein, the term “pathogenic protein aggregate” refers to protein aggregates that are associated with disease conditions. These disease conditions include but are not limited to the death of a cell or the partial or complete loss of the neuronal signaling among two or more cells. Pathogenic protein aggregates can be located inside of a cell, for example, pathogenic intracellular protein aggregates or outside of a cell, for example, pathogenic extracellular protein aggregates.

[0078] As used herein, the term “SBMA” refers to the disease spinal and bulbar muscular atrophy. Spinal and bulbar muscular atrophy is a disease caused by pathogenic androgen receptor protein accumulation intranuclearly.

[0079] As used herein, the term “ALS” refers to amyotrophic lateral sclerosis disease.

[0080] As used herein, the term “AD” refers to Alzheimer’s disease.

[0081] The term “neurotransmitter” refers to chemicals which transmit signals from a neuron to a target cell. Examples of neurotransmitters include but are not limited to: amino acids such as glutamate, aspartate, serine, β-aminobutyric acid, and glycine; monoamines such as dopamine, norepinephrine, epinephrine, histamine, serotonin, and melatonin; and other molecules such as aceticholine, adenosine, anandamide, and nitric oxide.

[0082] The term “synapse” refers to junctions between neurons. These junctions allow for the passage of chemical signals from one cell to another.

[0083] The term “G protein” refers to a family of proteins involved in transmitting chemical signals outside the cell and causing changes inside of the cell. The RhO family of G proteins is small G protein, which are involved in regulating actin cytoskeletal dynamics, cell movement, motility, transcription, cell survival, and cell growth. RhO, Rac1, and CDC42
are the most studied proteins of the Rho family. Active G proteins are localized to the cellular membrane where they exert their maximal biological effectiveness.

[0084] The terms "treat", "treating" or "treatment", as used herein, include alleviating, abating or ameliorating a disease or condition or one or more symptoms thereof, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disease or condition, e.g., arresting or suppressing the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or suppressing the symptoms of the disease or condition, and are intended to include prophylaxis. The terms also include relieving the disease or conditions, e.g., causing the regression of clinical symptoms. The terms further include achieving a therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the individual, notwithstanding that the individual is still be afflicted with the underlying disorder. For prophylactic benefit, the compositions are administered to an individual at risk of developing a particular disease, or to an individual reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease has not been made.

[0085] The terms "preventing" or "prevention" refer to a reduction in risk of acquiring a disease or disorder (i.e., causing at least one of the clinical symptoms of the disease not to develop in a subject that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease), The terms further include causing the clinical symptoms not to develop, for example in a subject at risk of suffering from such a disease or disorder, thereby substantially averting onset of the disease or disorder.

[0086] The term "effective amount" refers to an amount that is effective for the treatment of a condition or disorder by an Intranasal administration of a compound or composition described herein, in some embodiments, an effective amount of any of the compositions or dosage forms described herein is the amount used to treat a neural disease, disorder or condition and/or to reduce one or more negative effects of a neural disease, disorder or condition comprising administering intranasally any of the compositions or dosage forms
described herein to a subject in need thereof. In some embodiments, the condition or disorder that is treated with an effective amount of a compound or composition described herein is of the brain, spine and/or central nervous system.

[0087] The term "carrier" as used herein, refers to relatively nontoxic chemical compounds or agents that facilitate the incorporation of a compound into cells or tissues.

[0088] The term "axon" refers to projections of neurons that conduct signals to other cells through synapses. The term "axon growth" refers to the extension of the axon projection via the growth cone at the tip of the axon.

[0089] The term "neural disease" refers to diseases that compromise the cell viability of neurons. Neural diseases in which the etiology of said neural disease comprises formation of protein aggregates which are pathogenic to neurons provided that the protein aggregates are not related to the disease SBMA and are not intranuclear, include but are not limited to ALS, AD, Parkinson's Disease, multiple sclerosis, and prion diseases such as Kuru, Creutzfeldt-Jakob disease, Fatal familial insomnia, and Gerstmann-Straussler-Scheinker syndrome. These neural diseases are also different from SBMA in that they do not contain polyglutamine repeats. Neural diseases can be recapitulated in vitro in tissue culture cells. For example, AD can be modeled in vitro by adding pre-aggregated 13-amyloid peptide to the cells. ALS can be modeled by depleting an ALS disease-related protein, TDP-43. Neural disease can also be modeled in vitro by creating protein aggregates through providing toxic stress to the cell. One way this can be achieved is by mixing dopamine with neurons such as neuroblastoma cells. These neural diseases can also be recapitulated in vivo in mouse models. A transgenic mouse that expresses a mutant Sod1 protein has similar pathology to humans with ALS. Similarly, a transgenic mouse that over expresses APP has similar pathology to humans with AD.

Compounds:

GGA

[0090] This invention relates to compounds and pharmaceutical compositions of isomers of geranylgerany acetone. In certain aspects, this invention relates to a synthetic 5-trans isomer compound of formula VI:
wherein \( V \) is at least 80\% in the 5E, 9E, 13E configuration. In some embodiments of the invention, the compound of formula \( V \) wherein \( V \) is at least 85\%, or at least 90\%, or at least 95\%, or at least 97\%, or at least 98\%, or at least 99\%, or at least 99.5\%, or at least 99.9\% in the 5E, 9E, 13E configuration. In some embodiments, the invention for the compound of formula \( V \) does not contain any of the cis-isomer of GGA.

[0091] Another aspect of this invention relates to a synthetic 5-cis isomer compound of formula \( VI \):

![Chemical Structure](image)

wherein \( VII \) is at least 75\% in the 5E, 9E, 13E configuration. In certain embodiments of the invention, utilizes a compound of formula \( VII \) wherein \( VII \) is at least 80\% in the 5E, 9E, 13E configuration, or alternatively, at least 85\%, or at least 90\%, or at least 95\%, or at least 96\%, or at least 97\%, or at least 98\%, or at least 99\%, or at least 99.5\%, or at least 99.9\% in the 5E, 9E, 13E configuration. In some embodiments of the invention, the compound of formula \( VII \) does not contain any of the trans-isomer of GGA.

[0092] The configuration of compounds can be determined by methods known to those skilled in the art such as chiroptical spectroscopy and nuclear magnetic resonance spectroscopy.

[0093] The data contained in the examples herewith demonstrate at low concentrations the trans-isomer of GGA is pharmacologically active and shows a dose-dependent relationship. In contrast, the cis-isomer of GGA does not demonstrate a dose dependent relationship and is deemed to be at best of minimal activity.

GGA derivatives

In one aspect, the GGA derivative utilized herein is of Formula I:

\[
\begin{align*}
\text{R}^1 & - \text{C}- \text{C}- \text{R}^2 \\
\text{R}^3 & - \text{O} \cdot \text{Q}^1 \cdot \text{Q}^2 \\
\text{R}^4 & - \text{C}- \text{C}- \text{R}^5 \\
\text{R}^6 & - \text{C}- \text{C}- \text{C}- \text{C}- \text{C}- \text{C}- \text{C}- \text{C}- \\
\end{align*}
\]

(1)

or a tautomer or pharmaceutically acceptable salt thereof, wherein

- each \( R^1 \) and \( R^2 \) are independently \( \text{C}_{1-6} \) alkyl, or \( R^1 \) and \( R^2 \) together with the carbon atom they are attached to form a \( \text{C}_7 \) cycloalkyl ring optionally substituted with 1-3 \( \text{C}_{1-6} \) alkyl groups;
- each of \( R^3 \), \( R^4 \), and \( R^6 \) independently are hydrogen or \( \text{C}_{1-6} \) alkyl;
- \( Q^1 \) is -(C=0)-, -(C=S)-, or -(S(0)-);
- \( \text{R}^5 \) is hydrogen, \( -\text{O}-\text{R}^6 \), \( -\text{NR}^7 \text{R}^8 \), or is a chiral moiety;
- \( \text{R}^6 \) is:
  - \( \text{C}_{2-6} \) alkyl, optionally substituted with \(-\text{CO}_2\text{H}\) or an ester thereof, \( \text{C}_{1-6} \) alkoxy, oxo,
  - \(-\text{OH}\), \(-\text{CR}=\text{CR}\), \(-\text{C}=\text{CR}\), \text{c3-c10} cycloalkyl, \( \text{C}_2-\text{C}_9 \) heterocyclyl, \( \text{Ce}-\text{C}_{10} \) aryl, \( \text{C}_2-\text{C}_{10} \) heteroaryl,
  - where each R independently is hydrogen or \( \text{C}_{1-6} \) alkyl;
- \( \text{CO- C1-C5 alkyl}; \)
- \( \text{c3-c10 cycloalkyl}; \)
- \( \text{C}_3-\text{C}_8 \) heterocyclyl;
- \( \text{C}_6-\text{C}_{10} \) aryl; or
- \( \text{C}_2-\text{C}_{10} \) heteroaryl;

wherein each cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-3 alkyl groups; \(-\text{CF}_3\), 1-3 halo, preferably, chloro or fluoro, groups; 1-3 nitro groups; 1-3 \( \text{C}_{1-6} \) alkoxy groups; -(CO-phenyl); or \(-\text{N}(\text{R}^8)^{18}\text{R}^{19}\), each \( \text{R}^{18} \) and \( \text{R}^{19} \) independently is hydrogen; \( \text{C}_{1-7} \) alkyl, optionally substituted with \(-\text{CO}_2\text{H}\) or an ester thereof, \( \text{C}_{2-6} \) alkoxy, oxo, \(-\text{CR}=\text{CR}\), \(-\text{CCR}, \text{c3-c10 preferably } \text{C}_2-\text{C}_6 \) cycloalkyl, \( \text{C}_3-\text{C}_8 \) heterocyclyl, \( \text{C}_6-\text{C}_{10} \) aryl, or \( \text{C}_2-\text{C}_{10} \) heteroaryl, wherein each R independently is hydrogen or \( \text{C}_{1-7} \) alkyl; \( \text{C}_3-\text{C}_{10} \) cycloalkyl; \( \text{C}_3-\text{C}_9 \) heterocyclyl; \( \text{C}_6-\text{C}_{10} \) aryl; or \( \text{C}_2-\text{C}_{10} \) heteroaryl; wherein each cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-3 alkyl groups, optionally substituted with 1-3 halo, preferably, fluoro, groups, where \( \text{R}^{18} \) and \( \text{R}^{19} \) together with the nitrogen atom they are attached to form a 5-7 membered heterocycle;
each \( R^7 \) and \( R^8 \) are independently hydrogen or defined as \( \text{Ft} \); and

refers to a mixture of \( \text{cis} \) and \( \text{trans} \) isomers at the corresponding position wherein at least 80% and, preferably, no more than 95% of the compound of Formula (I) is present as a \( \text{trans} \) isomer.

[0096] In one embodiment, the GGA derivative utilized is of Formula (I-A):

\[
\begin{align*}
\text{(I-A)}
\end{align*}
\]

as a substantially pure \( \text{trans} \) isomer around the 2,3 double bond wherein, \( n^1, R^1, R^5, Q^1, \) and \( Q^2 \) are defined as in Formula (I) above.

[0097] In another embodiment, \( n^1 \) is 1. In another embodiment, \( n^1 \) is 2.

[0098] In another embodiment, the GGA derivative utilized is of Formula (I-B):

\[
\begin{align*}
\text{(I-B)}
\end{align*}
\]

as a substantially pure \( \text{trans} \) isomer around the 2,3 double bond wherein, \( R^1, R^3, Q^1, \) and \( Q^2 \) are defined as in Formula (I) above.

[0099] In another embodiment, the GGA derivative utilized is of Formula (I-C):

\[
\begin{align*}
\text{(I-C)}
\end{align*}
\]

wherein \( Q^1 \) and \( Q^2 \) are defined as in Formula (I) above.

[0100] In another embodiment, the GGA derivative utilized is of Formula (I-D), (I-E), or (I-F):

\[
\begin{align*}
\text{(I-D)}
\end{align*}
\]
wherein $R^i - R^s$ are defined as in Formula (l) above.

[0102] in another embodiment, the GGA derivative utilized is of Formula (l-G), (l-H), or (l-1):

![Chemical structure]

as a substantially pure trans isomer around the 2,3 double bond wherein $R^i - R^s$ are defined as in Formula (l) above.

[0103] in a preferred embodiment, $R^0$ is C$_7$-C$_{10}$ aryl, such as naphthyl. in another preferred embodiment, $R^0$ is a heteroaryl, such as quinolinyi.

[0103] in another aspect, the GGA derivative utilized in this invention is of Formula (l):

![Chemical structure]

or a pharmaceutically acceptable salt thereof, where $n$

- $n$ is 0 or 1;
- $n$ is 0, 1, or 2;

each $R^1$ and $R^2$ are independently C$_2$-C$_6$ alkyl, or $R^1$ and $R^2$ together with the carbon atom they are attached to form a C$_2$-C$_7$ cycloalkyl ring optionally substituted with 1-3 C$_1$-C$_6$ alkyl groups;

each of $R^3$, $R^4$, and $R^6$ independently are hydrogen or C$_1$-C$_6$ alkyl;

- $q$ is -OH, -NR$^3$R$^3$, -X-CO-NR$^3$R$^5$, -X-CS-NR$^3$R$^5$, or -X-S0$_2$NR$^3$R$^5$;
X is -0-, -S-, -NR<sup>24</sup>-R<sup>25</sup>, or -CR<sup>24</sup>R<sup>25</sup>;
each R<sup>26</sup> and R<sup>27</sup> independently is hydrogen; C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted with Cl-C<sub>6</sub> alkoxy; and C<sub>3</sub>-C<sub>10</sub> cycloalkyl;
each R<sup>28</sup> and R<sup>29</sup> independently is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted with -CO<sub>2</sub>H or an ester thereof, C<sub>1</sub>-C<sub>6</sub> alkoxyl, oxo, -CR=CR<sub>2</sub>, -C<sub>6</sub>H<sub>4</sub>-CR<sub>2</sub>Cr<sub>8</sub>, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> heterocyclyl, C<sub>6</sub>-C<sub>10</sub> aryI, or C<sub>2</sub>-C<sub>10</sub> heteroaryl, wherein each R independently is hydrogen, or C<sub>1</sub>-C<sub>6</sub> alkyl;
C<sub>3</sub>-C<sub>10</sub> cycloalkyl;
C<sub>2</sub>-C<sub>9</sub> heterocyclyl;
C<sub>6</sub>-C<sub>10</sub> aryI; or
C<sub>2</sub>-C<sub>10</sub> heteroaryl;
wherein each cycloalkyl, heterocyclyl, aryI, or heteroaryl is optionally substituted with 1-3 alkyl groups, preferably, 1-3 halo, chloro or fluoro, groups; 1-3 nitro groups; 1-3 C<sub>1</sub>-C<sub>6</sub> alkoxy groups; -CO-phenyl; or -NR<sup>13</sup>R<sup>9</sup>;
each R<sup>8</sup> and R<sup>9</sup> independently is hydrogen; C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted with -CO<sub>2</sub>H or an ester thereof, C<sub>6</sub>-C<sub>10</sub> alkoxy, oxo, -CR=CR<sub>2</sub>, -C<sub>6</sub>H<sub>4</sub>-CR<sub>2</sub>Cr<sub>8</sub>, preferably C<sub>2</sub>-C<sub>9</sub> cycloalkyl, C<sub>2</sub>-C<sub>9</sub> heterocyclyl, C<sub>6</sub>-C<sub>10</sub> aryI, or C<sub>2</sub>-C<sub>10</sub> heteroaryl, wherein each R independently is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl; C<sub>3</sub>-C<sub>10</sub> cycloalkyl; C<sub>3</sub>-C<sub>8</sub> heterocyclyl; C<sub>1</sub>-C<sub>6</sub> aryI; or C<sub>2</sub>-C<sub>10</sub> heteroaryl; wherein each cycloalkyl, heterocyclyl, aryI, or heteroaryl is optionally substituted with 1-3 alkyl groups, optionally substituted with 1-3 halo, preferably, fluoro, groups, where R<sup>18</sup> and R<sup>23</sup> together with the nitrogen atom they are attached to form a 5-7 membered heterocycle; R<sup>26</sup> is hydrogen or together with R<sup>24</sup> or R<sup>25</sup> and the intervening atoms form a 5-7 membered heterocyclic ring optionally substituted with 1-3 C<sub>1</sub>-C<sub>6</sub> alkyl groups; and
each R<sup>27</sup> and R<sup>28</sup> independently are hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -COR<sup>81</sup> or -COJR<sup>81</sup>, or R<sup>27</sup> together with R<sup>29</sup> or R<sup>30</sup> and the intervening atoms form a 5-7 membered heterocyclic ring optionally substituted with 1-3 C<sub>1</sub>-C<sub>6</sub> alkyl groups.

[0104] As used herein, the compound of Formula (II) includes optical isomers such as enantiomers and diastereomers. As also used herein, an ester refers preferably to a phenyl or a C<sub>6</sub> alkyl ester, which phenyl or alkyl group is optionally substituted with an amino group.

[0105] In one embodiment, ¼ is -NR<sup>22</sup>R<sup>23</sup>-X-CO-NR<sup>24</sup>R<sup>25</sup>, -X-CS-NR<sup>24</sup>R<sup>25</sup>, or -X-SO<sub>2</sub>-NR<sup>24</sup>R<sup>25</sup> in another embodiment, ¼ is -X-CO-NR<sup>24</sup>R<sup>25</sup>, -X-CS-NR<sup>24</sup>R<sup>25</sup>, or -X-SO<sub>2</sub>-NR<sup>24</sup>R<sup>25</sup> in another embodiment, ¼ is -NR<sup>22</sup>R<sup>23</sup>. In another embodiment, ¼ is -OH.
In one embodiment, the compound of Formula (I) is of formula:

\[
\begin{array}{c}
R^1 \\
R^2 \\
R^3 \\
R^4 \\
R^5 \\
R^6
\end{array}
\]

wherein \( R^1, R^2, R^3, R^4, R^5, \) and \( \beta \) are defined as in any aspect or embodiment herein.

In another embodiment, the GGA derivative utilized is of formula:

\[
\begin{array}{c}
R^1 \\
R^2 \\
R^3 \\
R^4 \\
R^5 \\
R^6
\end{array}
\]

wherein \( R^1, R^2, R^3, R^4, \) and \( \beta \) are defined as in any aspect and embodiment here.

In one embodiment, the compound of Formula (II) is of formula:

\[
\begin{array}{c}
R^1 \\
R^2 \\
R^3 \\
R^4 \\
R^5 \\
R^6
\end{array}
\]

wherein \( R^1, R^2, R^3, R^4, R^5, \) and \( Q_3 \) are defined as in any aspect or embodiment herein.

In another embodiment, the GGA derivative utilized is of formula:

\[
\begin{array}{c}
R^1 \\
R^2 \\
R^3 \\
R^4 \\
R^5 \\
R^6
\end{array}
\]

wherein \( R^1, R^2, R^3, R^4, m, n, x, R^{24} \) and \( P^{24} \) are defined as in any aspect and embodiment here.

In another embodiment, the GGA derivative utilized is of formula:

\[
\begin{array}{c}
R^1 \\
R^2 \\
R^3 \\
R^4 \\
R^5 \\
R^6
\end{array}
\]

wherein \( R^1, R^2, R^3, m, n, \) and \( R^{24} \) are defined as in any aspect and embodiment here.

In another embodiment, the GGA derivative utilized is of formula:

\[
\begin{array}{c}
R^1 \\
R^2 \\
R^3 \\
R^4 \\
R^5 \\
R^6
\end{array}
\]

wherein \( R^{24} \) is defined as in any aspect and embodiment here.

In another embodiment, the GGA derivative utilized is of formula:

\[
\begin{array}{c}
R^1 \\
R^2 \\
R^3 \\
R^4 \\
R^5 \\
R^6
\end{array}
\]

wherein \( R^{24} \) is defined as in any aspect and embodiment here.

In another embodiment, the GGA derivative utilized is of formula:
wherein $R^4$ is defined as in any aspect and embodiment here.

[0114] In another embodiment, the GGA derivative utilized is of formula:

\[
\begin{align*}
\text{Structure}
\end{align*}
\]

wherein $R^{24}$ is defined as in any aspect and embodiment here.

[0115] In another embodiment, the GGA derivative utilized is of formula:

\[
\begin{align*}
\text{Structure}
\end{align*}
\]

wherein $R^{24}$ and $R^{25}$ are defined as in any aspect and embodiment here.

[0116] In another embodiment, the GGA derivative utilized is of formula:

\[
\begin{align*}
\text{Structure}
\end{align*}
\]

wherein $R^{24}$ is defined as in any aspect and embodiment here.

[0117] In another embodiment, the GGA derivative utilized is of formula:

\[
\begin{align*}
\text{Structure}
\end{align*}
\]

wherein $R^{24}$ and $R^{25}$ are defined as in any aspect and embodiment here.

[0118] In one embodiment, $m$ is 0. In another embodiment, $m$ is 1.

[0119] In another embodiment, $n$ is 0. In another embodiment, $n$ is 1. In another embodiment, $n$ is 2.

[0120] In another embodiment, $m+n$ is 1. In another embodiment, $m+r$ is 2. In another embodiment, $m+n$ is 3.

[0121] In another embodiment, $R^1$ and $R^2$ are independently $C_1-C_6$ aikyi. In another embodiment, $R^1$ and $R^2$ independently are methyl, ethyl, or isopropyl.
[0122] In another embodiment, R² and R³ together with the carbon atom they are attached to form a C₅-C₇ cycloalkyl ring optionally substituted with 1-3 C₁-C₅ alky1 groups. In another embodiment, R² and R³ together with the carbon atom they are attached to form a ring that is:

In another embodiment, R⁴, R⁵, and R⁶ are independently C₃-C₅ alkyl. In another embodiment, one of R³, R⁴, and R⁵ are alky1, and the rest are hydrogen. In another embodiment, two of R³, R⁴, and R⁵ are alky1, and the rest are hydrogen. In another embodiment, R³, R⁴, and R⁵ are hydrogen. In another embodiment, R³, R⁴, and R⁵ are methyl.

[0124] In another embodiment, % is -X-CO₂-NR²⁵. In another embodiment, ⁴ is -X-CS₂-NR²⁵. In another embodiment, Q₂ is -X-SO₂-NR²⁵. In another embodiment, ⁴ is -OCNH₂⁺⁴⁴, -OCO⁻¹⁴⁰⁺²⁵, -NHCONH₂⁺⁴⁴, -NHCO⁻¹⁴⁰⁺²⁵, -OCSNH₂⁺⁴⁴, -OCNR₂⁺⁴⁴⁺²⁵. In another embodiment, X is -N-R²⁺⁴⁴. In another embodiment, X is or -CR₂⁺⁴⁴⁺²⁵.

[0126] In another embodiment, one of R²⁴ and R²⁵ is hydrogen. In another embodiment, one or both of R²⁴ and R²⁵ are C₁-C₅ alky1. In another embodiment, one or both of R²⁴ and R²⁵ are C₁-C₅ alky1, optionally substituted with an R⁰⁺ group, wherein R⁰⁺ is -CO₂H or an ester thereof, C₁-C₅ alky1, C₃-C₁₀ cycloalkyl, C₂-C₅ heterocycly1, C₆-C₁₂ aryl, or C₆-C₁₂ heteroaryl. In another embodiment, one or both of R²⁴ and R²⁵ are C₃-C₁₀ cycloalkyl. In another embodiment, one or both of R²⁴ and R²⁵ are C₃-C₁₀ cycloalkyl. In another embodiment, one or both of R²⁴ and R²⁵ are C₃-C₁₀ cycloalkyl substituted with 1-3 alky1 groups. In another embodiment, one or both of R²⁴ and R²⁵ are C₃-C₁₀ cycloalkyl. In another embodiment, one or both of R²⁴ and R²⁵ are Cs-C₁₀ aryl. In another embodiment, one or both of R²⁴ and R²⁵ are C₂-C₁₀ heteroaryl. In another embodiment, R²⁴ and R²⁵ together with the nitrogen atom they are attached to form a 5-7 membered heterocycle.

[0127] In another embodiment, R²⁰ is -CO₂H or an ester thereof. In another embodiment, R⁰⁺ is C₁-C₅ alky1. In another embodiment, R²⁰ is C₂-C₁₀ cycloalkyl. In another embodiment, R²⁰ is C₂-C₁₀ cycloalkyl. In another embodiment, R²⁰ is C₇-C₈ heterocycly1. In another embodiment, R²⁰ is C₆-C₁₀ aryl. In another embodiment, R²⁰ is or C₂-C₁₀ heteroaryl.
In another embodiment, the GGA derivative utilized is of formula (II):

or a pharmaceutically acceptable salt thereof, wherein

\( m \) is 0 or 1;
\( n \) is 0, 1, or 2;

each \( R^1 \) and \( R^2 \) are independently \( \text{C}_1-\text{C}_6 \) alkyl, or \( R^1 \) and \( R^2 \) together with the carbon atom they are attached to form a \( \text{C}_2-\text{C}_7 \) cycloalkyl ring optionally substituted with 1-3 \( \text{C}_1-\text{C}_6 \) alkyl groups;

each of \( R^3, R^4, \) and \( R^5 \) independently are hydrogen or \( \text{C}_1-\text{C}_6 \) alkyl;
\( \beta\gamma \) is \(-\text{X-CO-NR}^{24}\text{R}^{24} \) or \(-\text{X-SO}_2\text{NR}^{24}\text{R}^{25} \);
\( X \) is \(-\text{O}-.\), \(-\text{N}^{26}.\), or \(-\text{CR}^{27}\text{R}^{28} \);
\( \text{R}^{26} \) is hydrogen or together with \( \text{R}^{24} \) or \( \text{R}^{25} \) and the intervening atoms form a 5-7 membered ring optionally substituted with 1-3 \( \text{C}_1-\text{C}_6 \) alkyl groups;

each \( \text{R}^{27} \) and \( \text{R}^{28} \) independently are hydrogen, \( \text{C}_1-\text{C}_6 \) alkyl, \(-\text{COR}^{21} \) or \(-\text{CO}_2\text{R}^{21} \), or \( \text{R}^{27} \) together with \( \text{R}^{24} \) or \( \text{R}^{25} \) and the intervening atoms form a 5-7 membered cycloalkyl or heterocyclyl ring optionally substituted with 1-3 \( \text{C}_1-\text{C}_6 \) alkyl groups;

each \( \text{R}^{24} \) and \( \text{R}^{25} \) independently is hydrogen,

\( \text{C}_1-\text{C}_9 \) alkyl, optionally substituted with \(-\text{CO}_2\text{H} \) or an ester thereof, \( \text{C}_1-\text{C}_{10} \) preferably \( \text{C}_2-\text{C}_8 \) cycloalkyl, \( \text{C}_2-\text{C}_9 \) heterocyclyl, \( \text{C}_6-\text{C}_{10} \) aryl, or \( \text{C}_2-\text{C}_{10} \) heteroaryl,

\( \text{C}_3-\text{C}_{15} \) cycloalkyl,

\( \text{C}_3-\text{C}_8 \) heterocyclyl,

\( \text{C}_9-\text{C}_{11} \) aryl, or

\( \text{C}_2-\text{C}_{15} \) heteroaryl,

wherein each cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-3 \( \text{C}_1-\text{C}_6 \) alkyl groups, or \( \text{R}^{24} \) and \( \text{R}^{25} \) together with the nitrogen atom they are attached to form a 5-7 membered heterocycle.

[0129] In another embodiment, utilized herein are compounds of formula:
In another aspect, the GGA derivative utilized herein is of Formula (I) or a pharmaceutically acceptable salt of each thereof, wherein:

- $m$ is 0 or 1;
- $n$ is 0, 1, or 2;
- each $R^1$ and $R^2$ are independently $C_1-C_6$ alkyl, or $R^1$ and $R^2$ together with the carbon atom they are attached to form a $C_5-C_7$ cycloalkyl ring optionally substituted with 1-3 $C_1-C_6$ alkyl groups;
- each of $R^3$, $R^4$, and $R^5$ independently are hydrogen or $C_1-C_6$ alkyl;
- $Q_A$ is selected from the group consisting of:

$\begin{align*}
X^1 \text{SO}_2^- & , \\
X^1 \text{CR}^2 \text{R}^3 & , \\
X^2 & , \\
Y^1 & , \\
Y^2 & ,
\end{align*}$

when $X^1$ is bonded via a single bond, $X^1$ is $-\text{OR}^{10}$, $-\text{NR}^{11}$, or $-\text{CR}^{32}\text{R}^{33}$, and when $X^1$ is bonded via a double bond, $X^1$ is $-\text{CR}^{16}\text{R}^{17}$;

- $Y^1$ is hydrogen, $-\text{OH}$ or $-\text{OR}^{10}$, $Y^2$ is $-\text{OH}$, $-\text{OR}^{11}$ or $-\text{NHR}^{12}$, or $Y^1$ and $Y^2$ are joined to form an oxo group ($=\text{O}$), an imine group ($=\text{NR}^{13}$), a oxime group ($=\text{NOR}^{14}$), or a substituted or unsubstituted vinylidene ($=\text{CR}^{16}\text{R}^{17}$);

- $R^4$ is $C_1$ alkyl optionally substituted with 1-3 alkoxy or 1-5 halo group, $C_2-C_3$ alkenyi, $C_2-C_6$ alkylnyl, $C_3-C_7$ cycloalkyl, $C_6-C_{10}$ aryl, $C_5-C_8$ heterocyclyl, or $C_2-C_{10}$ heteroaryl, wherein each cycloalkyl or heterocyclyl is optionally substituted with 1-3 $C_1-C_6$ alkyl groups.
or wherein each aryl or heteroaryl is independently substituted with 1-3 C1-C6 alkyl or nitro groups, or R3 is - N R1 R5;  

R1 is hydrogen or together with R0 and the intervening atoms form a 5-7 membered ring optionally substituted with 1-3 C1-C6 alkyl groups;  

each R2 and R3 independently are hydrogen, C1-C6 alkyl, C1-C6 alkenyl, C1-C6 alkynyl, C2-C10 cycloalkyl, or 3 C3-C6 heterocycyi, wherein each cycloalkyl, heterocycyi, or aryl, is optionally substituted with 1-3 alkyi groups;  

R10 is C1-C6 alkyl;  

R8 and R12 are independently C1-C6 alkyl, C1-C6 alkenyl, or C1-C6 alkynyl, cycloalkyl, or CON(R15)2, or R8 and R12 together with the intervening carbon atom and oxygen atoms form a heterocycle optionally substituted with 1-3 C1-C6 alkyl groups;  

R13 is C1-C6 alkyi or C2-C10 cycloalkyl optionally substituted with 1-3 C1-C6 alkyl groups;  

R14 is hydrogen, C3-C6 heterocycyi, or C1-C6 alkyi optionally substituted with a ~C02H or an ester thereof or a C6-C10 aryl, C6-C10 alkenyl, C6-C10 alkynyl, C2-C10 cycloalkyl, or 3 C3-C6 heterocycyi, wherein each cycloalkyl, heterocycyi, or aryl, is optionally substituted with 1-3 alkyi groups;  

each R15 independently are hydrogen, C1-C10 cycloalkyl, C1-C6 alkyi optionally substituted with 1-3 substituents selected from the group consisting of -C02H or an ester thereof, aryl, or C1-C6 heterocycyi, or two R15 groups together with the nitrogen atom they are bonded to form a 5-7 membered heterocycle;  

R16 is hydrogen or C1-C6 alkyl;  

R17 is hydrogen, C2-C6 alkyl substituted with 1-3 hydroxy groups, -CHO, or is C02H or an ester thereof;  

each R14 and R15 independently is hydrogen, C1-C6 alkyl, optionally substituted with ~C02H or an ester thereof, C3-C10 cycloalkyl, C3-C6 heterocycyi, C6-C10 aryl, or C2-C10 heteroaryl, or is C1-C6 cycloalkyl, C1-C6 heterocycyi, C6-C10 aryl, or C2-C10 heteroaryl, wherein each cycloalkyl, heterocycyi, aryl, or heteroaryl is optionally substituted with 1-3 alkyi groups, or R14 and R15 together with the nitrogen atom they are attached to form a 5-7 membered heterocycle; and  

each R14 independently is C1-C6 alkyl.
In one embodiment, \( m \) is 0. In another embodiment, \( m \) is 1. In another embodiment, \( n \) is 0. In another embodiment, \( n \) is 1. In another embodiment, \( n \) is 2.

In one embodiment, the compound of Formula (1!!) is of formula:

\[
\begin{array}{c}
R^1 \\
\vdots \\
R^5 \\
\end{array}
\]

wherein \( R_3, R^1, R^2, R^4, R^5, R^6, X^1, Y^1 \), and \( Y^2 \) are defined as in any aspect or embodiment herein.

In one embodiment, the GGA derivative utilized is of formula:

\[
\begin{array}{c}
R^1 \\
\vdots \\
R^5 \\
\end{array}
\]

wherein \( R^1, R^2, R^3, R^4, R^5, X^1, Y^1 \), and \( Y^2 \) are defined as in any aspect and embodiment here.

In another embodiment, the GGA derivative utilized is of formula:

\[
\begin{array}{c}
R^1 \\
\vdots \\
R^5 \\
\end{array}
\]

wherein \( R^1, R^2, R^3, R^4, R^5, X^1 \), and \( Y^2 \) are defined as in any aspect and embodiment herein.

In another embodiment, the GGA derivative utilized is of formula:

\[
\begin{array}{c}
R^1 \\
\vdots \\
R^5 \\
\end{array}
\]

wherein \( R^1, R^2, R^3, R^4, R^5 \) and \( X^1 \) are defined as in any aspect and embodiment herein.

In another embodiment, the GGA derivative utilized is of formula:

\[
\begin{array}{c}
R^1 \\
\vdots \\
R^5 \\
\end{array}
\]

wherein \( R^1, R^2, R^3, R^5 \), and \( Q_4 \) are defined as in any aspect and embodiment herein.

In another embodiment, the GGA derivative utilized is of formula:

\[
\begin{array}{c}
R^1 \\
\vdots \\
R^5 \\
\end{array}
\]

wherein \( R^1, R^2, R^3, X^1 \), and \( R^6 \) are defined as in any aspect and embodiment here.

In another embodiment, the GGA derivative utilized is of formula:

\[
\begin{array}{c}
R^1 \\
\vdots \\
R^5 \\
\end{array}
\]

wherein \( R^1, R^2, R^3, R^4, R^5, m, n, X^1 \), and \( R^6 \) are defined as in any aspect and embodiment here.

In another embodiment, the GGA derivative utilized is of formula:
wherein $R^1$, $R^2$, $R^3$, $R^4$, $m$, $n$, and $R^{34}$ are defined as in any aspect and embodiment here.

[0139] In another embodiment, the GGA derivative utilized is of formula:

![Chemical Structure](image)

wherein $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $m$, $n$, and $R^{15}$ are defined as in any aspect and embodiment here.

[0140] In another embodiment, each $R^1$ and $R^2$ are $C_3$-$C_6$ alkyl. In another embodiment, each $R^3$ and $R^4$ are methyl, ethyl, or isopropyl. In another embodiment, $R^1$ and $R^2$ together with the carbon atom they are attached to form a 5-6 membered ring optionally substituted with 1-3 $C_1$-$C_6$ alkyl groups. In another embodiment, $R^1$ and $R^2$ together with the carbon atom they are attached to form a ring that is:

![Chemical Structure](image)

[0141] In another embodiment, $R^3$, $R^4$, and $R^5$ are $C_1$-$C_6$ alkyl. In another embodiment, one of $R^2$, $R^4$, and $R^5$ are alkyl, and the rest are hydrogen. In another embodiment, two of $R^2$, $R^4$, and $R^5$ are alkyl, and the rest are hydrogen. In another embodiment, $R^1$, $R^4$, and $R^5$ are hydrogen. In another embodiment, $R^2$, $R^4$, and $R^5$ are methyl.

[0142] In another embodiment, $X^1$ is $O$. In another embodiment, $X^1$ is $NR^{31}$. In another embodiment, $X^1$ is hydrogen. In another embodiment, $R^{31}$ together with $R^{30}$ and the intervening atoms form a 5-7 membered ring optionally substituted with 1-3 $C_1$-$C_6$ alkyl groups. In another embodiment, $X^3$ is $-CR^2R^{32}$. In another embodiment, $X^1$ is $-CR^3$. In another embodiment, each $R^{32}$ and $R^{30}$ independently are hydrogen, $C_1$-$C_6$ alkyl, $-COR^{81}$, or $-CO_2R^{32}$. In another embodiment, $R^{32}$ is hydrogen, and $R^{30}$ is hydrogen, $C_1$-$C_6$ alkyl, $-COR^{81}$, or $-CO_2R^{32}$.

[0143] In another embodiment, $R^{33}$ is hydrogen. In another embodiment, $R^{33}$ is $C_1$-$C_6$ alkyl. In another embodiment, $R^{33}$ is methyl. In another embodiment, $R^{33}$ is $-CO_2R^{32}$. In another embodiment, $R^{33}$ is $-COR^{81}$.

[0144] In another embodiment, $R^{32}$ together with $R^{30}$ and the intervening atoms form a 5-7 membered ring. In another embodiment, the moiety:
which is \( Q_4 \) has the structure:

wherein \( R^{33} \) is hydrogen, \( C_2-C_6 \) alkyl, or \(-C_0 \) :R\( ^{41} \) and \( n \) is 1, 2, or 3. Within these embodiments, in certain embodiments, \( R^{33} \) is hydrogen or \( C_1-C_6 \) alkyl. In one embodiment, \( R^{33} \) is hydrogen, in another embodiment, \( R^{33} \) is \( C_1-C_6 \) alkyl.

[0145] In another embodiment, \( R^{30} \) is \( d-C_6 \) alkyl. In another embodiment, \( R^{10} \) is methyl, ethyl, butyl, isopropyl, or tertiary butyl. In another embodiment, \( R^{10} \) is d-d alkyl substituted with 1-3 alkoxy or 1-5 halo group. In another embodiment, \( R^{30} \) is alkyl substituted with an alkoxy group. In another embodiment, \( R^{10} \) is alkyl substituted with 1-5, preferably, 1-3, halo, preferably fluoro, groups.

[0146] In another embodiment, \( R^{30} \) is \( NR^{24}R^{26} \). In a preferred embodiment, \( R^{15} \) is H. In a preferred embodiment, \( R^{14} \) is \( d-C_6 \) alkyl, optionally substituted with a group selected from the group consisting of \(-C_0 \) :H or an ester thereof, \( C_1-C_{12} \) cycloalkyl, \( C_3-C_8 \) heterocyclyl, \( C_5-C_{10} \) cycloalkyl, \( C_5-C_{10} \) aryl, or \( C_2-C_{10} \) heteroaryl. In another preferred embodiment, \( R^{24} \) is \( C_2-C_8 \) cycloalkyl, \( C_3-C_8 \) heterocyclyl, \( C_5-C_{10} \) aryl, or \( C_2-C_{10} \) heteroaryl. In a more preferred embodiment, \( R^{34} \) is \( C_2-C_{10} \) cycloalkyl.

[0147] In another embodiment, \( R^{30} \) is \( C_2-C_6 \) alkenyi or \( C_2-C_6 \) alkynyi. In another embodiment, \( R^{14} \) is \( C_1-C_{10} \) cycloalkyl. In another embodiment, \( R^{30} \) is \( C_1-C_{10} \) cycloalkyl substituted with 1-3 \( C_1-C_5 \) alkyl groups. In another embodiment, \( R^{30} \) is cyclopentyl, cyclohexyl, or adamantyl. In another embodiment, \( R^{10} \) is \( C_2-C_{10} \) heteroaryl. In another embodiment, \( R^{30} \) is a 3-7 membered heteroaryl containing at least 1 oxygen atom. In another embodiment, \( R^{11} \) is \( C_2-C_{10} \) aryl, \( C_3-C_6 \) heterocyclyl, or \( C_5-C_{10} \) heteroaryl, wherein each aryl, heterocyclyl, or heteroaryl is optionally substituted with 1-3 \( C_1-C_5 \) alkyl groups.

[0148] In another embodiment, \( Y^2 \) is \(-O-R^{13} \). In another embodiment, \( Y^1 \) and \( Y^2 \) are joined to form \( \equiv NR^{24} \). In another embodiment, \( Y^1 \) and \( Y^2 \) are joined to form \( \equiv NOR^{13} \). In another embodiment, \( Y^1 \) and \( Y^2 \) are joined to form \( \equiv CR^{13}R^{17} \).
In another embodiment, R is \(\text{COR}^3\). In another embodiment, \(R^3\) is \(C_1-C_6\) alkyl optionally substituted with an alkoxy group. In another embodiment, \(R^0\) is \(C_3-C_9\) cycloalkyl. In another embodiment, \(R^0\) is hydrogen. In another embodiment, \(R^3\) is \(C_1-C_6\) alkyl. In another embodiment, \(R^3\) is \(\text{COR}^3\).

In another embodiment, \(R^4\) is \(C_1-C_6\) alkyl, optionally substituted with \(-\text{CO}_2\text{H}\) or an ester thereof, \(C_1-C_8\) cycloalkyl, \(C_1-C_9\) heterocyclyl, \(C_1-C_{10}\) aryl, or \(C_1-C_{10}\) heteroaryl. In another embodiment, \(R^4\) is \(C_2-C_6\) cycloalkyl, \(c_3-c_8\) heterocyclyl, \(C_1-C_{10}\) aryl, or \(C_2-C_{10}\) heteroaryl.

In another embodiment, \(R^1\) is hydrogen. In another embodiment, \(R^4\) is \(C_1-C_6\) alkyl optionally substituted with a \(-\text{CO}_2\text{H}\) or an ester thereof or a \(C_6-C_{10}\) aryl optionally substituted with 1-3 alkoxy groups. In another embodiment, \(R^4\) is \(C_2-C_6\) alkenyl. In another embodiment, \(R^4\) is \(C_2-C_6\) alkenyl. In another embodiment, \(R^4\) is \(C_3-C_6\) cycloalkyl optionally substituted with 1-3 alkyl groups. In another embodiment, \(R^4\) is \(C_2-C_6\) heterocyclyl optionally substituted with 1-3 alkoxy groups.

In another embodiment, preferably, \(R^6\) is hydrogen. In another embodiment, \(R^7\) is \(-\text{CO}_2\text{H}\) or an ester thereof. In another embodiment, \(R^7\) is \(C_1-C_9\) alkyl substituted with 1-3 hydroxy groups. In another embodiment, \(R^7\) is \(C_1-C_3\) alkyl substituted with 1 hydroxy group. In another embodiment, \(R^7\) is \(-\text{CH}_2\text{OH}\).

In another embodiment, \(R^6\) and \(R^7\) together with the intervening carbon atom and oxygen atoms form a heterocycle of formula:

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{q} & \quad \text{R}^3 \\
\text{p} & \quad \text{R}^2
\end{align*}
\]

where \(q\) is 0 or 1, \(p\) is 0, 1, 2, or 3, and \(R^2\) is \(C_1-C_6\) alkyl.

In another embodiment, \(q\) is 1. In another embodiment, \(q\) is 2. In another embodiment, \(p\) is 0. In another embodiment, \(p\) is 1. In another embodiment, \(p\) is 2. In another embodiment, \(p\) is 3.
In one aspect, the GGA derivative utilized herein is of Formula (IV):

![Formula (IV)]

or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, where n

1. n is 0 or 1;
2. n is 0, 1, or 2;
3. each R₁ and R² are independently C₁-C₆ alkyl, or R¹ and R² together with the carbon atom
4. each of R₃, R₄, and R₅ independently are hydrogen or C₁-C₆ alkyl, or R³ and (R₄ and R₅ together with
5. the intervening carbon atoms form a 6 membered aryl ring, or a 5-8 membered cycloalkenyl
6. ring, or a 5-14 membered heteroaryl or heterocycle, wherein each aryl, cycloalkenyl, hetroaryi, or heterocycle, ring is optionally substituted with 1-2 substituents selected from
7. the group consisting of halo, hydroxy, oxo, -N(R³)₂ and C₁-C₆ alkyl group;
8. Q₅ is -C(=O)H, -CO₂H or -CH=CHCO₂H, or a C₁-C₆ alkyl ester or acyl halide thereof, wherein the ester is optionally substituted with -CO-phenyl; a 5-10 membered aryl or a 5-14
9. membered heteroaryl or heterocycle containing up to 6 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, and further wherein the aryl, heteroaryl, or heterocyclic ring is optionally substituted with 1-3 substituents selected from the group consisting of:
10. hydroxy, oxo, -N(R³)₂, C₁-C₆ alkoxy group, and C₁-C₆ alkyl group,
11. wherein the alkyl group is optionally substituted with 1-3 substituents selected from hydroxy, NH₂, C₁-C₆ aryl, -C₆H₅ or an ester or an amide thereof,
12. a 5-9 membered heteroaryl containing up to 3 ring heteroatoms, wherein the heteroaryl is optionally substituted with 1-3 hydroxy, -N(R³)₂, and C₁-C₆ alkyl group,
13. benzyl, and phenyl optionally substituted with 1-3 substituents selected from the group consisting of C₁-C₆ alkyl, alkoxy, hydroxy, and halo groups; and
wherein each R⁰ independently is hydrogen or C₁-C₆ alkyl.

As used herein, the compound of Formula (IV) includes tautomers and optical isomers such as enantiomers and diastereomers. As also used herein, an ester refers
preferably to a phenyl or a C_{2-6} alkyl ester, which phenyl or alkyl group is optionally substituted with an amino group. As used herein, an amide refers preferably to a moiety of formula -CON(R^1)R^2, wherein R^0 is defined as above.

In some embodiment, Q^6 is selected from a group consisting of oxazole, oxadiazole, oxazoline, azalactone, imidazole, diazole, triazole, and thiazole, wherein each heteroaryl or heterocycle is optionally substituted as disclosed above.

[0158] In one embodiment, the GGA derivative utilized is of formula IV-A:

\[
\text{IV-A}
\]

[0159] In another embodiment, the GGA derivative utilized is of formula IV-B:

\[
\text{IV-B}
\]

wherein R^1, R^2, R^4, and c^6 are defined as in any aspect and embodiment here.

[0160] In another embodiment, Q^6 is selected from the group consisting of:

\[
\text{and}
\]

wherein R^{11} is C_{2-6} alkyl, C_{5-10} aryl, C_{3-5} heteroaryl, C_{5-10} cycloalkyl, and the alkyl group is optionally substituted with 1-3 C_{1-6} aryl, C_{2-6} heteroaryl, C_{3-6} heteroaryl, C_{3-10} cycloalkyl groups, and the aryl, heteroaryl, heteroaryl, cycloalkyl groups are optionally substituted with 1-3 C_{1-6} alkyl, C_{1-6} alkoxy, halo, preferably chloro or fluoro, C_{6-10} aryl, C_{2-6} heteroaryl, C_{1-6} heteroaryl, C_{3-10} cycloalkyl group.

[0161] In another embodiment, Q^6 is phenyl, optionally substituted as described herein. In another embodiment, Q^6 is benzimidazole, benzindazole, and such other 5-6 fused 9-membered bicyclic heteroaryl or heterocycle. In another embodiment, Q^6 is quinoline, isoquinoline, and such other 6-6 fused 10 membered heteroaryl or heterocycle. In another r
em bodiment, \( \frac{3}{4} \) is benzodiazepine or a derivative thereof, such as, a benzodiazepinone. Various benzodiazepine and derivatives thereof are well known to the skilled artisan.

[0182] In another embodiment, \( m \) is 0. In another embodiment, \( m \) is 1.

[0183] In another embodiment, \( n \) is 0. In another embodiment, \( n \) is 1. In another embodiment, \( n \) is 2.

[0184] In another embodiment, \( m+n \) is 1. In another embodiment, \( m+n \) is 2. In another embodiment, \( m+n \) is 3.

[0185] In another embodiment, \( R^1 \) and \( R^2 \) are independently \( C_1-C_6 \) alkyl. In another embodiment, \( R^1 \) and \( R^2 \) independently are methyl, ethyl, or isopropyl.

[0186] In another embodiment, \( R^1 \) and \( R^2 \) together with the carbon atom they are attached to form a \( C_5-C_7 \) cycloalkyl ring optionally substituted with 1-3 \( C_1-C_6 \) alkyl groups, in another embodiment, \( R^1 \) and \( R^2 \) together with the carbon atom they are attached to form a ring that is:

\[
\text{OR} \quad \text{OR}
\]

[0187] In another embodiment, \( R^1, R^4, \) and \( R^5 \) are independently \( C_1-C_6 \) alkyl. In another embodiment, one of \( R^3, R^4, \) and \( R^5 \) are alkyl, and the rest are hydrogen. In another embodiment, two of \( R^3, R^4, \) and \( R^5 \) are alkyl, and the rest are hydrogen. In another embodiment, \( R^3, R^4, \) and \( R^5 \) are hydrogen, in another embodiment, \( R^3, R^4, \) and \( R^5 \) are methyl.

[0188] In another embodiment, this invention utilizes a compound selected from the group consisting of:
wherein \( R^{11} \) is defined as above.

[0169] in another aspect, GGA derivatives utilized herein are of formula (V):

\[
(V)
\]

or a pharmaceutically acceptable salt thereof, wherein

- \( m \) is 0 or 1;
- \( n \) is 0, 1, or 2;
- each \( R^1 \) and \( R^2 \) independently are \( C_1^x-C_3^x \) alkyl, or \( R^1 \) and \( R^2 \) together with the carbon atom they are attached to form a \( C_2^z-C_7 \) cycloalkyl ring optionally substituted with 1-3 \( C_1^x-C_3^x \) alkyl groups;
- each of \( R^3, R^4, \) and \( R^5 \) independently is hydrogen or \( C_1-C_5 \) alkyl;
- \( Q_6 \) is selected from the group consisting of:

\[
\begin{align*}
\text{when } X^2 \text{ is bonded via a single bond, } X^2 & = -Q, -MR^{2}, \text{ or } -CR^5R^4; \\
\text{and when } X^3 \text{ is bonded via a double bond, } X^2 & = -CR^5; \\
Y^{11} & \text{ is hydrogen, -OH or -OR};
\end{align*}
\]

\]
is -OH, -OR, -NHR\textsuperscript{1}, -NR\textsuperscript{2}, or -\textsuperscript{1}CO-NR\textsuperscript{8}R\textsuperscript{9}.

\( \gamma \) and \( \gamma \) are joined to form an oxo group (=\( \text{O} \)), an imine group (=\( \text{N} \) R\textsuperscript{6}), a oxime group (=\( \text{N} \) O R\textsuperscript{6}), or a substituted or unsubstituted vinylidene (=\(-\text{CF}_4\)).

\( R\textsuperscript{51} \ = \ C_1-Q \) alkyl, \( C_2-Q \) alkyl, or \( C_2-Q \) alkenyl, \( C_2-Q \) alkynyl, \( C_2-Q \) cycloalkyl, \( C_2-Q \) heterocyclic, \( C_2-Q \) aryl, \( C_2-Q \) heteroaryl, or \( NR\textsuperscript{3}\textsuperscript{3}R\textsuperscript{4} \), wherein each cycloalkyl or heterocyclic is optionally substituted with 1-3 C\textsuperscript{1}-Q alkyl groups, and wherein each ary! or heteroaryl is optionally substituted independently with 1-3 nitro and C\textsuperscript{1}-C\textsuperscript{1} alky! groups;

\( R\textsuperscript{52} \ = \) hydrogen or together with \( R\textsuperscript{51} \) and the intervening atoms form a 5-7 membered ring optionally substituted with 1-3 C\textsuperscript{1}-Q alkyl groups;

each \( R\textsuperscript{53} \) and \( R\textsuperscript{54} \) independently are hydrogen, C\textsuperscript{1}-Q alkyl, -\textsuperscript{2}COR\textsuperscript{1}, -\textsuperscript{2}CO, 2-R\textsuperscript{1}, or -\textsuperscript{2}CO-NH\textsuperscript{1}R\textsuperscript{1}; or \( R\textsuperscript{55} \) together with \( R\textsuperscript{56} \) and the intervening atoms form a 5-7 membered cycloalkyl or heterocyclic ring optionally substituted with 1-3 C\textsuperscript{1}-Q alkyl groups;

\( R\textsuperscript{55} \ = \ C_1-Q \) alkyl;

each \( R\textsuperscript{56} \) and \( R\textsuperscript{57} \) independently are C\textsuperscript{1}-Q alkyl, C\textsuperscript{3}-Q cycloalkyl, -\textsuperscript{0}O R\textsuperscript{1}; or CO-N[R\textsuperscript{52}] R\textsuperscript{2}; or \( R\textsuperscript{55} \) and \( R\textsuperscript{56} \) together with the intervening carbon atom and oxygen atoms form a heterocyclic optionally substituted with 1-3 C\textsuperscript{1}-Q alkyl groups;

\( R\textsuperscript{58} \ = \ C_3-Q \) cycloalkyl, C\textsuperscript{1}-Q alkyl optionally substituted with -HO, CO\textsuperscript{2}H or an ester thereof, or C\textsuperscript{3}-C\textsuperscript{10} cycloalkyl.

\( R\textsuperscript{59} \ = \) hydrogen or C\textsuperscript{1}-C\textsuperscript{1} alkyl;

\( R\textsuperscript{60} \ = \) C\textsuperscript{1}-C\textsuperscript{6} alkyl or C\textsuperscript{3}-C\textsuperscript{10} cycloalkyl optionally substituted with 1-3 C\textsuperscript{1}-Q alkyl groups, or is:

\( R\textsuperscript{61} \ = \) hydrogen, C\textsuperscript{2}-C\textsuperscript{8} heterocyclic, or C\textsuperscript{1}-Q alkyl optionally substituted with a -\textsuperscript{2}CO\textsuperscript{2}H or an ester thereof or a C\textsuperscript{6}-C\textsuperscript{10} aryl, C\textsuperscript{2}-C\textsuperscript{6} alkenyl, C\textsuperscript{2}-C\textsuperscript{6} alkynyl, C\textsuperscript{3}-C\textsuperscript{10} cycloalkyl, or a...
C$_1$-C$_8$ heterocyclyl, wherein each cycloalkyl, heterocyclyl, or aryl, is optionally substituted with 1-3 alkyl groups;

each R$_2^6$ independently are hydrogen, C$_3$-C$_{10}$ cycloalkyl, C$_1$-C$_6$ alkyl optionally substituted with 1-3 substituents selected from the group consisting of -CO$_2$H or an ester thereof, aryl, C$_3$-C$_8$ heterocyclyl, or two R$_2^5$ groups together with the nitrogen atom they are bonded to form a 5-7 membered heterocyde;

R$_5^6$ is hydrogen or C$_1$-C$_6$ alkyl;

R$_4^1$ is hydrogen, C$_1$-C$_6$ alkyl substituted with 1-3 hydroxy groups, -CHO, or is CO$_2$H or an ester thereof;

one or both of R$_5^5$ and R$_6^6$ independently are hydrogen, C$_1$-C$_6$ alkyl, optionally substituted with -CO$_2$H or an ester thereof, C$_3$-C$_{10}$ cycloalkyl, C$_3$-C$_8$ heterocyclyl, C$_2$-C$_{20}$ aryl, or C$_2$-C$_{10}$ heteroaryl, or is C$_3$-C$_{10}$ cycloalkyl, C$_1$-C$_6$ heterocyclyl, C$_3$-C$_{10}$ aryl, or C$_2$-C$_{12}$ heteroaryl, wherein each cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-3 alkyl groups, or R$_5^8$ and R$_6^6$ together with the nitrogen atom they are bonded to form a 5-7 membered heterocyde, and if only one of R$_6^8$ and R$_6^6$ are defined as above, then the other one is

R$_5^5$ is C$_2$-C$_6$ alkyl; and

R$_6^6$ is:

provided that, when X$_2$ is bonded via a single bond, and R$_5^5$ or R$_6^6$ is not -CONH$R^2_2$, Y" and Y" are joined to form an imine group (=NR$_6^6$), and R$_6^8$ is:

or Y" is -O-CO-NR$_5^5$R$_6^6$;

or provided that, when $\theta_4$ is:

40
and \( R^{63} \) is not \(-CONHR^{32}, Y^\prime \) is \(-\text{O}\text{-}\text{O}-\text{NR}^{58}R^{65}; \)

or provided that, when \( \gamma \) is \(-\text{OCO-NR}^{6}R^{56}, \) then at least one of \( R^{66} \) and \( R^{66} \)
is:

![Chemical structures](image)

[0170] In one embodiment, the GGA derivative utilized are of formula:
In another aspect, the GGA derivatives useful according to this invention is selected from:

\[ \text{Vil: } R_{12} = -\text{OH} \]
\[ \text{IX: } R_{12} = \text{Br} \]
\[ \text{X: } R_{12} = -\text{CH}_2\text{COOH}_3 \]
\[ \text{XII: } R_{13} = -\text{COOR}_{17} \]
\[ \text{XIII: } R_{15} = -\text{CH}_2\text{OH} \]

In another embodiment, examples of compounds utilized by this invention include certain compounds tabulated below.

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in another embodiment, examples of compounds utilized by this invention include certain compounds tabulated below.

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Exemplary compounds include:

- (6E,10E,14E)-7,11,15,19-tetramethyllicos-6,10,14-8-tetraen-3-one
- (6E,10F)-7,11,15-trimethylhexadeca-6,10,14-4-irien-3-one
- (E)-7,11-diracethyldec-6,10-dien-3-one
- (5E,9E,13E)-1,3,1-trifluoro-6,10,14-tetramethylnonadeca-5,9,13-tetraen-3-one

In certain aspects, the GGA derivative is a compound of Formula (XVI), (XIX) or (XX):

\[
\text{r a pharmaceutically acceptable salt thereof}
\]

wherein
$R^1$ is $C_3$-$C_{10}$ alkyl or $C_5$-$C_{10}$ alkenyl optionally substituted with 1-3 $C_6$-$C_{20}$ arylenes groups in the chain and that is optionally substituted with 1-3 halo, trifluoromethyl, -OR, -P(=O)(OR) or -NR=NR groups; $R^2$ is ($C_5$-$C_{10}$) alkyl, or $C_5$-$C_{10}$ alkenyl optionally substituted with 1-3 $C_6$-$C_{20}$ aryl groups, which are optionally substituted with 1-3 halo, trifluoromethyl, -OR, -P(=O)(OR) or -NR groups; each $R^3$, $R^4$, $R^5$, and $R^6$ is independently OH or $C_2$-$C_6$ alkoxy; each $R^7$, $R^8$, and $R^9$ is independently hydrogen, $C_3$-$C_6$ alkyl or $C_5$-$C_{20}$ aryl; and each $R^{10}$ is independently hydrogen, $C_1$-$C_6$ alkyl or $C_1$-$C_{20}$ aryl; or $R^{100}$ and $R^{101}$ together with the nitrogen to which they are attached form a $C_3$-$C_7$ heterocycle;

wherein each aryl group of $R^7$, $R^8$, $R^9$, $R^{100}$ and $R^{101}$ is optionally substituted with 1-3 $C_1$-$C_5$ alkyl, $C_2$-$C_6$ alkoxy, $C_5$-$C_{10}$ alyknyl, $C_1$-$C_6$ alkenoyloxy, $C_1$-$C_6$ alkoxyacrylonyl, halo, cyano, nitro, carboxy, trifluoromethyl, trifluoromethoxy, $NR^{102}R^{103}$, or $S(0)=NR^{102}R^{103}$ groups, wherein each $R^{102}$ and $R^{103}$ is independently hydrogen or $C_1$-$C_6$ alkyl;

$R^{104}$ and $R^{105}$ are independently selected from the group consisting of hydrogen, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_5$-$C_{10}$ alkenyln, optionally substituted $C_1$-$C_{20}$ aryl, optionally substituted $C_5$-$C_{10}$ aryloxy-$C_1$-$C_6$ alkyl, optionally substituted heteroaryly-$C_1$-$C_7$ alkyl, each heteroaryl having 2-14 ring carbon atoms and 1-6 ring heteroatoms selected preferably from N, O, S, and P, wherein each substituted aryl or substituted heteroaryl is independently substituted with 1-3 substituents selected from -OH, halo, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, -NO, and $NR^{100}R^{101}$ groups; or $R^{104}$ and $R^{105}$ together with the carbon atom to which they are attached form a $C_3$-$C_7$ cycloalkyl ring optionally substituted with 1-3 $C_1$-$C_6$ alkyl groups; $R^{106}$ and $R^{107}$ independently are hydrogen or $C_1$-$C_6$ alkyl; each $R^{108}$ and $R^{109}$ are independently selected from the group consisting of a hydrogen, $C_1$-$C_6$ alkyl, and a group of formula (XXI);
wherein \( R^{104}, R^{107} \) and \( n \) are as defined herein;

\[ Y = P = (OR^{108})(OR^{109}) \cdot -C0 \cdot 2R^{11} \] or \(-SO_2OR^{110}\), wherein \( R^{110} \) is selected from the group consisting of a hydrogen and \( C_1-C_6 \) alkyl;

\[ Z = \frac{N}{N} \quad (CH_2)_n \cdot \frac{N}{N} \]

wherein \( R^{111} \) is hydrogen or \( C_1-C_6 \) alkyl; \( A \) is \( C_2-C_9 \) alkylene which may have a substituent selected from \(-OH, \text{halo}, C_1-C_8 \) alkyl, and \( C_2-C_9 \) alkoxy groups on each carbon;

\( r \) is 0, 1, 2, 3, 4 or 5; and

\( n \) is 0, 1, 2, 3, 4 or 5.

In one aspect, the GGA derivative utilized herein is of formula (VII):

\[
\begin{align*}
R_{126} & \quad R_{125}CH_2 \\
R_{124}CH_2 & \quad R_{123}CH_2 \\
R_{122} & \quad Y \cdot R_{121}
\end{align*}
\]

wherein \( R_{121} \) is a lower (e.g. \( C_1-C_6 \)) alkyl group, optionally substituted with 1 to 4 substituents selected from the group consisting of halogen, hydroxy, lower alkyi, lower alkoxy, halogenated lower alkyl, halogenated lower alkoxy, cyano, a 5- or 6-membered (hetero) aromatic ring which may be substituted by hydroxy, lower alkoxy, halogen, amino, lower alkyiamino, cyano, nitro, and other (substituted) (hetero) aromatic rings;

\( R_{122} \) is hydrogen or \( C_1-C_4 \) alkyl; Both the \( R \) and \( S \) configurations are encompassed.

\( R_{123}, R_{124} \) and \( R_{125} \) are independently selected from hydrogen, substituted and nonsubstituted \( C_1-C_4 \) alkyi groups.

\( R_{126} \) is \( CH(O) \) or \( C_mH_{2r}X \), wherein \( m \) is 1-3 and \( X \) is -H, -OH or a 5- or 6-membered (hetero) aromatic ring; and

\( Y \) is \(-C(O)- \) or \(-C(=NO(R_{127})) \cdot \) wherein \( R_{127} \) is hydrogen or a \( C_1-C_6 \) alkyl group.

In another aspect, the compound is formula (VII):
in some embodiments, \( R^{100} \) and \( R^{101} \) together with the nitrogen to which they are attached form together with the nitrogen to which they are attached form a pyrrolidino, piperidino, morpholino, or thiomorpholino ring.

[0180] In another aspect, the GGA derivative utilized is of formula (XIXa):

\[ \text{(XIXa)} \]

wherein \( R^{104} \) and \( R^{105} \) each represent a hydrogen atom, a lower alkyl, cycloalkyl, alkenyl or alkynyl group, an aryl group which may be substituted, an aryalkyl group in which the aryl group may be substituted, or a heteroaryl or heteroaryalkyl group; \( R^{108} \) and \( R^{109} \) each represent a hydrogen atom, a lower alkyl group or an alkali metal; \( Y \) represents a group represented by the formula:

\[ \text{(XIXa)} \]

wherein \( R^{130} \) and \( R^{131} \) each represent a hydrogen atom, a lower alkyl group or an alkali metal; or a group represented by the formula : \(-\text{CO}\, R^{132} \) (wherein \( R^{132} \) represents a hydrogen atom, a lower alkyl group or an alkali metal); \( Z \) represents a group represented by the formula : \(-\text{(CH}_2\text{)}_m\text{ -} \) (wherein \( m \) is an integer of 0 to 3), a group represented by the formula : \(-\text{(CH}_2\text{)}_p\text{-CH}=\text{CH- -(CH}_2\text{)}_q\text{-} \) (wherein \( p \) is 0 or 1 and \( q \) is 1 or 2) or a group represented by the formula:

\[ \text{(XIXa)} \]

wherein \( R^{111} \) represents a hydrogen atom or a lower alkyl group; \( A \) represents an alkyne chain which has 1 to 5 carbon atoms and which may have a substituent on each carbon atom; and \( r \) is zero or an integer of 1 to 5; and \( n \) is zero or an integer of 1 to 5.
Exemplary compounds further include:

\[ \text{[0181]} \]
H \_3 O O C H \textsuperscript{+} \textsuperscript{(OCH}_3 \textsubscript{2} ; and

\begin{align*}
\text{H}_3 \text{C} & - \text{CH}_3 - \text{CH}_3 - \text{PO}(\text{OCH}_3)_2 \\
\text{H}_3 \text{C} & - \text{CH}_3 - \text{CH}_3 - \text{PO}(\text{OCH}_3)_2
\end{align*}

and the corresponding ethyl and other C\textsubscript{1}-C\textsubscript{6} alkyl esters.

[0182] A skilled artisan will understand that trans forms of GGA and GGA derivatives utilized herein can be replaced with the various corresponding cis forms and utilized in accordance with this invention. Such compounds can be in solely or substantially, such as at least 90%, at least 80%, at least 70%, at least 50% or at least 20% in the cis form. As will also be understood, various mixtures of cis and trans forms of GGA and GGA derivatives are also useful in accordance with this invention. In certain preferred embodiments, GGA and GGA derivatives containing substantially or solely a cis form of the compound may not be useful, without being mixed or conjugated with a drug, for treating a disease or a disorder.

[0183] Illustrative and nonlimiting anticancer agents and conjugates and their methods of synthesis are shown below. Illustrative and nonlimiting viral agents, such as Vidarabine, and conjugates and their methods of synthesis are also shown below.
Geranylgeranyl (GG)-alcohol/camptothecin conjugate:

\[
\text{MOM ether of GG-alcohol}
\]

\[
\text{GG-alcohol - I conjugate}
\]

Carbonate containing GG-alcohol/camptothecin conjugate:

\[
\text{GG-alcohol}
\]

\[
\text{GG-alcohol - I conjugate}
\]

Carbamate GG-alcohol/5-FU codrug or carrier conjugate:
Other antiviral drugs may be attached in similar fashion to the GG-alcohol or GG-acetone.

[0184] Illustrative and non-limiting examples of antibiotics useful in such compounds and certain non-limiting points of attachment (shown by an "\rightarrow") of such antibiotics to GGA or a GGA derivative are shown below.
Ciprofloxacin

Illustrative and non-limiting examples of glaucoma drugs useful in such compounds and certain non-limiting points of attachment (shown by an "\(-\rightarrow\)" of such drugs to GGA or a GGA derivative are shown below.

Synthesis of GGA derivatives

Certain methods for making GGA or certain GGA derivatives utilized herein are described in PCT publication nos. WO 2012/031028, WO 2013/052148, and WO 2013/130654, each of which are incorporated herein by reference in its entirety. Other GGA derivatives can be prepared by appropriate substitution of reagents and starting materials, as will be well known to the skilled artisan upon reading this disclosure.
The reactions are preferably carried out in a suitable inert solvent that will be apparent to the skilled artisan upon reading this disclosure, for a sufficient period of time to ensure substantial completion of the reaction as observed by thin layer chromatography, ^1H-NMR etc. If needed to speed up the reaction, the reaction mixture can be heated, as is well known to the skilled artisan. The final and the intermediate compounds are purified, if necessary, by various art known methods such as crystallization, precipitation, column chromatography, and the likes, as will be apparent to the skilled artisan upon reading this disclosure.

The compounds utilized in this invention are synthesized, e.g., from a compound of formula (III-A):

![Chemical Structure](image)

wherein n, R^1-R^5 and R^6 are defined as in Formula (I) above, following various well known methods upon substitution of reactants and/or altering reaction conditions as will be apparent to the skilled artisan upon reading this disclosure. The compound of Formula (III-A) is itself prepared by methods well known to a skilled artisan, for example, and without limitation, those described in PCT Pat. App. Pub. Nos. WO 2012/031028, WO 2013/052 148, and WO 2013/130654 (each supra). An illustrative and non-limiting method for synthesizing a compound of Formula (III-A), where n is 1, is schematically shown below.
Starting compound (iii), which is synthesized from compound (i) by adding isoprene derivatives as described here, is alkylated with a beta keto ester (iv), in the presence of a base such as an alkoxide, to provide the corresponding beta-ketoester (v). Compound (v) upon alkaline hydrolysis followed by decarboxylation provides ketone (vi). Keto compound (vi) is converted, following a Wittig Horner reaction with compound (vii), to the conjugated ester (viii). Compound (vi if) is reduced, for example with LiAlH₄, to provide alcohol (ix).

As will be apparent to the skilled artisan, a compound of Formula (H1), where n is 2, is synthesized by repeating the reaction sequence of alkylation with a beta-keto ester, hydrolysis, decarboxylation, Wittig-Horner oxidation, and LiAlH₄ reduction.

Certain illustrative and non-limiting synthesis of compounds utilized in this invention are schematically shown below. Compounds where Q¹ is -(OS)- or --SO₂- are synthesized by substituting the carbonyl group of the reactants employed, as will be apparent to the skilled artisan.

[001332] R¹ in these schemes may also correspond to R²₀ and R⁵₁ as defined herein. R² in the schemes below may also correspond to R₂⁶, R₃¹ and R₅² as defined herein. R₃ in the schemes below may also correspond to R₂⁷. R₄ and R₅₃ as defined herein. R⁰ in the schemes below may also correspond to R₂⁸, R₃³ and R₅⁴ as defined herein. R₃ in the schemes below
may also correspond to \( R^8 \) as defined herein. \( R^{14} \) in the schemes below may also correspond to \( R^9 \) as defined herein. \( R^{15} \) in the schemes below may also correspond to \( R^{14} \), \( R^{16} \) and \( R^{17} \) as defined herein. \( R^{18} \) in the schemes below may also correspond to \( R^{15} \), \( R^{16} \) and \( R^{17} \) as defined herein. \( \mathrm{L} \) is a leaving group as known to one of ordinary skill in the art.

As shown above, \( R^6 \) is alkyl.

[0193] Compound (x) with alcohol functionality is an intermediate useful for preparing the compounds utilized in this invention. Compound (x), where \( L \) is an \( R'S\text{SO}_2^- \) group, is made by
reacting compound (ix) with \( R^1SO_2Cl \) in the presence of a base. The transformation of compound (iii) to compound (x) illustrates methods of adding isoprene derivatives to a compound, which methods are suitable to make compound (iii) from compound (i).

Intermediate (ix) containing various \( FT-R^2 \) substituents are prepared according to this scheme as exemplified herein below. The transformation of compound (iii) to compound (x) illustrates methods of adding isoprene derivatives to a compound, which methods are suitable to make compound (iii) from compound (i).

[0194] The intermediates prepared above are converted to the compounds utilized in this invention as schematically illustrated below:

![Chemical structure](image)

[0195] As used herein, for example, and without limitation, \( m \) is 0 or 1 and \( R^1-R^5 \) are as defined herein, and are preferably alkyl, or more preferably methyl, intermediate (ixa), prepared according to the scheme herein above, is converted to amino intermediate (ixb) via the corresponding bromide. Intermediates (ixa) and (ixb) are converted to the compounds utilized in this invention by reacting with suitable isocyanates or carbamoyl chlorides, which are prepared by art known methods. The thiocarbamates and thioureas of this invention are prepared according to the methods described above and replacing the
isocyanates or the carbamoyl chlorides with isothiocyanates \((R^1 - N=C=S)\) or thiocarbamoyl chlorides \((R^1 - NH-C(=5)Cl\) or \(R^1 - R^3 - N-C(=S)Cl\). [0196] These and other compounds utilized in this invention are also prepared by art known methods, which may require optional modifications as will be apparent to the skilled artisan upon reading this disclosure. Intermediates for synthesizing compounds utilized in this invention containing various \(R^1 R^2\) substituents are illustrated in the examples section and/or are well known to the skilled artisan.

[0197] Certain GGA derivatives utilized herein are synthesized as schematically shown below.

\[
\begin{align*}
R_1 & \quad R_2 & \quad R_3 & \quad R_4 & \quad R_5 & \quad R_6 \\
& \quad & \quad & \quad & \quad & \quad \\
& \quad & \quad & \quad & \quad & \quad \\
& \quad & \quad & \quad & \quad & \quad \\
\end{align*}
\]

[0198] Certain compounds utilized herein are obtained by reacting compound (x) with the anion \(\text{Q}^-\), which can be generated by reacting the compound \(\text{QH}\) with a base. Suitable nonlimiting examples of bases include hydroxide, hydride, amides, aikoxides, and the like. Various compounds utilized in this invention, wherein the carbonyl group is converted to an imine, a hydrazone, an alkoxyimine, an enolcarbamate, a ketal, and the like, are prepared following well known methods.

[0199] Other methods for making the compounds utilized in this invention are schematically illustrated below;
The metaliation is performed, by reacting the ketone with a base such as dimsyl anion, a hindered amide base such as diisopropylamide, or hexamethyldisilazide, along with the corresponding metai cation, \( M \). The amino carbonyl chloride or the isocyanate is prepared, for example, by reacting the amine \( (R^\text{15})_2\text{NH} \) with phosgene or an equivalent reagent well known to the skilled artisan.

The beta keto ester is hydrolyzed while ensuring that the reaction conditions do not lead to decarboxylation. The acid is activated with various acid activating agent well...
known to the skilled artisan such as carbonyl diimodozio, or 0-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate (HBTU) and reacted with the amine.

Various other compounds utilized in this invention are prepared from the compounds made in the scheme above based on art known methods.

As shown above, R^E is alkyi.

The intermediates prepared above are converted to the compounds utilized in this invention as schematically illustrated beiovv:

\[
\begin{align*}
&\text{Hydrolysis} \\
&\text{Oxalyl Chloride} \\
&\text{DMF, DCM}
\end{align*}
\]
[0204] Compound (viii) is hydrolyzed to the carboxylic acid (x), which is then converted to the acid chloride (xi). Compound (xi) is reacted with a suitable nucleophile such as a hydrazide, a hydroxyamine, an amino alcohol, or an amino acid, and the intermediate dehydrated to provide a compound of Formula (IV). Alternatively, the allylic alcohol (fix) is oxidized to the aldehyde (xi), which is then reacted with a cyanohydrin or cyanotosylmethane to provide further compounds utilized in this invention.

[0205] GGA derivatives utilized in this invention can also be synthesized employing art known methods and those disclosed here by alkene-aryl, alkene-heteroaryl, or alkene-akene couplings such as Heck, Stille, or Suzuki coupling. Such methods can use (vi) to prepare intermediate (xii) that can undergo Heck, Stille, or Suzuki coupling under conditions well known to the skilled artisan to provide compounds utilized in this invention.

[0206] Higher and lower isoprenyl homologs of intermediates (x), (xi), and (xii), which are prepared following the methods disclosed here, can be similarly employed to prepare other compounds utilized in this invention.

[0207] Compounds utilized in this invention are also prepared as shown below.
L is a leaving group and '¾ are as defined herein, Ar is a preferably any group such as phenyl, the base employed is an alkoxide such as tertiarybutoxide, a hydride, or an alkyl lithium such as n-butyl lithium. Methods of carrying out the steps shown above are well known to the skilled artisan, as are conditions, reagents, solvents, and/or additives useful for performing the reactions and obtaining the compound of Formula (IV) in the desired stereochemistry.

Other methods for making the compounds utilized in this invention are schematically illustrated below:

The metathesis is performed, by reacting the ketone with a base such as dimethyl anion, a hindered amide base such as diisopropylamide, or hexamethylidisilazide, along with the corresponding metal cation, M. The amino carbonyl chloride or the isocyanate is
prepared, for example, by reacting the amine R\textsuperscript{13}R\textsuperscript{16}NH with phosgene or an equivalent reagent well known to the skilled artisan.

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{R}^3 & \quad \text{R}^4 \\
\text{R}^5 & \quad \text{R}^6 \\
\text{CONH}R^{82} & \\
\end{align*}
\]

activation of -CO\textsubscript{2}H group;

\[
\begin{align*}
\text{R}^{15}NH_2
\end{align*}
\]

[0211] The beta keto ester is hydrolyzed while ensuring that the reaction conditions do not lead to decarboxylation. The acid is activated with various acid activating agent well known to the skilled artisan such as carbonyl diimidazole, or O-Benzotriazole- \( N,N,N',N' \)-tetramethyl-uronium-hexafluoro-phosphate (HBTU) and reacted with the amine. Certain other methods of preparing the conjugates are shown below.

\[
\begin{align*}
\text{R}^1NH_2/dehydrating agent \\
\text{R}^{15}NH_2/dehydrating agent
\end{align*}
\]

such as molecular sieves

[0212] As shown above, R is a memantine or a riluzole residue.

[0213] Polyprenyl amine- GGA derivatives can be prepared by reductive amination employing the appropriate polyprenyl aldehyde, a primary or secondary amine and a borohydride reducing agent, as is well known to the skilled artisan. The reaction can be
carried out in THF or diethyl ether, optionally in presence of a protic acid, preferably a mild protic acid catalyst,

[0214] illustrative and nonlimiting methods of making antibiotic and glaucoma drug conjugates of GGA and derivatives thereof are schematically shown below and/or can be adapted by the skilled artisan based on this disclosure. See, also, Expert Opinion on Therapeutic Patents, Prodrug strategies in nasal drug delivery, 2002, vol. 12, No. 3, Pages 331-340.

Ciprofloxacin conjugate.

![Chemical structure of Ciprofloxacin conjugate with annotations]

GG-alcohol

GG-aiconol conjugate
Betaxoiol conjugate

GG-acetone

Betaxoiol

Z = protecting group

ketal of GG-acetone

GG-acetone- I conjugate

BCl₃

a) I
b) deprot
Pharmaceutical Compositions

[0215] In another aspect, this invention provides and/or utilizes a composition comprising a GGA or a GGA derivative provided herein and a pharmaceutically acceptable excipient.

[0216] Such compositions can be formulated for different routes of administration. Although compositions suitable for oral delivery will probably be used most frequently, other routes that may be used include transdermal, intravenous, intramuscular, pulmonary, rectal, nasal, vaginal, lingual, intramuscular, intraperitoneal, intracutaneous, intracranial, and subcutaneous routes. Suitable dosage forms for administering the GGA or GGA derivatives of this invention include tablets, capsules, pills, powders, aerosols, suppositories, parenterals, and oral liquids, including suspensions, solutions and emulsions. Sustained release dosage forms may also be used, for example, in a transdermal patch form. All dosage forms may be prepared using methods that are standard in the art (see e.g., Remington’s Pharmaceutical Sciences, 16th ed., A. Oslo editor, Easton Pa. 1980).
Pharmaceutically acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the compound of this invention. Such excipients may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art. Pharmaceutically compositions in accordance with the invention are prepared by conventional methods using known methods in the art.

The compositions disclosed herein may be used in conjunction with any of the vehicles and excipients commonly employed in pharmaceutical preparations, e.g., talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous solvents, oils, paraffin derivatives, glycols, etc. Coloring and flavoring agents may also be added to preparations, particularly to those for oral administration. Solutions can be prepared using water or physiologically compatible organic solvents such as ethanol, 1,2-propylene glycol, polyethylene glycols, dimethyl sulfoxide, fatty alcohols, triglycerides, partial esters of glycerin and the like.

Solid pharmaceutical excipients include starch, cellulose, hydroxypropyl cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. In certain embodiments, the compositions provided or utilized herein comprises one or more of α-tocopherol, gum arabic, and/or hydroxypropyl cellulose.

In one embodiment, this invention provides or utilizes sustained release formulations such as drug depots or patches comprising an effective amount of a compound provided or utilized herein. In another embodiment, the patch further comprises gum Arabic or hydroxypropyl cellulose separately or in combination, in the presence of α-tocopherol. Preferably, the hydroxypropyl cellulose has an average MW of from 10,000 to 100,000. In a more preferred embodiment, the hydroxypropyl cellulose has an average MW of from 5,000 to 50,000.

In one embodiment, this invention provides pharmaceutical compositions in the form of an enterocoated capsule or tablet that facilitates increased delivery of GGA to the intestine.
Compounds and pharmaceutical compositions of this invention, including the intranasal formulations below, may be used alone or in combination with other compounds. When administered with another agent, the co-administration can be in any manner in which the pharmacological effects of both are manifest in the patient at the same time. Thus, co-administration does not require that a single pharmaceutical composition, the same dosage form, or even the same route of administration be used for administration of both the compound of this invention and the other agent or that the two agents be administered at precisely the same time. However, co-administration will be accomplished most conveniently by the same dosage form and the same route of administration, at substantially the same time. Obviously, such administration most advantageously proceeds by delivering both active ingredients simultaneously in a novel pharmaceutical composition in accordance with the present invention.

In some aspects of the invention, a composition suitable for intranasal administration is provided for treatment of a neural disease, disorder or condition or for reducing the negative effects of a neural disease, disorder or condition, where the composition includes GGA, preferably all trans GGA, or a GGA derivative as described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient for introducing GGA and/or derivatives thereof via the intranasal route into a subject. The intranasal dosage form may be prepared using methods that are standard in the art (see e.g., Remington's Pharmaceutical Sciences, 16th ed., A. Oslo editor, Easton Pa. 1980). The concentration of the excipient is one that can readily be determined to be effective by those skilled in the art, and can vary depending on the particular excipient used. The total concentration of the excipients in the solution can be from about 0.001% to about 90% or from about 0.001% to about 10%.

Currently, intranasal administration has not gained wide acceptance. For example, all therapeutic agents cannot be effectively administered by the intranasal route. At present, the molecules which have proved suitable for this route of administration are still very few and consist essentially of only small peptide or hormone molecules (such as calcitonin, cerulean, beta-endorphin, glucagon, horseradish peroxidase, B-interferon, oxytocin and insulin) in special formulations. The ability of drug molecules to be absorbed by the nasal mucous membranes is utterly unpredictable, as is the ability of intranasal formulations to avoid irritation of the mucous nasal membranes. Mucous membrane
irritation caused by the drug and/or excipient is the most common reason for which intranasal administration has not gained wider acceptance.

[0225] The compositions according to the Invention include GGA or a derivative thereof in quantities ranging from 1-55, 5-50, 10-40, or 20-30 mg/kg/day, diluted in excipients such as humectants, isotonic agents, antioxidants, buffers and preservatives. A calcium chelating agent is also preferably included.

[0226] The invention makes it possible to have single-dose dosage forms, which ensure application of an optimum quantity of GGA or a derivative thereof. The intranasal formulations of the invention contain concentrations of GGA or a derivative thereof ranging from 0.1 to 20%, preferably about 5-10% weight/volume. Selection of the particular excipients depends on the desired formulation dosage form, i.e., on whether a solution to be used in drops or as a spray (aerosol) is desired or a suspension, ointment or gel to be applied in the nasal cavity are desired.

[0227] Vehicles useful in the compositions according to the invention comprise solvent systems containing ethyl alcohol, isopropyl alcohol, propylene glycol, polyethylene glycol, mixtures thereof or mixtures of one or more of the foregoing with water.

[0228] Suitable vehicles for the formulations according to the invention include aqueous suspensions or emulsions containing an appropriate isotoning agent selected among those commonly used in pharmaceutics. Substances used for this purpose are, for instance, sodium chloride and glucose. The quantity of isotoning agent should impart to the vehicle (taking into account the osmotic effect of the active ingredient), an osmotic pressure similar to that of biological fluids, i.e. generally from about 150 to about 850 mOsm.

[0229] Nasal mucous membranes are also capable of tolerating slightly hypertonic solutions. Should a suspension or gel be prepared instead of a solution, appropriate oily or gel vehicles may be used or one or more polymeric materials may be included, which desirably should be capable of conferring bioadhesive characteristics to the vehicle.

[0230] Several polymers may be used for the preparation of a gel; nonlimiting examples include hydroxypropyl cellulose (KLUCEL®), hydroxypropyl methyl cellulose (METHOCEL®), hydroxyethyl cellulose (NATROSGL®), sodium carboxymethyl cellulose (BLANOSE®), acrylic polymers (CARBOPOL®, POLYCARBOPHIL®), gum xanthan, gum tragacanth, alginates and agar-agar.
Some of them, such as sodium carboxymethyl cellulose and acrylic polymers, have marked bioadhesive properties and are preferred if bioadhesiveness is desired.

Other formulations suitable for intranasal administration of GGA or a derivative thereof can be obtained by adding to the aqueous vehicle polymers capable of changing the rheologic behavior of the composition in relation to the temperature. These polymers make it possible to obtain low viscosity solutions at room temperature, which can be applied for instance by nasal spray and which increase in viscosity at body temperature, yielding a viscous fluid which ensures a better and longer contact with the nasal mucous membrane. Polymers of this class include without limitation polyoxyethylene-polyoxypropylene block copolymers (POE-POPMER*).

In some embodiments, the formulation is a small particle liposome or lipid complex aerosol formulation. Methods of preparing such formulation are with in the skill of the skilled artisan. See, for example, US 6,090,407.

In some embodiments, a pharmaceutically acceptable buffer is present to stabilize a pH range of about 4 to about 8; preferably about 5.5 to 7.5. Suitable non-limiting buffers include tris (tromethamine) buffer, phosphate buffer, etc.

Further excipients include chemical enhancers such as intranasal absorption promoters. These include chelating agents, fatty acids, bile acid salts and other surfactants, fusidic acid, lysophosphatides, cyclic peptide antibiotics, preservatives, carboxylic acids (ascorbic acid, amino acids), glycyrrhetinic acid, o-acylcarnitine. Preferred promoters are diisopropyladipate, POE (9) fauryi alcohol, sodium glycocholate and lysophosphatidylchoitne which proved to be particularly active. Finally, the new compositions according to the invention preferably contain preservatives which ensure the microbiological stability of the active ingredient. Suitable preservatives include without limitation, methyl paroxybenzoate, propyl paroxybenzoate, sodium benzoate, benzyl alcohol, benzalkonium chloride and chlorobutanol.

The liquid formulations of GGA or a derivative thereof, preferably in the form of solutions, may be administered from a nasal spray devise of this invention comprising GGA or a GGA derivative, in the form of drops or spray, using atomizers equipped with a mechanical valve and possibly including a propellant of a type commercially available, such as butane, N₂, Ar, CO₂, nitrous oxide, propane, dimethyl ether, chlorofluorocarbons (e.g. FREON) etc. Vehicles suitable for spray administration are water, alcohol, glycol and
propylene glycol, used alone or in a mixture of two or more. In some embodiments, this invention provides multifunctional nasal spray devices. In other embodiments, this invention provides unit dose nasal spray devices.

[0237] Generally, illustrative and non-limiting formulations can contain the following ingredients and amounts (weight/volume):

**[Ingredient] Broad Range (%) Preferred Range (%)**
- Na₂EDTA 0.001-1 0.05-0.1
- Nipagin 0.01-2
- POE (9) Lauryle alcohol 0.1-10 1-10
- NaCM C (Blanose 7m8 sf d) 0.1-5 0.3-3
- Carbopol 940 0.05-2 0.1-1.5
- Glycerol 1-99 Sodium glycocholate 0.05-5 0.1-1

[0238] It will be appreciated by those of ordinary skill that ingredients such as sodium carboxymethyl cellulose and Carbopol exist in many types differing in viscosity. Their amounts are broad and can be adjusted accordingly. Different adjustments to each formulation may also be necessary including omission of some optional ingredients and addition of others, it is thus not possible to give an all-encompassing amount range for each ingredient, but the optimization of each preparation according to the invention is within the skill of the art.

[0239] An alternative for the Intranasal administration of compositions including GGA or a derivative thereof comprises a suspension of finely micronized active ingredient (generally from 1 to 200 micrometers, preferably from 5 to 100 micrometers) in a propellant or in an oily vehicle in another vehicle in which the drug is not soluble. The vehicle is mixed or emulsified with the propellant. Vehicles suitable for this alternative are, for instance, vegetable and mineral oils and triglyceride mixtures. Appropriate surfactants, suspending agents and diluents suitable for use in pharmaceuticals are added to these vehicles.

Surfactants Include without limitation sorbitan sesquioleate, sorbitanmonooxicate, sorbitan trioleate (amount: between about 0.25 and about 1%); suspending agents include without limitation isopropylmyristate (amount: between about 0.5 and about 1%) and colloidal silica (amount: between about 0.1 and about 0.5%); and diluents include without limitation zinc stearate (about 0.6 to about 1%).

[0240] In certain preferred embodiments of this invention, there is provided or utilized a pharmaceutical composition comprising GGA or a GGA derivative and a-tocopherol. A related embodiment provides and/or utilizes a pharmaceutical composition comprising GGA or a GGA derivative, a-tocopherol, and hydroxypropyl cellulose. In another embodiment, there is provided or utilized a pharmaceutical composition comprising GGA or a GGA derivative, a-tocopherol, and optionally gum arable. In a further embodiment, there is a
pharmaceutical composition comprising GGA or a GGA derivative, and gum arabic. In a related embodiment, there is provided or utilized GGA or a GGA derivative, gum arabic and hydroxypropyl cellulose.

[0241] When a-tocopherol is used alone or in combination with other excipients, the concentration by weight can be from about 0.001% to about 1% or from about 0.001% to about 0.005%, or from about 0.005% to about 0.01%, or from about 0.01% to about 0.015%, or from about 0.015% to about 0.03%, or from about 0.03% to about 0.05%, or from about 0.05% to about 0.07%, or from about 0.07% to about 0.1%, or from about 0.1% to about 0.15%, or from about 0.15% to about 0.3%, or from about 0.3% to about 0.5%, or from about 0.5% to about 1% by weight. In some embodiments, the concentration of a-tocopherol is about 0.001% by weight, or alternatively about 0.005%, or about 0.008%, or about 0.01%, or about 0.02%, or about 0.03%, or about 0.04%, or about 0.05% by weight.

[0242] When hydroxypropyl cellulose is used alone or in combination with other excipients, the concentration by weight can be from about 0.1% to about 30% or from about 1% to about 20%, or from about 1% to about 5%, or from about 1% to about 10%, or from about 2% to about 4%, or from about 5% to about 10%, or from about 10% to about 15%, or from about 15% to about 20%, or from about 20% to about 25%, or from about 25% to about 30% by weight. In some embodiments, the concentration of hydroxypropyl cellulose is about 1% by weight, or alternatively about 2%, or about 3%, or about 4%, or about 5%, or about 6%, or about 7%, or about 8%, or about 10%, or about 15% by weight.

[0243] When gum arabic is used alone or in combination with other excipients, the concentration by weight can be from about 0.5% to about 50% or from about 1% to about 20%, or from about 1% to about 10%, or from about 3% to about 6%, or from about 5% to about 10%, or from about 4% to about 6% by weight. In some embodiments, the concentration of hydroxypropyl cellulose is about 1% by weight, or alternatively about 2%, or about 3%, or about 4%, or about 5%, or about 6%, or about 7%, or about 8%, or about 10%, or about 15% by weight.

[0244] In certain embodiments, the concentration of GGA or a GGA derivative in the pharmaceutical composition is about 5% by weight, or alternatively, about 10%, or about 20%, or about 1%, or about 2%, or about 3%, or about 4%, or about 6%, or about 7%, or about 8%, or about 9%, or about 11%, or about 12%, or about 14%, or about 16%, or about 18% by weight.
[0245] In some embodiments, solid dosage forms may further include granules, pellets, beads, spheroids, a minitablet, a microtablet, granules in a capsule, pellets in a capsule, microtablets in a capsule, and minitablets in a capsule, each of which may be enteric coated.

[0246] In certain aspects, the enteric formulations provide herein are useful for treating or alleviating the negative effects of various neurological diseases and disorders described herein and inflammatory bowel disease, chronic liver disease, a disorder selected from liver injury, preferably acute liver injury, acute liver failure, cardiac ischemia, myocardial infarction, repulsion injury and heart transplants, or a related disorder or condition.

[0247] The compositions of the present invention may be prepared using conventional methods and materials known in the pharmaceutical arts.

[0248] Certain illustrative and non-limiting enteric polymers and coatings useful in this invention are described herein.

[0249] Enteric polymers used to coat pharmaceutical dosage forms include cellulose, vinyl, and acrylic derivatives. Enteric polymeric materials are primarily weak acids containing acidic functional groups, which are capable of ionization at elevated pH.

[0250] In some embodiments, the enteric coating coats a core of a dosage form disclosed herein and controls the location in the digestive tract where the active agent contained in the dosage form's core is released and absorbed. In certain embodiments, the enteric coating is in the form of one or more components selected from the group including polymers, fatty acids, waxes, shellac, plastics, and plant fibers.

[0251] In certain embodiments, the enteric coating comprises one or more of the following: acrylates and acrylate copolymers, including methacrylic acid/methacryliic acid methylester copolymer and methacrylic acid/ethyl acrylate copolymer; cellulose esters, including cellulose acetate phthalate, cellulose acetate trimellitate, and cellulose acetate succinate; hydroxypropyl methylcellulose phthalate; hydroxypropyl methylcellulose acetate succinate; polyvinyl derivatives, including polyvinyl acetate phthalate; and carboxymethyl ethyl cellulose. In some specific embodiments, the enteric coating includes one or more components sold under trade names, for example EMCOAT 120 N, MARCOAT 125, AQUACOAT CP®, SEP FILM®, AQUACOAT ECD, METOLOSE®, SURETERIC®, AND EUDRAGIT®. In certain embodiments, the enteric coating may comprise colorants. In a specific embodiment, the enteric coating comprises a EU D RAG IT® polymer and a colorant, and is sold under the trade name ACRYL-EZE ORANGE®.
In some embodiments, the enteric coating may further comprise a plasticizer. In some embodiments, the plasticizer will influence, i.e., increase or decrease, the rate of dissolution of the enteric coating. In some embodiments, the plasticizer may be lipophilic, in other embodiments, the plasticizer may be hydrophilic.

In other embodiments, the plasticizer comprises one or more of the group including cetanol, triacetin, citric acid esters such as triethyl citrate, phthalic acid esters such as diethyl phthalate and dibutyl phthalate, dibutyl succinate, propylene glycol, polyethylene glycol (PEG), and oils and glycerides such as fractionated coconut oil.

Exemplary and non-limiting coating formulations include excipients as illustrated below:

<table>
<thead>
<tr>
<th>Component</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Hydroxypropyl methylcellulose E5</td>
<td>5</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose E15</td>
<td>2</td>
</tr>
<tr>
<td>Polyethylene glycol 6000</td>
<td>1</td>
</tr>
<tr>
<td>Polyethylene glycol 4000</td>
<td>1</td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>6</td>
</tr>
<tr>
<td>Purified water to 100</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Component</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Eudragit L30D</td>
<td>15</td>
</tr>
<tr>
<td>Antifoam M</td>
<td>less than 1</td>
</tr>
<tr>
<td>Acetyl triethyl citrate</td>
<td>2</td>
</tr>
<tr>
<td>Talc micronised</td>
<td>3</td>
</tr>
<tr>
<td>Pumpey water to 100</td>
<td></td>
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</tbody>
</table>

In some embodiments, a compound of this invention can be used as an adjunct to conventional drug therapy of the conditions described herein.

Methods of Treatment

Some embodiments provided herein describe a method of treating a neural disease via an intra nasal administration of GGA or a derivative thereof. In some instances, neural diseases are characterized by neuroinflammation. Examples of such neural diseases include, but are not limited to, amyotrophic lateral sclerosis (ALS), Alzheimer’s disease, Parkinson’s disease, multiple sclerosis, prion diseases such as Kuru, Creutzfeldt-Jakob disease, fatal familial insomnia, Gerstmann-Straussler-Scheinker syndrome, and damage to the spinal cord.
cord. Also provided herein in some embodiments is a method of treating visual disorders such as optic neuropathy, glaucoma, degeneration of optic nerves, age-related macular degeneration (AMD) and ophthalmoplegia. Some embodiments described herein provide a pharmaceutical formulation for preventing neural death during epileptic seizures. Any pharmaceutical formulation and/or compounds described above are useful in the methods described herein.

[0257] Provided herein, in some embodiments, are methods for using effective amounts of GGA or a derivative thereof preferably having the (5E,9E,13E) configuration or the, optionally with at least one pharmaceutically acceptable excipient for inhibiting neural death and/or increasing neural activity. In some embodiments, GGA is the trans-GGA or the synthetic trans-GGA. For example, and without limitation, methods provided herein describe impeding the progression of neural diseases or injury using GGA or a derivative thereof.

[0258] In one aspect, methods for increasing the axon growth of neurons by contacting said neurons with the pharmaceutical compositions are provided herein. In some cases, neural diseases result in an impairment of signaling between neurons. In some cases, this impairment is due in part to a reduction in the growth of axonal projections. In some embodiments, contacting neurons with GGA or a derivative thereof enhances axonal growth. In some embodiments, GGA or a derivative thereof restores axonal grown in neurons afflicted with a neural disease. In a related embodiment, the pre-contacted neurons exhibit a reduction in the axon growth ability.

[0259] One embodiment provided herein describes a method for inhibiting the cell death of neurons susceptible to neuronal cell death, which method comprises contacting said neurons with the pharmaceutical compositions provided or utilized herein. Neurons susceptible to neuronal cell death include those that have the characteristics of a neural disease and/or those that have undergone injury or toxic stress. One method of creating toxic stress to a cell is by mixing dopamine with neurons such as neuroblastoma cells. Another source of toxic stress is oxidative stress. Oxidative stress can occur from neuronal disease or injury, it is contemplated that contacting neurons with GGA or a derivative thereof will inhibit their death as measured by a MTT assay or other techniques commonly known to one skilled in the art.
in another aspect, there are methods for increasing the neurite growth of neurons by contacting said neurons with the pharmaceutical compositions provided or utilized herein. The term "neurite" refers to both axons and dendrites. Neural diseases can result in an impairment of signaling between neurons. In some cases, this impairment is due in part to a reduction in the growth of axonal and/or dendritic projections. It is contemplated that contacting neurons with GGA or a derivative thereof will enhance neurite growth. It is further contemplated that GGA or a derivative thereof will restore neurite growth in neurons afflicted with a neural disease. In a related embodiment, the pre-contacted neurons exhibit a reduction in the neurite growth ability.

One embodiment of this invention is directed to a method for increasing the expression and/or release of one or more neurotransmitters from a neuron fay contacting said neurons with the pharmaceutical compositions provided or utilized herein. It is contemplated that contacting neurons with an effective amount of GGA and/or derivatives thereof will increase the expression level of one or more neurotransmitters. It is also contemplated that contacting neurons with GGA or a derivative thereof will increase the release of one or more neurotransmitters from neurons. The release of one or more neurotransmitters refers to the exocytotic process by which secretory vesicles containing one or more neurotransmitters are fused to cell membrane, which directs the neurotransmitters out of the neuron. It is contemplated that the increase in the expression and/or release of neurotransmitters will lead to enhanced signaling in neurons, in which levels of expression or release of neurotransmitters are otherwise reduced due to the disease. The increase in their expression and release can be measured by molecular-techniques commonly known to one skilled in the art.

One embodiment of this invention is directed to a method for inducing synapse formation of a neuron by contacting said neurons with the pharmaceutical compositions provided or utilized herein. A synapse is a junction between two neurons. Synapses are essential to neural function and permit transmission of signals from one neuron to the next. Thus, an increase in the neural synapses will lead to an increase in the signaling between two or more neurons. It is contemplated that contacting the neurons with an effective amount GGA or a derivative thereof, via intranasal administration, will increase synapse formation in neurons that otherwise experience reduced synapse formation as a result of neural disease.
Another embodiment of this invention is directed to a method for increasing electrical excitability of a neuron by contacting said neurons with the pharmaceutical compositions provided or utilized herein. Electrical excitability is one mode of communication among two or more neurons. It is contemplated that contacting neurons with an effective amount of GGA or a derivative thereof, via intranasal administration, will increase the electrical excitability of neurons in which electrical excitability and other modes of neural communication are otherwise impaired due to neural disease. Electrical excitability can be measured by electrophysiological methods commonly known to one skilled in the art.

In each of the three previous paragraphs above, the intranasal administration of GGA or a derivative thereof enhances communication between neurons and accordingly provides for a method of inhibiting the loss of cognitive abilities in a mammal that is at risk of dementia or suffering from incipient or partial dementia while retaining some cognitive skills. Incipient or partial dementia in a mammal is one in which the mammal still exhibits some cognitive skills, but the skills are being lost and/or diminished over time. Method comprises administering via intranasal the route to said patient an effective amount of GGA or a derivative thereof.

In another embodiment, this invention is directed to a method for inhibiting the death of neurons due to formation of or further formation of pathogenic protein aggregates between, outside or inside neurons, wherein said method comprises contacting said neurons at risk of developing said pathogenic protein aggregates with the pharmaceutical compositions provided or utilized herein, provided that said pathogenic protein aggregates are not related to SBMA. In one embodiment of this invention, the pathogenic protein aggregates form between or outside of the neurons. In another embodiment of this invention, the pathogenic protein aggregates form inside said neurons. In one embodiment of this invention, the pathogenic protein aggregates are a result of toxic stress to the cell.

One method of creating toxic stress to a cell is by mixing dopamine with neurons such as neuroblastoma cells. It is contemplated that contacting neurons with an effective amount of GGA or a derivative thereof, via intranasal administration, will inhibit their death as measured by a MTT assay or other techniques commonly known to one skilled in the art.

Another embodiment of the invention is directed to a method for protecting neurons from pathogenic extracellular protein aggregates which method comprises
contacting said neurons and/or said pathogenic protein aggregates with the pharmaceutical compositions provided or utilized herein. In one embodiment of this invention, contacting said neurons and/or said pathogenic protein aggregates with the pharmaceutical compositions provided or utilized herein. Without being limited to any theory, it is contemplated that contacting the neurons and/or the pathogenic protein aggregates with GGA or a derivative thereof, via intranasal administration, will solubilize at least a portion of the pathogenic protein aggregates residing between, outside, or inside of the cells. It is further contemplated that contacting the neurons and/or the pathogenic protein aggregates with GGA or a derivative thereof, via intranasal administration, will alter the pathogenic protein aggregates in such a way that they are non-pathogenic. A non-pathogenic form of the protein aggregate is one that does not contribute to the death or loss of functionality of the neuron. There are many assays known to one skilled in the art for measuring the protection of neurons either in cell culture or in a mammal. One example is a measure of increased cell viability by a MTT assay. Another example is by immunostaining neurons in vitro or in vivo for cell death-indicating molecules such as, for example, caspases or propidium iodide.

[0267] In yet another embodiment of the invention is directed to a method for protecting neurons from pathogenic intracellular protein aggregates which method comprises contacting said neurons with the pharmaceutical compositions provided herein provided that said protein aggregation is not related to SBMA. This method is not intended to inhibit or reduce negative effects of neural diseases in which the pathogenic protein aggregates are intranuclear or diseases in which the protein aggregation is related to SBMA. SBMA is a disease caused by pathogenic androgen receptor protein accumulation. It is distinct from the neural diseases mentioned in this application since the pathogenic protein aggregates of SBMA contain polyglutamates and are formed intranuclearly. It is also distinct from the neural diseases described in this application because the protein aggregates are formed from androgen receptor protein accumulation. It is contemplated that contacting neurons via intranasal administration with an effective amount of GGA or a derivative thereof will alter the pathogenic protein aggregate into a non-pathogenic form.

[0268] One embodiment of the invention is directed to a method of modulating the activity of G proteins in neurons which method comprises contacting said neurons with the pharmaceutical compositions provided or utilized herein. It is contemplated that contacting
neurons via intranasal administration with an effective amount of GGA or a derivative thereof will alter the sub-cellular localization, thus changing the activities of the G protein in the cell. In one embodiment of the invention, contacting neurons via intranasal administration with an effective amount of GGA and/or derivatives thereof will induce the expression of heat shock proteins (HSPs) in the way contacting neurons via intranasal administration with an effective amount of GGA and/or derivatives thereof will alter the activity of G proteins in neurons, it is contemplated that contacting neurons via intranasal administration with an effective amount of GGA and/or derivatives thereof will increase the expression level of proteins. It is also contemplated that contacting neurons via intranasal administration with an effective amount of GGA and/or derivatives thereof will enhance the activity of G proteins by changing their sub-cellular localization to the cell membranes where they must be to exert their biological activities.

[0269] One embodiment of the invention is directed to a method of modulating or enhancing the activity of G proteins in neurons at risk of death which method comprises contacting said neurons with the pharmaceutical compositions provided or utilized herein. Neurons may be at risk of death as a result of genetic changes related to ALS. One such genetic mutation is a depletion of the TDP-43 protein, it is contemplated that neurons with depleted TDP-43 or other genetic mutations associated with ALS will have an increase or change in the activity of G proteins after being contacted via intranasal administration with an effective amount of GGA or a derivative thereof. It is further contemplated that an effective amount of GGA or a derivative thereof will result in an increase in the activity of G proteins in these cells by changing their sub-cellular localization to the cell membranes where they must be to exert their biological activities.

[0270] Another embodiment of the invention is directed to a method for inhibiting the neurotoxicity of β-amyloid peptide by contacting the β-amyloid peptide with the pharmaceutical compositions provided herein. In one embodiment of the invention the β-amyloid peptide is between or outside of neurons. In yet another embodiment of the invention, the β-amyloid peptide is part of the β-amyloid plaque. It is contemplated that contacting neurons via intranasal administration with an effective amount of GGA or a derivative thereof will result in solubilizing at least a portion of the β-amyloid peptide, thus decreasing its neurotoxicity. It is further contemplated that an effective amount of GGA or a derivative thereof will decrease the toxicity of the β-amyloid peptide by altering it in such a way that it is no longer toxic to the cell. It is also believed that an effective amount of GGA and/or derivatives thereof will induce the expression of heat shock proteins (HSPs) in the
neurons. It is also contemplated that HSPs will be induced in support cells such as glial cells. The induced heat shock proteins in the neurons or glial cells may be transmitted extracellularly and act to dissolve extracellular protein aggregates. Cell viability can be measured by standard assays known to those skilled in the art. One such example of an assay to measure cell viability is a MTT assay. Another example is a MTS assay. The modulation of protein aggregation can be visualized by immunostaining or histological staining techniques commonly known to one skilled in the art.

[0271] One embodiment of the invention is directed to a method for inhibiting neural death and increasing neural activity in a mammal suffering from neural diseases, wherein the etiology of said neural diseases comprises formation of protein aggregates which are pathogenic to neurons, and which method comprises administering to said mammal the pharmaceutical compositions provided or utilized herein. This method is not intended to inhibit neural death and increase neural activity in neural diseases in which the pathogenic protein aggregates are intranuclear or diseases in which the protein aggregation is related to SBMA.

[0272] Neural diseases such as AD and ALS have the common characteristic of protein aggregates either inside neural cells in cytoplasm or in the extracellular space between two or more neural cells. This invention relates to a method for using, via intranasal administration, an effective amount of GGA or a derivative thereof to inhibit the formation of the protein aggregates or alter the pathogenic protein aggregates into a non-pathogenic form. It is contemplated that this will attenuate some of the symptoms associated with these neural diseases.

[0273] In one embodiment the mammal is a human afflicted with a neural disease. In one embodiment of this invention, the negative effect of the neural disease being inhibited or reduced is ALS. ALS is characterized by a loss of functionality of motor neurons. This results in the inability to control muscle movements. ALS is a neurodegenerative disease that does not typically show intranuclear protein aggregates. It is contemplated that an effective amount of GGA and/or derivatives thereof will prevent or inhibit the formation of extracellular or intracellular protein aggregates that are cytoplasm, not intranuclear and not related to SBMA. It is also contemplated that an effective amount of GGA or a derivative thereof will alter the pathogenic protein aggregates into a form that is non-pathogenic. Methods for diagnosing ALS are commonly known to those skilled in the art. Additionally,
there are numerous patents that describe methods for diagnosing ALS. These include U.S. 585,1783 and U.S. 735,652.1 both of which are incorporated herein by reference in their entirety.

[0274] In one embodiment of the invention the negative effect of the neural disease being inhibited or reduced is AD. AD is a neurodegenerative disease that does not typically show intranuclear protein aggregates. It is contemplated that the intranasal administration of an effective amount of GGA or a derivative thereof will prevent or inhibit the formation of extracellular or intracellular protein aggregates. It is also contemplated that the intranasal administration of an effective amount of GGA or a derivative thereof will alter the pathogenic protein aggregates into a form that is non-pathogenic. Methods for diagnosing AD are commonly known to those skilled in the art. Additionally, there are numerous patents that describe methods for diagnosing AD. These include U.S. 6,130,048 and U.S. 6,391,553 both of which are incorporated herein by reference in their entirety.

[0275] In another embodiment, the mammal is a laboratory research mammal such as a mouse. In one embodiment of this invention, the neural disease is ALS. One such mouse model for ALS is a transgenic mouse with a Sod1 mutant gene. It is contemplated that the intranasal administration of an effective amount of GGA or a derivative thereof will enhance the motor skills and body weights when administered to a mouse with a mutant Sod1 gene. It is further contemplated that the intranasal administration of an effective amount of GGA or a derivative thereof to this mouse will increase the survival rate of Sod1 mutant mice. Motor skills can be measured by standard techniques known to one skilled in the art. In yet another embodiment of this invention, the neural disease is AD. One example of a transgenic mouse model for AD is a mouse that overexpresses the APP (Amyloid beta Precursor Protein). It is contemplated that the intranasal administration of an effective amount of GGA or a derivative thereof to a transgenic AD mouse will improve the learning and memory skills of said mouse. It is further contemplated that the intranasal administration of an effective amount of GGA or a derivative thereof will decrease the amount and/or size of β-amyloid peptide and/or plaque found inside, between, or outside of neurons. The β-amyloid peptide or plaque can be visualized in histology sections by immunostaining or other staining techniques.

[0276] In one embodiment of the invention the intranasal administration of an effective amount of GGA or a derivative thereof to a mammal alters the pathogenic protein aggregate
present into a non-pathogenic form, in another embodiment of the invention, the intranasal administration of an effective amount of GGA or a derivative thereof to a mammal will prevent pathogenic protein aggregates from forming.

Another aspect of this invention relates to a method for reducing seizures in a mammal in need thereof, which method comprises administering the pharmaceutical compositions provided or utilized herein, thereby reducing seizures. The reduction of seizures refers to reducing the occurrence and/or severity of seizures. In one embodiment, the seizure is epileptic seizure. In another embodiment, the methods of this invention prevent neural death during epileptic seizures. The severity of the seizure can be measured by one skilled in the art.

In some embodiments, an intranasal formulation of GGA or a derivative thereof described herein exerts cytoprotective effects on a variety of organs, e.g., the brain and heart. (See, for example Tanito M, et al., J Neurosci 2005; 25:2396-404; Fujiki M, et al., J Neurotrauma 2006; 23:1164-78; Yasuda H, et al., Brain Res 2005; 1032:176-82; Ooie T, et al., Circulation 2001; 20; 104:1837-43; and Suzuki s. et al., Kidney Int 2005; 67:2210-20).

Method of treating bacterial infections, viral infections, or cancers of the eye, brain, and spinal cord, and the nerves in the brain, eye, and the spinal cord are well known in the art and can be appropriately adapted for practicing the methods of this invention upon reading this disclosure by the skilled artisan.

EXAMPLES

The following examples of formulations for the intranasal administration of GGA or a GGA derivative serve to illustrate the invention without limiting its scope.

**Example 1: Time Course of CNS-102 induced HSP70 Expression In Vivo.**

The time course of protein expression, as measured by western blot for HSP70, was determined in triplicate for hippocampus, and cortex tissue samples taken from each of 5 animals per group at each of four time points (24, 48, 72, and 96 h) after treatment with either PBS or 12 mg/kg CNS-102, administered orally. The average expression for each treatment group is calculated at each time point for each tissue using PROC MIXED in SAS and are tabulated, along with the difference (delta) between treatment averages and a p-value comparing the difference to zero, below.
HSP70 Expression Following Administration of CNS-102 vs PBS

<table>
<thead>
<tr>
<th>CNS – PBS</th>
<th>Treatment; Statistic</th>
<th>Cortex</th>
<th>Hippocampus</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hours</td>
<td>CNS</td>
<td>-0.016</td>
<td>-0.159</td>
</tr>
<tr>
<td></td>
<td>PBS</td>
<td>-0.256</td>
<td>-0.072</td>
</tr>
<tr>
<td></td>
<td>delta</td>
<td>0.24</td>
<td>-0.088</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>0.002</td>
<td>0.16</td>
</tr>
<tr>
<td>48 hours</td>
<td>CNS</td>
<td>-0.45</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>PBS</td>
<td>-0.56</td>
<td>-0.18</td>
</tr>
<tr>
<td></td>
<td>delta</td>
<td>0.11</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>0.15</td>
<td>0.14</td>
</tr>
<tr>
<td>72 hours</td>
<td>CNS</td>
<td>0.14</td>
<td>-0.06</td>
</tr>
<tr>
<td></td>
<td>PBS</td>
<td>0.01</td>
<td>-0.2</td>
</tr>
<tr>
<td></td>
<td>delta</td>
<td>0.13</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>0.13</td>
<td>0.032</td>
</tr>
<tr>
<td>96 hours</td>
<td>CNS</td>
<td>0.04</td>
<td>-0.32</td>
</tr>
<tr>
<td></td>
<td>PBS</td>
<td>-0.15</td>
<td>-0.49</td>
</tr>
<tr>
<td></td>
<td>delta</td>
<td>0.19</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>0.09</td>
<td>0.07</td>
</tr>
</tbody>
</table>

[0282] Expression of HSP70 was observed after CNS-102 administration and the difference between CNS-102 and PBS induced expression (delta, in the table) in both the cortex at 24 h and the hippocampus at 72 h was statistically significant (bolded in the table).

[0283] These results demonstrate that CNS-102 induces expression of HSP70 as measured in the cortex 24 h after administration while in the hippocampus the level of HSP70 was not significant until 72 h after administration. No significant levels of HSP70 were found in the cortex after 24 h; however since no time points before 24 h were taken, it may be that HSP70 is expressed earlier in the hippocampus the expression appears to peak after 48 h with significant levels measured at 72 hours.
CNS-102 at 12 mg/kg or PBS was administered orally to Sprague-Dawley rats and the time course of HSP70 protein expression in tissues, was measured by ELISA. HSP70 protein expression was determined for lung, testicle, spleen, liver, kidney, blood plasma, skin, peripheral blood monocytes, heart, eye, muscle, intestine, and stomach at each of three time points (8h, 17h, 24h).

Table: Time Course of HSP70 expression as measured by ELISA in select tissues following 12mg/kg p.o of CNS-102

<table>
<thead>
<tr>
<th>Tissue</th>
<th>8h</th>
<th>17h</th>
<th>24h</th>
<th>48h</th>
</tr>
</thead>
<tbody>
<tr>
<td>testicle</td>
<td>1.10</td>
<td>1.03</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>spleen</td>
<td>0.64</td>
<td>1.09</td>
<td>1.04</td>
<td></td>
</tr>
<tr>
<td>liver</td>
<td>1.24</td>
<td>1.00</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>kidney</td>
<td>1.11</td>
<td>1.08</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>plasma</td>
<td>0.88</td>
<td>1.09</td>
<td>1.05</td>
<td></td>
</tr>
<tr>
<td>PBMC</td>
<td>1.67</td>
<td>1.05</td>
<td>1.09</td>
<td></td>
</tr>
<tr>
<td>heart</td>
<td></td>
<td>1.89</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>intestine</td>
<td>1.63</td>
<td>1.26</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>1.07</td>
<td>1.30</td>
<td>0.96</td>
<td></td>
</tr>
</tbody>
</table>

Example 2: Treatment of Inflammatory Bowel Disease (IBD) with GGA or a GGA derivative.

A pharmaceutical composition comprising GGA or a GGA derivative as described herein is prepared. A subject is diagnosed with mild to moderate IBD. The subject receives a daily administration of GGA or a GGA derivative, or a pharmaceutically acceptable salt thereof. Subjects are treated for 12 weeks. Subjects keep daily diaries and record the number and nature of bowel movements. The effect of the treatments is assessed by grading clinical symptoms of fecal blood, mucus, and urgency. In addition, sigmoidoscope assessment and biopsies are performed, and efficacy of treatment assessed, based on grading of sigmoidoscope and degree of histological inflammation in rectal biopsy specimens. Safety is assessed based on spontaneous side effect reporting.

It is contemplated that GGA or a GGA derivative, or a pharmaceutically acceptable
salt thereof, of this example will demonstrate efficacy in inflammatory bowel disease IBD in terms of both treating the condition and maintaining remission from disease symptoms.

Example 3: Treatment of Inflammatory Bowel Disease (IBD) with GGA or a GGA derivative in gastrectomized patients.

[0288] A pharmaceutical composition comprising GGA or a GGA derivative as described herein is prepared. A subject is diagnosed with mild to moderate IBD following gastrectomy. The subject receives a daily administration of GGA or a GGA derivative, or a pharmaceutically acceptable salt thereof. Subjects are treated for 12 weeks. Subjects keep daily diaries and record the number and nature of bowel movements. The effect of the treatments is assessed by grading clinical symptoms of fecal blood, mucus, and urgency, in addition, sigmoidoscopic assessment and biopsies are performed, and efficacy of treatment assessed, based on grading of sigmoidoscopic and degree of histological inflammation in rectal biopsy specimens. Safety is assessed based on spontaneous side effect reporting.

[0289] It is contemplated that GGA or a GGA derivative, or a pharmaceutically acceptable salt thereof, of this example will demonstrate efficacy in Inflammatory Bowel Disease IBD in terms of both treating the condition and maintaining remission from disease symptoms.

Example 4: GGA and derivatives thereof protect intestinal epithelial cells from oxidative stress in vitro.

[0290] Rat intestinal epithelial cell line (IEC-18) cells are pretreated with GGA or a GGA derivative and then subjected to injury induced by NH_4Cl. Cell viability is assessed, and endogenous HSP70 levels are determined by enzyme-linked immunosorbent assay (ELISA) in IEC-18 cells. Treatment with GGA or a derivative thereof rapidly elevates HSP70 levels and protects against NH_4Cl-induced injury in IEC-18 cells.

Example 5: GGA and GGA derivatives protect mice from dextran sulfate sodium (DSS)-induced colitis.

[0291] SALS/c mice are given 3% DSS solution orally for 7 days to induce colitis. The disease activity of colitis is assessed clinically every day, and histology in the colon is evaluated at 7 days post-DSS. The levels of myeloperoxidase (MPO) activity, tumor necrosis factor (TNF)-alpha and interferon (IFN)-gamma in the colon tissues are also examined, in addition, expression of HSPs 25, 40, 70 and 90 in the colon tissue is determined by Western blot analysis or ELISA. GGA or a GGA derivative is administered orally to mice when treatment of DSS is initiated. GGA or a derivative thereof significantly reduces the clinical severity of...
colitis and suppresses the levels of MPO activity, TNF-alpha and IFN-gamma induced by DSS in the colon. On the other hand, GGA enhances the expression of HSP70 in the colon of mice given DSS.

**Example 6:** Preyjentjon of acute liver damage after hepatectomy.

[0292] Acute liver failure after massive hepatectomy remains a challenging problem. Male Wister rats weighing 230-260 g are obtained. After an overnight fast, GGA or a GGA derivative (as an emulsion with 5% gum arabic and 0.004% a-tocopherol) or vehicle (5% gum arabic emulsion with 0.004% a-tocopherol) is intragastrically administered into rats 4 h prior to the operation. After rats are anesthetized, 90% heptectomy is performed. Briefly, the left, median, right-upper, and right-lower lobes are removed, leaving the caudate lobes, which represent 10-1 1% of the origin al liver mass. Liver specimens and blood samples are collected after laparotomy and exsanguinations under deep anesthesia immediately before (0) and 4, 8, 12, and 24 h after the operation. Small pieces of liver tissue are immediately stored in an RNeasy stabilization kit (Gjagen, Hilden, Germany). Sera are immediately separated, and the activities of alanine (ALT) and aspartate (AST) aminotransferases are measured.

A single oral administration of GGA or a GGA derivative significantly suppresses the release of aminotransferases and improves survival compared with vehicle administration. Gene expression and immunobiot analyses shows that, in addition to HSP70 and HSP27, GGA or GGA derivatives induce an endoplasmic reticulum chaperone, BiP.

**Example 7:** Protection from acetaminophen-induced hepatotoxicity in vitro.

[0293] In order to test the protective activity of GGA and GGA derivatives from acetaminophen-induced hepatotoxicity, a cytotoxicity assay is employed using human hepatoma (Bel-7402) cells in the presence of S9 mixtur e. Cell viability and mitochondrial permeability transition (MPT) is assessed in the presence or absence of GGA or GGA derivatives in combination with a cytotoxic concentration of acetaminophen. GGA or GGA derivatives show increased cell viability and protect from MPT disruption in the presence of acetaminophen compared with control conditions.

**Example 8:** Treatment of non-alcoholic steatohepatitis.

[0294] 100 adults with nonalcoholic steatohepatitis are randomly assigned to receive GGA or a GGA derivative, each at a daily dose of about 10-200 mg, or placebo, for up to 12 months. The primary outcome is an improvement in histological features of nonalcoholic ic
steatohepatitis. The extent of lobular inflammation, hepatocellular ballooning, and/or fibrosis is measured. The results are analyzed following methods well known in the art.

**Example 9: Treatment of non-alcoholic fatty liver disease (NAFLD)**

A randomized, blinded, placebo-controlled study is performed on 100 patients with NAFLD diagnosed by ultrasound (US) and confirmed by liver biopsy (40 patients). The patients are randomized to receive GGA or a GGA derivative (each at a daily dose of 10-200 mg for up to 12 months) or placebo. All patients participate in an identical behavioral weight loss program, and undergo monthly evaluation by abdominal US. Liver enzyme levels, lipid profiles, insulin levels, and anthropometric parameters are also monitored, and all patients undergo nutritional follow-up evaluation. Patients also undergo a further liver biopsy examination as the study progresses. Serum alanine transaminase levels and steatosis by US are measured as non-limiting endpoints. The results are analyzed following methods well known in the art.

**Example 10: GGA and GGA derivative activity in a cardiac ischemic ischemia and reperfusion in vitro model.**

GGA and GGA derivatives are tested for protective effects in an in vitro ischemia/reperfusion cardiac disease model based on the contractile HL-1 cell line. Activity is assessed via apoptosis signaling, cell structure and energy-metabolism. The HL-1 cardiomyocytes (murine atrial tumor cell line) are maintained in monolayer culture with Claycomb-medium (Sigma, Germany). Having reached confluence and contractile activity, cells are maintained as subcultures, induction of ischemia was carried out on vital cardiomyocytes at culture day four. The subconfluent, contractile HL-1 cardiomyocytes are placed in nutrient-deficiency medium containing 2.5 mM hydrogen peroxide solution in order to enhance the oxidative stress in HL-1 cells. In control cultures the medium exchange is carried out with standard supplemented Claycomb-medium. 8 h after ischemia induction samples are harvested and revitalization is induced in parallel by replacing nutrient-deficiency medium with fresh Claycomb-medium and incubating cells for another 16 hours. Cell proliferation analysis is done by flow cytometry. Apoptosis analysis is performed by terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling. Total number of cells are determined using 7-AAD nucleus staining. Additionally formaldehyde- fixed cells on glass coverslips are prepared for immunocytochemical staining. TUNEL assay is performed.
using an In Situ Cell Death Detection Kit, GGA and GGA derivatives reduce ischemia induced apoptosis and rescue ischemia-induced reduction of cell proliferation.

Example 11: GGA and GGA derivatives protect against myocardial ischemia and reperfusion injury in rats.

[0297] Anesthetized male rats are treated once orally with GGA or a GGA derivative 2.4 h before ischemia, and subjected to ischemia for 30 min, followed by reperfusion for 4 h. Lactate dehydrogenase (LDH), creatine kinase (CK), malondialdehyde (MDA), superoxide dismutase (SOD) activity and infarct size are measured. The results show that pre-treatment with GGA or a GGA derivative significantly reduces the Infarct size and the levels of LDH and CK after 4 h of reperfusion. GGA also significantly inhibits the increase in MDA levels and the decrease in SOD levels.

Example 12: Host shock protein 70 induced by GGA or GGA derivative protects heterotopically transplanted hearts in rats.

[0298] A total of 20 donor rats are randomly divided into 2 groups. One of those receives an oral dose of GGA or a GGA derivative and one is a control group. Donor hearts are heterotopically transplanted into recipient rats 24 h after GGA administration. The levels of HSP70 expression in donor hearts and the variation of myocardial enzymes in receptor bioc or donor hearts are measured 24 h after transplantation. The donated hearts are also examined under a microscope for pathological changes. HSP70 expression is increase in the GGA-treated group. Lactate dehydrogenase and creatine kinase muscle band concentrations in receptor blood are decreased in the GGA group compared to the control group. Moreover, the GGA group shows the lower malondialdehyde concentration and the higher triphosphate concentration than the control group, demonstrated by the milder inflammatory injury in the transplanted hearts.

Example 13: Treatment of Cardiac Ischemia and Related indications.

[0299] A randomized, blinded, placebo-controlled study is performed on 100 patients diagnosed with cardiac ischemia, myocardial infarction or acute coronary syndrome based on coronary angiograms. The patients are randomized to receive GGA or a GGA derivative (each at a daily dose of 10-200 mg for up to 12 months) or placebo. GGA or a GGA derivative is directly administered, e.g., in an emergency room setting, to the coronary artery via a PCI/stent catheter followed by oral administration of GGA or a GGA derivative for several weeks. In some patients, administration of GGA or a GGA derivative occurs
during percutaneous intervention (PCI) while stenting through a catheter directly to the coronary artery and the site of infarction. Oral treatment follows preferably for at least 1 month following the heart attack. The incidence of angina is ascertained. The results are analyzed following methods well known in the art.

Example 14:

<table>
<thead>
<tr>
<th>Composition</th>
<th>%</th>
<th>For 10 liters</th>
</tr>
</thead>
<tbody>
<tr>
<td>GGA or a GGA derivative</td>
<td>0.1-20%</td>
<td>10-2,000 g</td>
</tr>
<tr>
<td>EDTA disodium (chelating agent)</td>
<td>0.01-0.1</td>
<td>1-10 g</td>
</tr>
<tr>
<td>NIPAGIN (preservative) **</td>
<td>0.1-0.5</td>
<td>10-50 g</td>
</tr>
<tr>
<td>Purified water</td>
<td>100</td>
<td>10 L</td>
</tr>
</tbody>
</table>

Methylparaoxybenzoate (Nipagin): BDH Chemical LTD, Poole, Dorset, UK

Method of Preparation:

in a suitable vessel equipped with mixer and heating sleeve, introduce about 9 liters of purified water and heat to a temperature of 80 °C. Dissolve Nipagin and EDTA disodium. Stir the solution constantly to complete dissolution of the components. Cool the obtained solution to room temperature.

Dissolve or suspend GGA or a GGA derivative by stirring. Bring to volume with water. The isotonicity of this composition can be adjusted, if needed, by the addition e.g., of 0.3% NaCl or 2.03% of glucose.

Example 15: Argatroban conjugates of GGA or a GGA derivative. Described below are representative synthetic routes to small molecule e.g., Argatroban conjugates of GGA or a GGA derivative. Methods for synthesizing these Argatroban conjugates will be apparent to the skilled artisan in view of this disclosure.
**Example 16: Zofran conjugates of GGA or a GGA derivative**

Described below are representative synthetic routes to small molecule e.g., Zofran conjugates of GGA or a GGA derivative. **Methods** for synthesizing these Zofran conjugates will be apparent to the skilled artisan in view of this disclosure.

![Chemical diagram](image)

**Example 17: Representative linkages for drug conjugates of GGA or a GGA derivative**

Described below are representative synthetic routes to drug conjugates of GGA or a GGA derivative. **Methods** for synthesizing these drug conjugates will be apparent to the skilled artisan in view of this disclosure.
Esters, amides, ureas, carbamates and carbonates:

\[ R_1 \cdots R_m \rightarrow R_1 \cdots R_m \rightarrow H_2O \rightarrow Z_{\text{Drug}} \]

\[ Z = \text{bond, } O, \text{ NH, } N(C_1-C_{\text{alkyl}}) \]

Drug = small molecule, peptide, protein, antibody, etc.

\[ X = O, S \text{ or NH} \]
Schiff’s bases

\[ R^1 \rightarrow \text{starting material} \rightarrow \text{Drug} \]

Formulated for Sublingual Delivery

\[ R^{14} = H \text{ or CH} \_ \]

Hydrolytic conditions \textit{in vivo}

Revert to Starting Materials

Drug = small molecule, peptide, protein, antibody, etc.

Sulfenyfated amides

\[ R^1 \rightarrow \text{starting material} \rightarrow \text{Drug} \]

Formulated for Sublingual Delivery

\[ Z = \text{bond, O, NH, N(C}_1\text{C}_{\text{alky}}\text{S)} \]

Reductive conditions \textit{in vivo}

Revert to Starting Materials

\[ \text{Drug} = \text{small molecule, peptide, protein, antibody, etc.} \]

[0300] All abbreviations for scientific terms used herein have their ordinary scientific meaning as known to the skilled artisan.
CLAIMS

1. An intranasal composition, the composition comprising an effective amount of geranyigeranyl acetone (GGA) or a GGA derivative, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

2. The composition of claim 1, wherein the GGA or a GGA derivative exists at least 80%, or at least 90%, or at least 95%, or at least 99% in the trans isomer.

3. An intranasal composition, the composition comprising an effective amount of geranyigeranyl acetone (GGA) or a GGA derivative, or a GGA derivative conjugated with a drug optionally via a linker that is labile in vivo, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

4. The composition of claim 3, wherein the GGA or a GGA derivative exists at least 80%, or at least 90%, or at least 95%, or at least 99% in the cis isomer or wherein a GGA derivative exists at least 80%, or at least 90%, or at least 95%, or at least 99% in the trans form.

5. The composition of any one of claims 1-4 comprising 0.1-20% (weight/volume) of GGA or a GGA derivative, or a pharmaceutically acceptable salt thereof.

6. The composition of any one of claims 1-4 comprising 5-10% (weight/volume) of GGA or a GGA derivative, or a pharmaceutically acceptable salt thereof.

7. The composition of any one of claims 1-6 in the form of a solution, suspension or emulsion.

8. The composition of any one of claims 1-7 wherein said excipient comprises a bioadhesive and/or an intranasal absorption promoter.

9. The composition of claim 8, wherein said intranasal absorption promoter is selected from the group consisting of a chelating agent.

10. An enteric composition, the composition comprising an effective amount of GGA or a GGA derivative or a pharmaceutically acceptable salt thereof, and 3 pharmaceutically acceptable excipient.

11. A method comprising administering intranasally an effective amount of a composition of any one of claims 1-9 to a subject in need thereof.
12. A method for treating a neural disease, disorder or condition and/or reducing one or more negative effects of a neural disease, disorder or condition comprising administering intranasally an effective amount of a composition of any one of claims 1-9, or administering orally an enteric composition of claim 10, to a subject in need thereof.

13. A method for treating inflammatory bowel disease and/or reducing one or more negative effects of inflammatory bowel disease comprising administering an effective amount of a composition of GGA or a GGA derivative to a subject in need thereof.

14. A method for treating chronic liver disease and/or reducing one or more negative effects of chronic liver disease comprising administering an effective amount of a composition of GGA or a GGA derivative to a subject in need thereof.

15. A method of treating a disorder selected from liver injury, preferably acute liver injury (from trauma, surgery or as a side effect of cancer treatment), acute liver failure, preferably caused by drug toxicity such as acetaminophen toxicity, cardiac ischemia, myocardial infarction, reperfusion injury and heart transplants, or a related disorder or condition, comprising administering a composition comprising an effective amount of geranylgeranyl acetone (GGA) or a GGA derivative, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, to a subject in need thereof.

16. The method of any one of claims 13-15, wherein the composition is that of any one of claims 1-10.
INTERNATIONAL SEARCH REPORT

INTERNATIONAL SEARCH REPORT

PCT/US2014/026263

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/121(2006.01)i, A61K 9/107(2006.01)i, A61P 25/00(2006.01)i

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)
A61K 31/121; A61K 31/675; C07K 2/00; C07C 29/147; A61K 31/045; A61K 9/107; A61P 25/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
eKOMPASS(KIPO internal) & keywords: geranylgeranyl acetone (GGA), trans form, cis form, conjugate, intranasal formulation, enteric formulation

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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</thead>
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<td>X</td>
<td>US 2012-0172453 Al (BABA, B. A. et al.) 5 July 2012 See abst sect; paragraphs [0061], [0066], [0075]; and claims 1, 4.</td>
<td>1-6, 10</td>
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<td>A</td>
<td>US 2002-0082244 Al (RESZKA, A. A. et al.) 27 June 2002 See abst sect; and claim 3.</td>
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<td>A</td>
<td>US 2009-0054623 Al (DEFreeS, S.) 26 February 2009 See abst sect; paragraphs [0002]-[0003], [0009H010], [0045], [0201H0202]; and claims 1, 31.</td>
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<td>A</td>
<td>WANG, G. et al., 'Bisphosphonate doped lipid nanoparticles designed as drug carriers for bone diseases', 31 March 2012, Journal of Biomedical Materials Research, Part A, Vol. 100, No. 3, pp. 684-693 See abst sect; and figure 1.</td>
<td>1-6, 10</td>
</tr>
</tbody>
</table>

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
07 August 2014 (07.08.2014)

Date of mailing of the international search report
07 August 2014 (07.08.2014)

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Form PCT/ISA/210 (second sheet) (July 2009)
INTERNATIONAL SEARCH REPORT

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

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

1. ☑ Claims Nos.: 11-16
   because they relate to subject matter not required to be searched by this Authority, namely:
   Claims 11-16 pertain to a method for treatment of the human by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv), to search.

2. ☑ Claims Nos.: 9
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
   Claim 9 is unclear since they are referring to the multiple dependent claims which do not comply with PCT Rule 6.4(a).

3. ☑ Claims Nos.: 7,8,11-12, 16
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☑ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☑ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fees.

3. ☑ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☑ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

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

Form PCT/ISA/210 (continuation of first sheet (2)) (July 2009)
### Patent document cited in search report

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